INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA

UMI®
800-521-0600

Classical and Bayesian Approaches to Nonlinear Models Based on Human *in vivo* Cadmium Data

by

SHAN LIANG SHENG, B.Sc., M.Sc.

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree

Doctor of Philosophy

McMaster University

August 1998

Classical and Bayesian Approaches to Nonlinear Models Based on Human *in vivo* Cadmium Data

DOCTOR OF PHILOSOPHY (1998) McMaster University

(Mathematics and Statistics) Hamilton, Ontario

TITLE: Classical and Bayesian Approaches to Nonlinear Models Based on Human *in vivo* Cadmium Data

AUTHOR: Shan Liang Sheng M. Sc (McMaster University, Hamilton)

SUPERVISOR: Dr. N. Balakrishnan

SUPERVISORY COMMITTEE: Dr. N. Balakrishnan
Dr. D. R. Chettle
Dr. P. D. M. Macdonald

Number of pages: xvi, 193

ABSTRACT

In the major part of this thesis, two-compartment and four-compartment models in the form of systems of linear differential equations, associated with human *in vivo* cadmium data, have been constructed to describe a particular biological phenomenon of cadmium metabolism in the human body. The two-compartment model constitutes the preliminary work, and the complete analysis and discussions are finally achieved through the four- compartment model.

Since it was expensive to technically perform the *in vivo* measurements and also difficult to collect the data over a period of a decade, the data set analyzed in this thesis are quite precious and one of very few such existing data sets in the area of cadmium research. Cadmium researchers are very much interested in drawing as much information as possible from these data. A method is developed for deriving the expectation functions and analyzing this special data set. The parameter estimation for the compartment models developed is based on two parameter estimation methods based on classical and Bayesian approaches. It is the first time a whole system of the human body has been analyzed **simultaneously** without any additional assumptions on the derivation of the compartment models. This contrasts with the approach of discussing each compartment separately with a large number of assumptions from different sources as in Kjellström's model. The results obtained from these statistical approaches based on simpler and more direct mathematical

models are not only interpreted very reasonably in terms of the biological phenomenon, but they also show great consistency with previous studies, even though the data are sparse and noisy which poses a special difficulty in this study.

This thesis also considers the application of segmented models to examine the relationship between renal dysfunction and blood or urine cadmium, and to locate abrupt change points as kidneys become abnormal.

ACKNOWLEDGMENTS

I wish to extend my appreciation to my supervisor Professor N. Balakrishnan for his wonderful teaching in many Statistics courses I took with him and for his encouragement and guidance throughout the course of this research.

I would like to express my gratitude to Professor D. R. Chettle for his valuable advice and guidance on the biophysical issues of this thesis and for giving financial support and confidence throughout the research work and preparation of this thesis.

I would also like to express my thanks to Professor P. D. M. Macdonald, who is a member of my supervisory committee, for his impressive course that I took as my first statistics course at McMaster University and for his assistance and comments on this thesis.

Additionally, my thanks go to Professor S. Walter for his time and advice at the early stages of my Ph.D study.

Finally, my husband and daughter, who displayed great enthusiasm which did much to make this thesis possible for me, deserve special thanks.

In Memory of My Father,

Professor Yongkang Liang

To

My Husband, Chen

and

My Daughter, Gloria

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

1.1 Scope of the Thesis

There are four chapters in this thesis. Chapter 1 gives the background to cadmium and its use in both general and working environments. It also describes toxic effects of exposure to cadmium and cadmium metabolism that is, a system of absorption, transport, distribution, accumulation and excretion in the human body. Then, it introduces several measurements used in the data of this thesis. Lastly, Kjellström's model[29] is introduced briefly.

Chapter 2 investigates a relationship between renal dysfunction and blood or urine cadmium in the human body, and locates points where the abrupt change might occur in blood or urine cadmium as the kidneys become abnormal. The discussions are based on the models for cross-sectional studies on populations occupationally exposed to cadmium. In addition to that, effectiveness of blood and urine cadmium for biological monitoring of cadmium in the workplace is studied in this chapter. In the last part of Chapter 2, a brief discussion is provided about the effectiveness of kidney and liver cadmium for monitoring cadmium.

Chapters 3 and 4 form the major part of this thesis. These chapters focus on two-compartment and four-compartment models in the form of systems of linear differential equations. Since it was expensive to technically perform the *in vivo* measurements and also difficult to collect these cadmium data over a period of a decade, the data set analyzed in this thesis is quite precious and one of very few such existing data sets in the area of cadmium research. Cadmium researchers are very much interested in drawing as much information as possible from these data. The two-compartment model in Chapter 3 is the prelude to the four-compartment model, and constitutes the preliminary work. Going a step further, the complete analysis and discussions are finally achieved by the four-compartment model in Chapter 4.

Chapter 4 is composed of five sections. In Section 4.1, the four-compartment model in the form of a linear non-homogeneous system of ordinary differential equations, is given, both analytically and graphically. The four compartments are cadmium in blood, cadmium in urine, cadmium in kidney, and cadmium in liver. Moreover, the expectation functions of the four-compartment model are derived analytically in terms of eigenvalues and corresponding eigenvectors of a matrix of transfer rates. In Section 4.2, blood cadmium and the total body burden are discussed briefly. In Section 4.3, the discussion is on obtaining starting values for fitting the unknown parameters based on two methods, namely, graphical analysis and grid search. In the last two sections, the discussions and conclusions are focused on the estimation of parameters by classical and Bayesian approaches. Two numerical methods, namely, Gauss-

Newton and Newton-Raphson methods, are presented specifically, for the optimization involved. I then made a comparison between the model developed in this thesis and Kjellström's Model by pointing out the similarity and differences. The sophisticated model derived by Kjellström[29] in 1977 is based on many assumptions, since it involves 21 coefficients. These parameters must be fixed through prior knowledge. In contrast, this thesis presents parameter estimation, based on two statistical methods, using classical and Bayesian approaches, directly from the human data, and constructs a model to describe a particular biological phenomenon of cadmium metabolism in the human body. This has never been done before.

It is first time a whole system of the human body has been analyzed **simultaneously** without any additional assumptions on the compartment models. Previous works discussed each compartment separately and involved a large number of assumptions from different sources such as Kjellström's model[29].

1.2 Background to Cadmium

Cadmium is a rare metallic element of silver-white appearance which falls in Group IIB of the Periodic Classification, between zinc and mercury, with atomic weight 112.4, atomic number 48, density 8.6, melting point 321 C°, and boiling point 765 C°[21].

Cadmium is obtained as a by-product from the refining of zinc and other metals, particularly, copper and lead. It displays chemical similarity to zinc.

Unlike other metals, cadmium has been recognized only for a relatively short time. It was first identified as an element in 1817 by Friedrich Stromeyer and did not come into even limited use until some 60-70 years ago. Large consumption dates only from the 1940s[23] and dispersion into environment by human activity is relatively recent.

1.3 Industrial Usage of Cadmium

Cadmium has been used in a wide range of industrial applications, even though its toxic effects have been acknowledged for decades.

There are several metals that are frequently electroplated with cadmium to protect them from rusting. Cadmium plating is applied on automobiles, aircraft, and is also used on marine and textile equipment, as well as goods such as nuts and bolts, locks, hinges and screws.

Cadmium sulfide and cadmium sulfoselenide are commonly used as red, orange and yellow pigments in plastics and various types of paint. More than 70% of cadmium pigments are used in plastics with others being used to color rubber and industrial and car paints.

Cadmium stearate is used as a stabilizer in plastics to inhibit the process in which plastics darken, harden or become fragile under the effect of heat or light.

Because of the ability of cadmium to stiffen copper and increase its mechanical resistance at increased temperatures, cadmium is used in copper-cadmium alloys for electrical cables. Cadmium serves as an electrode component in nickel/cadmium batteries. Cadmium is also used in welding electrodes and 'silver' solders for joining metals like domestic pipe work and refrigerators as well as other heat exchangers such as car radiators.

In application such as pigments and plating, cadmium can be replaced by other less toxic materials, and its use has therefore been restricted by law in some countries. However, it is more difficult to replace cadmium for some other uses of cadmium in products (e.g., electric batteries and electronic components).

The data sets analyzed in Chapter 2 are by Prescote[10], Prayon and Balen[38]. The Prescot data were collected from industrially exposed male workers in 1983 in a copper alloy factory in the United Kingdom, for manufacturing overhead electrical cable with cadmium being used in the alloy to strengthen the copper[10]. The Balen and Prayon data were gathered from workers volunteering to participate in a study in two zinc-cadmium-producing plants in Belgium[38]. The data sets of Prescot, Prayon and Balen were included in the author's Master's Project for different statistical analyses. The Jaguar data analyzed in Chapters 3 and 4 were collected from the British Leyland Jaguar workers, engaged in

brazing and silver soldering. The silver solder contained cadmium and the resulting fumes constituted the exposure[23]. The Jaguar data set is given in Table 4.1 in Chapter 4.

1.4 Cadmium in the Environment

1.4.1 General environment

Water, air, cigarettes, soil, and food are main sources for uptake of cadmium in the general environment. There are two routes of entry to the human body, which are the respiratory route by inhalation and the gastrointestinal route by ingestion. Between 10 and 50% of inhaled cadmium is absorbed, while 5% of ingested cadmium is absorbed in the human body[21]. In the respiratory route, absorption is greater for small particles and fumes than for large particle dust. The gastrointestinal absorption increases with a low intake of calcium and iron.

In natural water, cadmium is found mainly in bottom sediments and suspended particles. The concentration of cadmium in water is low. Contamination of drinking water may occur as a result of cadmium impurities in the zinc of galvanized pipes or cadmium-containing solders in fittings, water heaters, water coolers, and taps. Leaching of cadmium to ground water from dumped cadmium oxide sludge has also been observed. Sea water contains between 0.04 and 0.3 µg/l of cadmium. Regular drinking water usually does not have concentrations of cadmium exceeding 5 µg/l[21].

Cadmium in air occurs in particulate form and can be inhaled. The levels of inhaled cadmium are the highest around certain cadmium-emitting industries. Average cadmium concentrations are lower in rural areas than in urban areas. It was reported that levels are 10 to 1000 times lower in remote areas than in urban areas[13, 14]. Smoking increases the level of inhaled cadmium. Since each cigarette contains from 1 to 2 μg cadmium, smoking one cigarette results in the inhalation of 0.1-0.2 μg cadmium, assuming 10% of cadmium to be inhaled[14].

Both waterborne and airborne cadmium can cause increased concentrations in soil. Soil contamination may arise from cadmium-polluted irrigation water, well water acidified pipes, by acid precipitation, or fertilizers formed by cadmium-containing sewage sludge and superphosphate in agriculture. The cadmium concentration in soil is usually less than 1 mg /kg in non-polluted areas, but higher in contaminated soil in certain polluted areas[21].

Food is the main source of cadmium uptake in humans. Rice, wheat and certain vegetables may contain raised cadmium concentrations, since plants and crops absorb cadmium contained in soil. Most foods in uncontaminated areas of several countries have cadmium from the range of 0.005-0.1 mg/kg[14]. Certain foods (e.g., oysters, liver and kidney) may contain much higher concentrations since the bodies of animals and shellfish accumulate cadmium contained in plants and grass or from sewage sludge at river estuaries. Elinder reported that the average daily intake in an uncontaminated area is

usually in the range of 10 to 60 μg for a 70-kg person. There is tendency for cadmium average daily intake to be lower in Europe and North America than in Japan[21].

1.4.2 Working environment

Most exposure to cadmium in the working environment is via inhalation, although exposure via ingestion through contaminated food, drink or cigarettes consumed at work may also be of significance. Skin exposure is minor because of the low absorption through skin.

High inhalation exposures may occur among workers from welding and soldering fumes. Smokers in a cadmium-exposed workplace may contaminate their cigarettes or pipes with cadmium and increase their cadmium level even further.

Long-term excessive exposure to cadmium via both food and air may lead to kidney damage in the human body. Long-term exposure to low air levels may lead to chronic obstructive lung disease and possibly lung cancer, while short-term exposure with high cadmium concentrations in the air is extremely dangerous and may occasionally result in death.

In the past, exposure levels to cadmium in some cadmium-product factories have been quite high. With the development of modern industrial technology, it has gradually been reduced over time in some factories, and it is possible to lessen the occupational air cadmium concentrations to below 10-20 μg /m^3 in cadmium-product manufacturing[21].

Since cadmium exposure continues in industry, it is desirable in cadmium research to design the simple measurements that can be used to determine when to remove a worker from exposure that is discussed in Chapter 2. Furthermore, it is motivated to improve understanding of long term human cadmium metabolism in order to regulate current exposure to present future damage that is discussed in Chapter 3 and 4.

1.5 Cadmium Metabolism in the Human Body

The objective of this thesis is to construct mathematical models which are in accordance with observations describing a particular biological phenomena of cadmium metabolism in the human body. This section gives detailed description about absorption, transportation, distribution, accumulation and excretion of cadmium, in order to understand the metabolism of cadmium inside the human body.

1.5.1 Absorption by inhalation and ingestion

Exposure to cadmium occurs mainly through the pulmonary or gastrointestinal route. Cadmium exposure through skin is negligible.

Cadmium exposure via inhalation is in the form of an aerosol. Cadmium compounds are deposited in the nasopharyngeal, the tracheobronchial, and/or the

pulmonary (alveolar) parts of respiratory tract in different proportions, depending on particle size and an individual's respiratory characteristics.

Larger particles with a mass median aerodynamic diameter (MMAD) of 5 μm might be deposited mainly 75% in the nasopharyngeal part, 20% in alveolar and 5% in tracheobronchial part. While smaller particles with a MMAD of 0.05 μm might be deposited 10% in the nasopharyngeal part, 55% in alveolar and nothing in tracheobronchial part, the remaining 35% being exhaled[29].

After inhalation of cadmium, between 10-50% of inhaled cadmium is absorbed[21]. Larger particles with high MMAD and low solubility is probably in the lower part of this range, while smaller particles with low MMAD and high solubility account for the upper part[21].

Cadmium exposure via ingestion originates in food or drink. After ingestion, cadmium passes into the gastrointestinal GI tract. The larger proportion of ingested cadmium is excreted via feces, while a small proportion is either absorbed in the mucosal cells or cleared to blood. Approximately 5% of ingested cadmium is absorbed. A low intake of calcium, lack of iron or protein may considerably increase the absorption of cadmium. The gastrointestinal absorption rate may be as high as 20% in individuals with iron deficiency[21].

1.5.2 Transport and distribution

After absorption from the lungs or the intestines, cadmium is transported via blood to other parts of the body where it is stored, but some of it might return to the blood for redistribution.

Whole blood is composed of 55% plasma and 45% red blood cells with a small fraction (less than 1%) of white blood cells.

Cadmium in the blood is mainly found in the blood cells where it is bound to a high molecular-weight fraction and a low molecular-weight fraction[21, 36] similar to metallothionein, a protein which also binds cadmium in plasma.

Cadmium in blood plasma is bound to both low molecular-weight proteins and high molecular-weight proteins. The main part of plasma cadmium being bound to high molecular-weight proteins, particularly albumin, is transported to the liver, while the smaller part of plasma cadmium, bound to the low molecular-weight protein, metallothionein, is taken up by the kidneys[23].

The molecular weight for metallothionein is about 6000-7000 daltons. Up to 11% of its weight can consist of cadmium and other bivalent metals such as zinc, copper and mercury. Metallothionein plays an important role in the transport of cadmium to the kidneys in humans.

1.5.3 Accumulation

Cadmium is transported by blood to several organs where it is accumulated. Binding of cadmium to proteins causes the accumulation. Distribution of cadmium among the organs is largely dependent on the duration of exposure, the exposed person's age, and the bonding of cadmium to metallothionein.

A large proportion of cadmium is accumulated in the liver, kidneys and muscles. Two major cadmium accumulation sites are the liver and kidneys, which account for approximately 16% and 53% of the total body burden, respectively[4].

The decrease in tubular reabsorptive capacity which can result from chronic cadmium exposure may result from a decrease in the total number of tubular cells. A loss of tubular cells might cause an increase in the transport of cadmium from kidney tubules to blood and increased excretion of cadmium from tubules to urine.

1.5.4 Excretion

The major cadmium excretion routes are via feces and urine. Total daily excretion rate is about 0.01-0.02% of the total body burden of cadmium in human beings[21]. The fecal cadmium level mainly reflects the unabsorbed part of ingested cadmium. The average urine cadmium level correlates well with the average kidney cadmium level in current exposure. Urine cadmium level will be expected to increase rapidly both after the high inhaled exposure and after damage to the kidneys.

1.6 Toxic Effects of Cadmium Exposure

About 50 years ago, Friberg drew attention to the toxicity of cadmium[22]. Toxic effects of cadmium become visible if some significant biological mechanism is stimulated beyond a certain level. Those effects depend on many factors like uptake, elimination process and binding to proteins. Since those body conditions differ from individual to individual or even from one kind of cell to another, the toxicological response will vary widely.

1.6.1 Acute poisoning

Acute cadmium poisoning normally occurs only in cadmium processing industries like plating or welding, nickel/cadmium battery manufacturing plants or zinc or cadmium producing plants.

Ingestion of highly contaminated food or beverages results in acute gastrointestinal effects. Symptoms caused by ingestion of cadmium-containing food or drink are vomiting, abdominal cramps, headache and nausea. In more severe cases, diarrhea and shock may develop. The beginning of symptoms is usually within minutes after ingestion of contaminated food or drink by cadmium. The minimum concentration of cadmium in water to induce vomiting is about 15 mg/l. The minimum concentration in protein-containing food that causes vomiting might be larger[21].

Occupational exposure to airborne cadmium under conditions of poor ventilation leads to inhalation of cadmium fume, particularly in cadmium oxide form. The predominant symptoms are fever, general weakness, and shortness of breath. In severe cases, there can be respiratory insufficiency with shock and death. Approximately 1 mg/m^3 inhaled cadmium over a period of 8 hours might give rise to clinically evident symptoms. The lethal level of cadmium exposure is approximately 5 mg/m^3 over the same period[14].

1.6.2 Chronic poisoning

Chronic poisoning may occur after an acute or chronic occupational exposure and/or in cadmium polluted areas. The most typical feature of chronic cadmium intoxication is kidney damage. The kidney is one of the major accumulation organs in cadmium exposure by both inhalation and ingestion and is sometimes termed as the "critical" organ for chronic intoxication. It would be helpful to outline the kidney function in detail before discussing the toxic effects of cadmium in the kidneys.

The basic structural and functional unit of the kidney is the nephron, in which blood is filtered and urine is elaborated. Two kidneys possess about 2 million nephrons.

The nephrons are packed closely together in the kidneys in such way that the adjacent structures tend to influence each other's function[16]. A nephron consists of a glomerulus and a urine tubule divided into several segments, the proximal convoluted tubule, descending and ascending limbs of the loop of Henle, the distal convoluted tubule,

and the collecting tubule of Bellini[25]. The glomerulus, proximal convoluted tubule and distal convoluted tubule, and part of the loops of Henle are in the cortex of the kidney, and the deepest part of the loops of Henle and collecting tubules are in the medulla of the kidney.

The glomerulus, a rounded structure, is formed by the opening out of a capillary tuft between two arterioles, afferent and efferent. It is responsible for filtering the blood plasma. The glomerular membrane, one of the layers of glomerulus, acts as a sieve almost totally excluding from filtration proteins with molecular weights greater than 65000 daltons. A diagram of the nephron is presented in Figure 1.1. In order to maintain the body's metabolic process, the proximal tubules reabsorb necessary proteins, salts, sugars and amino acids from the filtrate. 60-80% of the glomerlar filtrate, including several proteins, is reabsorbed in the proximal convoluted tubules, which is made up of cells, particularly the proximal tubular epithelial cells. Low molecular weight proteins, like β_2-microglobulin and retinol binding protein (RBP), are nearly 99.9% absorbed normally, thus allowing little or none to pass into urine.

This process has a maximum reabsorption rate and appears to require energy from cells, even though only minimal amounts of the proteins pass into urine along with the other waste products.

Cadmium is transported in plasma bound to metallothionein, then is quickly and easily filtered through the renal glomerulus and reabsorbed into the proximal tubule

epithelial cells. In particular, metallothionein moves to the cell interior and fuses with the lysosomes, which contains enzymes to digest and break down the cadmium-metallothionein into the amino acids, peptides and free cadmium irons. These smaller complexes can be reused by the cell or expelled.

The unbound cadmium enters the intracellular fluid. This cadmium will stimulate new intracellular metallothionein production which binds the cadmium in the renal tubular cells. If the amount of cadmium is excessive and the capacity for metallothionein production is reached, a rapid increase of free cadmium will cause damage to the cell function.

Friberg discovered that the first and most common sign of intoxication is usually a relatively large increase in excretion of low molecular-weight proteins, known as tubular proteinuria[22]. The kidney damage induced by cadmium is permanent and may even progress after exposure ceases. The tubular proteinuria may increase even after exposure ceases mainly due to the transport protein metallothionein. Tubule damage might also affect the accumulation of cadmium in the kidneys. A decrease in reabsorptive capacity induced by excessive amount of free cadmium may decrease the kidney cadmium.

Some experimental studies have shown that blocking the renal tubular reabsorption increases the urinary albumin by about forty times, but the excretion of β_2-microglobulin and retinol binding protein (RBP) more than thousandfold[34, 21].

Liver is another major accumulation organ for cadmium. However, changes in hepatic function in cadmium workers are generally slight compared to those in renal function.

Cadmium damage to the lung can develop either some time after acute intoxication or by chronic inhalation of low cadmium levels. Impairments are usually mild but might induce respiratory disorders and chronic lung disease like emphysema and bronchitis[23]. Several studies appear to indicate that long-term occupational exposure to cadmium may increase prevalence of cancer of the prostate and the lung[21]. However, there have not been sufficient analyses to show conclusive evidence of causal link between cadmium exposure and cancer.

1.7 Measurements Related to the Data

1.7.1 Measurements on blood, urine and β_2-microglobulin

In order to measure blood and urine cadmium concentrations, 5 ml of venous blood can be gathered from each worker as blood sample, along with a urine sample. Occasionally, 35 ml of venous blood were obtained as blood sample from each person as in the Prescot data. Urine "time" samples, called 'time' sample, can be collected by complete bladder emptying at the beginning of collection and collecting all urine, including the final bladder emptying at the end of collection. The period lasts about 3 hours. A urine

'spot' sample is only collected once. The blood and urine cadmium concentrations were measured by graphite-furnace atomic absorption spectrometry[12, 31].

β_2-microglobulin has already been mentioned several times in earlier sections of this chapter. It is low molecular weight protein of 11600 daltons. Tubule and/or glomerular damage in the kidneys occurs and can be noticed by an enhanced excretion of proteins. As a consequence of renal damage, β_2-microglobulin can serve as an indicator, but it suffers from degradation at urine PH values less than 5.5. Hence, the measurement of β_2-microglobulin in urine with PH values less than 5.5 is not stable and gives a value lower than the real one.

1.7.2. Measurements on liver and kidney

As mentioned above, cadmium accumulation occurs in the liver, kidneys, and other tissues of the human body. In particular, the liver and kidneys are principal storage organs. Previously, the data on the body burden of cadmium in man has been derived primarily from autopsy studies. *In vivo* measurement techniques, however, have made it possible to evaluate the status of the active workers[15]. *In vivo* measurements of liver and kidney cadmium can be performed by prompt-gamma neutron activation analysis (PGNAA).

The use of PGNAA for the measurement of cadmium was suggested initially by Ettinger, Biggin, Chen and other researchers in 1971[6, 43] and some preliminary results were published in 1974 by the same people[7, 43]. Applications of the technique were subsequently

reported in 1979 by Thomas and Harvey as well as some other researchers[43]. The measurement techniques have been applied and successfully redesigned at Birmingham University, where Chettle studied and worked, as reviewed by Scott[39] and Chettle[10].

There are two measurement systems, which use either the Nuffield cyclotron in operation at Birmingham University or sealed isotopic sources to produce neutrons, to measure cadmium concentration in the liver and the left kidney. Initially, the Nuffield cyclotron was used and later changed to the use of sealed isotopic neutron sources. Both systems can be used to produce a fast neutron beam.

Although the cyclotron system is very sensitive for measuring, there are some disadvantages. The cyclotron system can not be transported easily, and the neutron beam must be aimed vertically towards the subject while the subject is lying down. In this posture, a person's kidneys are relatively mobile, moving through 3-4 cm during normal respiration. The system using sealed isotopic neutron sources, on the other hand, can be dismantled and transported easily, and the neutron beam is aimed horizontally towards the subject so that the subject is sitting, in which case kidney movement is only slight. The use of the transportable system results in a slight of loss precision but the gain from the transportability of the system outweighs the disadvantages[1, 20, 43]. In the cadmium data analyzed in this thesis, kidney and liver cadmium were measured by transportable systems using sealed isotopic neutron sources.

During the measurements, the neutrons are collimated to irradiate the measured organ, the position and depth of which is found by ultrasound, and then slowed mainly by elastic collisions with hydrogen in the body. Cadmium present in the subject can undergo neutron capture. The low energy neutrons produce an excited state of ^{114}Cd through undergoing capture by the stable isotope of cadmium (^{113}Cd). The de-excitation of ^{114}Cd is accomplished by the emission of γ rays, the most prominent of which has an energy of 559 keV[23].

A high resolution detector is used externally to the body to identify the 559 keV γ rays from photons with neighboring energies. The resulting γ ray spectrum is accumulated on a multi-channel analyzer (MCA) and the data are collected on a computer; thus, the amount of cadmium can be quantified by means of the most prominent of the prompt γ rays.

For calibration purposes, two sets of liver and kidney phantoms were used. Each phantom is the approximate shape and size of either human liver or kidney. Phantoms were made to contain several fixed concentrations of cadmium solution, carrying the range expected in the *in vivo* measurements. The net peak area of the 559keV y-rays arising from cadmium is obtained respectively cadmium counts is obtained respectively for the different phantom distances from the collimator front, and then the calibration curve can be generated for either liver or kidney system after the cadmium counts versus cadmium

concentration. By using the *in vivo* cadmium counts obtained from the subject and the calibration lines, final cadmium concentration for subjects can be calculated.

The units for measuring cadmium in the liver and kidney are different. The levels of cadmium in the liver are expressed as parts per million (ppm), for the cross-sectional area of the neutron beam is less than the cross-sectional area of liver. As the kidney fits within the dimensions of the neutron beam, the total amount of cadmium in milligrams (mg) is obtained.

There are uncertainties in the *in vivo* measurement techniques. The Poisson-distribution counts in the cadmium γ ray peak and in the underlying background continuum set a limit to the precision of measurement. Additional variance arises because the cadmium counts in the net area for fixed cadmium concentration change as the depth of the subject changes, ultrasonic scanning records the subject's organ depth imprecisely; the organ moves during the measurement; etc. The uncertainties in the *in vivo* measurement techniques have been reduced but still occur to an extent that leads to difficulties in the statistical analysis based on the measured data, although the efforts have been made to decrease the influence of these factors. Table 1.1 below shows the notations which are abbreviations of the measurements. These notations are used throughout this thesis.

TABLE 1.1 Notations of abbreviations of measurements

Cd_u	measurements of urine cadmium
Cd_b	measurements of blood cadmium
Cd_l	measurements of liver cadmium
Cd_k	measurements of kidney cadmium
u_β₂	measurements of urinary β_2-microglobulin

1.8 Kjellström's Model

Figure 1.2 shows a flow scheme of the kinetic model of cadmium metabolism used as a basis for the modeling, as established by Tord Kjellström and Gunnar F Nordberg in 1977[29]. The eight-compartment kinetic model with 21 distribution coefficients contains compartments of liver, kidney, feces, urine, other tissues, blood 1, blood 2, and blood 3 cadmium. Blood 1 contributes to accumulation of cadmium in liver and other tissues, while blood 3 contributes to accumulation of cadmium in kidneys. Blood 2 between blood 1 and blood 3 contains the accumulation of cadmium bound to cells and molecules. The following are the brief description for symbols used in Figure 1.2.

A — pulmonary route

G — gastrointestinal route

C1 — from pulmonary route to gastrointestinal route intake

C2 — from pulmonary route to lung

C3 —from lung to daily uptake

C4 —from lung to gastrointestinal route intake

C5 —from gastrointestinal route intake to intestine wall

C6 — from intestine wall to daily uptake

C7 —from daily uptake to blood 3

C8 —maximum amount of C7 × daily intake

C9 —from blood 1 to other tissues

C10 —from other tissues to blood 1

C11 — from blood 1 to feces

C12 —from blood 1 to liver

C13 —from liver to blood 1

C14 —from liver to blood 3

C15 —from liver to feces

C16 —from blood 1 to blood 2

C17 —from blood 3 to kidney

C18 —from kidney to blood 1

C19 —from kidney to urine

Cx —1-(C9+C11+C12)

C20 —modified coefficient for blood 1 and blood 3

C21—modified coefficient for C19 with age

Background information for the Kjellström's model had been obtained partly from animal experiments and partly from observations on the human beings in industrial and general environmental exposure situations. Generally accepted principles for intake and absorption of cadmium constituted part of the flow scheme in Kjellström's model. The

ranges of C1, C2 and C3 were determined according to principles described by Task Group on lung Dynamics and/or Task Group on Metal Accumulation[29], depending on particle size and respiratory characteristics. The principles state that particles with MMAD of 5 μm were estimated to be deposited mainly in the nasopharyngeal compartment 75% and less, in the alveolar 20%, and tracheobronchial compartment 5%, whereas smaller particles with MMAD of 0.05 μm are deposited in the alveolar compartment 55%, with 10% in tracheobronchial compartment, and nothing in the nasopharyngeal compartment, which are sources for two cases of C1, C2 and C3. The first case (cadmium in cigarette smoke) was assumed to be in the form of cadmium oxide fumes with very small MMAD. The second case (cadmium oxide dust in factory), on the other hand, had a larger MMAD but was still mainly less than 5 μm. C4, C5 and C6 were based on some assumptions and some observed animal data[29].

The distribution was designed to involve blood compartments, giving rise to tissue accumulation in three body compartments of liver, kidney, and tissues and excretion by urinary and fecal routes. The transport of cadmium between the compartments was assumed to follow first-order exponential functions. Since about 34% of body burden is in the kidneys, 16%, in liver and 50% in tissues, C7, C9 and C12 were assumed in accordance with the corresponding body burden[29]. C8 represents a maximum amount of C7×daily intake in micrograms per day, which was only an assumption since there were no data available for it. C13, C14 and C15 were estimated by Tsuchiya in 1972 according to

the estimation of half-life time in liver of 4 to 19 years. C18 and C19 were derived from the estimation of a half-life time in kidneys of 6 to 38 years[29]. Since a half-life time in muscles was estimated to be much longer than in liver and kidneys[29], C10 was assumed to be corresponding to a half-life time of 9 to 47 years. Biologically, there is no accumulation in blood 1 and turnover is very rapid from blood 1 to tissues and liver, and summation of C9, C11 and C12 were assumed very large[29]. For the same reason in blood 3 as in blood 1, C17 was assumed to be large, which is close to 1[29]. Cx is just the difference between 1 and the summation of C9, C11 and C12.

The model, with a series of assumptions, is very sophisticated, and provides particular biological explanation and general reference for the metabolism of cadmium in the human body. In this thesis, the simpler and more direct mathematical models has been developed from statistical approaches. The comparison between these two models is discussed in the last section of Chapter 4.

Figure 1.1 Diagram of a nephron: 1. glomerulus; 2. proximal convoluted; 3. descending limb of the loop of Henle; 4. ascending limb of the loop of Henle; 5. distal convoluted tubule; 6. collecting tubule

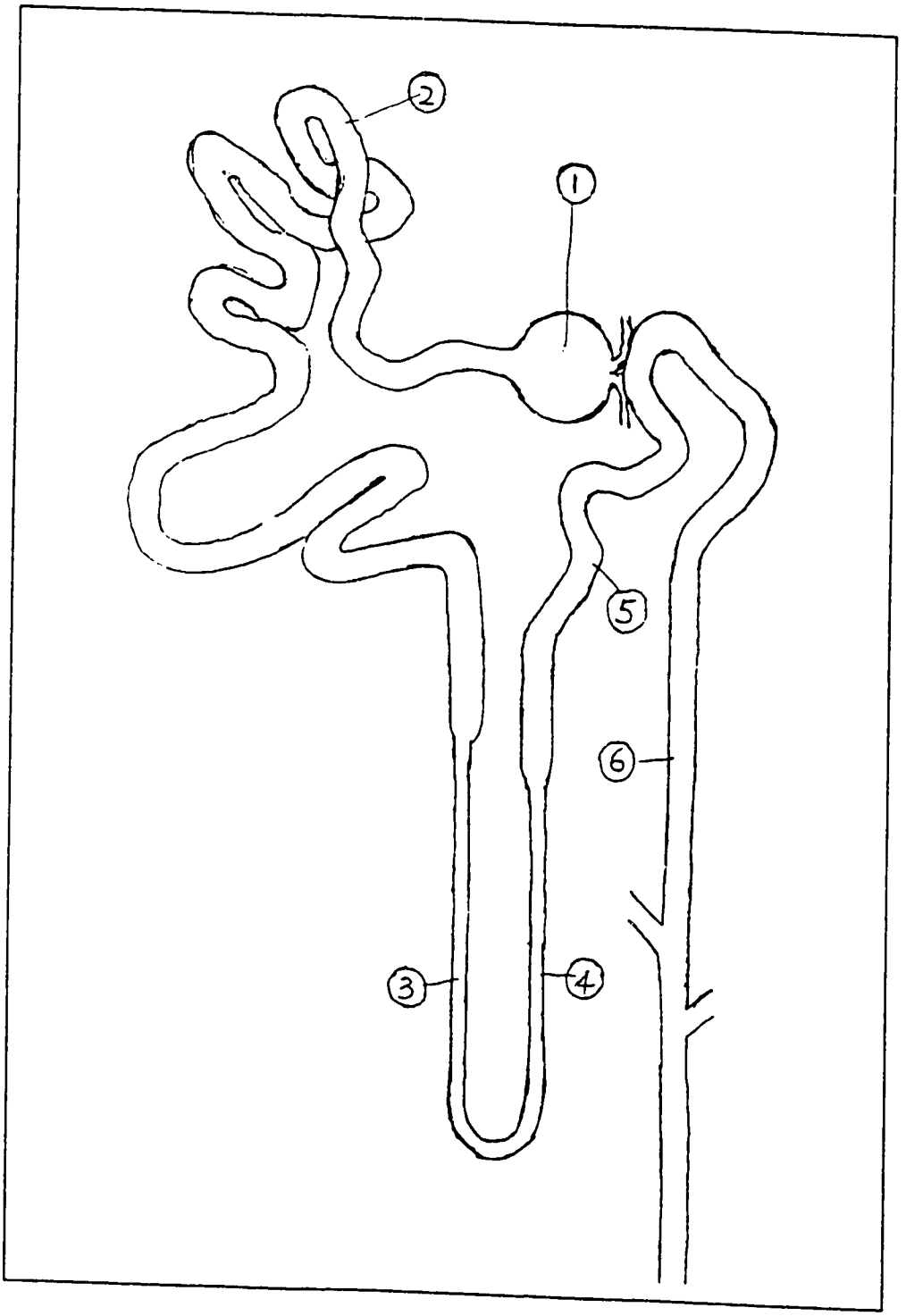
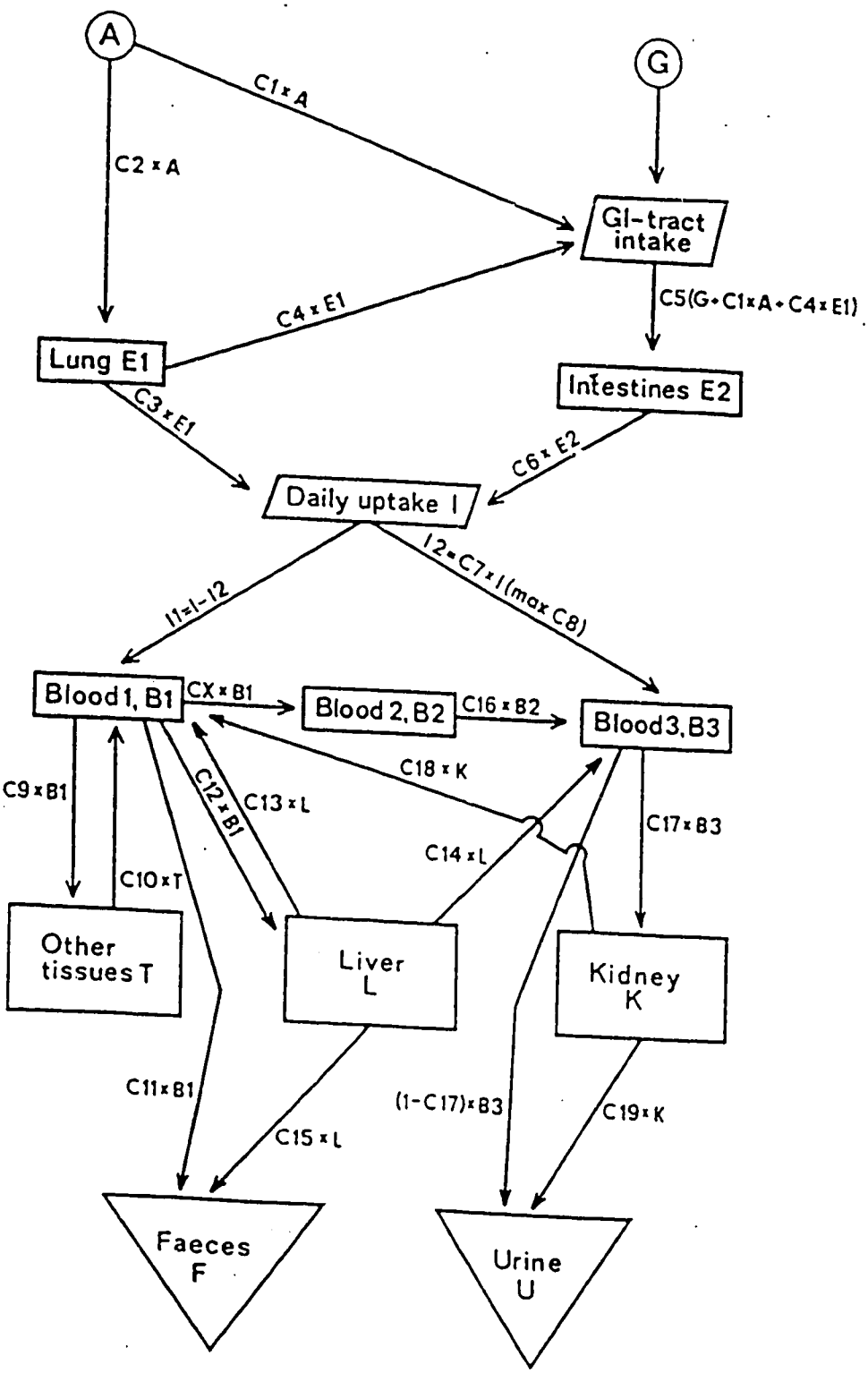


Figure 1.2. Flow scheme of Kjellström' model of cadmium metabolism



CHAPTER TWO

SEGMENTED MODELS

2.1 Segmented Models

2.1.1 Introduction

Three data sets (Prescot, Prayon, and Balen), selected from populations occupationally exposed to cadmium, were used for the analysis in this chapter. These three data sets had each been previously studied and reported for different purposes[31, 38]. In this chapter, the relationship between renal function and blood cadmium along with the relationship between renal function and urine cadmium are examined initially among the three sets of data. The analysis is based on segmented models.

General segmented models are defined by different functions on different intervals. Typically the end points of intervals, called change points, are unknown and need to be estimated. Regression models, with a pair of straight lines and a structural change point between two lines, were applied here.

The segmented model is expressed[35] as follows:

$$y_i = \beta_0 + \beta_1 x_i + \beta_2 (x_i - x_0) a + \varepsilon_i , \qquad i = 1, \ldots, n , \tag{2.1}$$

where a is a indicator variable such that

$$a = \begin{cases} 0 & \text{if } x_i - x_0 < 0 \\ 1 & \text{otherwise}, \end{cases} \qquad i = 1, \ldots, n; \text{ and } x_0 \text{ denotes as the change point.}$$

The model above is the same as

$$y_i = \begin{cases} \beta_0 + \beta_1 x_i + \varepsilon_i & \text{if} \quad x_i < x_0 \\ \beta_0 + \beta_1 x_i + \beta_2 (x_i - x_0) + \varepsilon_i, & \text{if} \quad x_i \geq x_0 . \end{cases}$$

In the segmented models considered in this chapter, the dependent variable y_i ($i = 1, \ldots, n$) is always the logarithm of urinary β_2-microglobulin which describes renal function status, while the independent variable x_i is the logarithm of either urine or blood cadmium. The aim of using the segmented models here is to locate where the abrupt changes occur in either blood cadmium or urine cadmium for each data set. Furthermore, it is of interest to investigate how sensitively both blood cadmium and urine cadmium can be used as monitoring parameters to define renal dysfunction for a subject, since a sample of urine and blood cadmium is not technologically sophisticated enough to be collected compared to the *in vivo* measurements.

There are two steps taken to find the change points. In the first step, even though the change point x_0 is an unknown point, it can be treated as a known value through Model (2.1). When the change point is assumed to be known, the problem becomes an ordinary linear problem. By fixing the change point and hence dividing the points between the first and second lines, the remaining parameters can be estimated in Model (2.1) by least-squares, and the residual sum of squares could be evaluated for each division separately. After calculation, the division and set of estimates which give rise to the smallest residual sum of squares could be picked out, and the corresponding change point could be chosen as the starting value of unknown parameter x_0 for the second step. In the second step, the change point can be estimated directly through Model (2.2), which is given by

$$y_i = \beta_0 + \beta_1 x_i + \beta_2 (x_i - x_0)\frac{sign(x_i - x_0)\times[(1 - sign(x_i - x_0)]+2}{2} + \varepsilon_i,$$
$$i = 1,\ldots,n, \qquad (2.2)$$

where $sign(x_i - x_0)$ is a sign function defined as

$$sign(x_i - x_0) = \begin{cases} 1 & if\ x_i - x_0 > 0 \\ -1 & if\ x_i - x_0 < 0 \\ 0 & if\ x_i - x_0 = 0 \end{cases}, \qquad i = 1,\ldots,n, \text{ and}$$

$$a = \frac{\{sign(x_i - x_0)\times[(1 - sign(x_i - x_0)]\}+2}{2}, \qquad i = 1,\ldots,n.$$

The starting values for the change points in the second step were obtained from the first step. Model (2.1) does not differ from Model (2.2) essentially, since a implicitly depends on the change point x_0 in Model (2.1), a is expressed as a function of the $sign(x_i - x_0)$ functions in Model (2.2). The three data sets, Prescot, Prayon and Balen, were analyzed as described below.

2.1.2 Prescot

The Prescot data were collected from industrially exposed male workers in 1983 in a copper alloy factory in the United Kingdom, which was manufacturing overhead electrical cable with cadmium being used in the alloy in order to strengthen the copper. The manufacturing process first involves melting copper (melting point 1083°C) in furnaces, then adding cadmium (boiling point 765°C), mixing the molten alloy, and finally casting as soon as mixing is complete. Yellow brown fumes of cadmium from the boiling process could be inhaled or ingested by the workers. The exposure in that factory was related to both cadmium fume and dust. The measurements from 180 male workers are the basis of the Prescot data. Of those measured, 77

of the 180 workers had had at least one year's exposure to cadmium, whereas 103 selected from the same factory had not been occupationally exposed to cadmium[30].

Besides variables of blood and urine cadmium, 14 biochemical variables including total protein, albumin, urinary β_2-microglobulin, retinol binding protein, alkaline phosphatase, lactate dehydrogenase, N-acetyl glucosaminidase, γ-glutamyl transferase, urate clearance, amylase clearance, phosphate clearance, creatinine clearance, serum β_2-microglobulin and serum urea, which all relate to renal function, were also used for the analysis. Those 14 parameters can be combined to produce a single best estimate of whether an individual has normal or abnormal renal function[24]. Three different ways of combining the information from all 14 parameters were used to identify those subjects with renal dysfunction. These were: firstly, to count the number of parameters in which a subject recorded an abnormal test result; secondly, the z value was computed for each parameter for each subject by comparison with the mean and standard deviation of a derived normal population and then these z scores were then summed; lastly, a multivariate distance measure, Mahalanobis' D^2, was determined for each subject from the distribution of normal subjects. The three approaches showed a considerable degree of agreement in identifying subjects with renal dysfunction[24]. The results from these three methods were then used to identify renal status on individuals in the Prescot data analyzed in this chapter.

The scatter plot of $\ln(u\_\beta_2)$ against $\ln(Cd\_b)$ and the plot of $\ln(u\_\beta_2)$ against $\ln(Cd\_u)$ clearly indicate a particular linear relation in some range of either $\ln(Cd\_b)$ and $\ln(Cd\_u)$ and a different linear relation elsewhere. Hence, it is reasonable to apply the segmented regression model to describe the relationship between $\ln(u\_\beta_2)$ and $\ln(Cd\_u)$, and the relationship between $\ln(u\_\beta_2)$

and ln(*Cd_b*), respectively.

First, the possible change point was chosen from 30 nmol/l to 90 nmol/l of *Cd_b* with an interval of 5 nmol/l. By applying Model (2.1), 13 sets of estimates were obtained. It was found that the residual sum of squares was smallest when *Cd_b* was around 40 nmol/l.

Additionally, the possible change point of *Cd_b* was selected consecutively in the range of 30 nmol/l and 50 nmol/l with increment of 1 nmol/l, and Model (2.1) was applied again for another 21 sets, respectively.

Finally, *Cd_b*=44 nmol/l was selected as the starting value of change point, since the residual sum of squares is smallest and R^2 is largest at this point. The corresponding model is as follows:

$$\ln(u\_\beta_2) = -1.8575 - 0.0194\ln(Cd\_b) + 2.1547(\ln(Cd\_b) - 3.784)a + \varepsilon .$$

Since the coefficient of ln(*Cd_b*) is not statistically significant, this model, by eliminating ln(*Cd_b*), was reduced to:

$$\ln(u\_\beta_2) = -1.9107 + 2.1204(\ln(Cd\_b) - 3.784)a + \varepsilon .$$

Therefore, the slope of ln(*Cd_b*) is not significantly different from zero when *Cd_b* is equal to or less than 44 n mol/l, whereas the slope of ln(*Cd_b*) is 2.1204 when *Cd_b* is greater than 44 n mol/l.

A similar procedure was applied for urine cadmium as well. After selecting the range from 1 μg/g creat to 10 μg/g creat with interval 1 μg/g creat, the possible change point for *Cd_u* was found at 4 μg/g creat in the first step, at which the residual sum of squares was smallest. The corresponding model is:

$$\ln(u\_\beta_2) = -1.8755 - 0.2498\ln(Cd\_u) + 1.4476(\ln(Cd\_u) - 1.3863)a + \varepsilon .$$

The coefficient of ln(*Cd_u*) was not highly significant. If the term ln(*Cd_u*) was removed, the model turns out to be

$$\ln(u\_\beta_2) = -1.8434 + 1.9056(\ln(Cd\_u) - 1.3863)a + \varepsilon .$$

The slope of ln(*Cd_u*) is not significantly different from zero when *Cd_u* is equal to or less than 4 µg/g creat, whereas the slope of ln(*Cd_u*) is 1.9056 when *Cd_u* is larger than 4 µg/g creat.

2.1.3 Prayon

The Prayon data were collected in 1978 from 129 male workers in Belgian zinc-cadmium plant. The Prayon data set contains measurements of blood cadmium, urine cadmium, total protein, albumin and urinary β_2-microglobulin. For the combined parameters, discriminatory levels of 250 mg/g creatinine for total protein and 12 mg/g creatinine for albumin were used, along with 0.2 mg/g creatinine for β_2-microglobulin. A person was considered to have abnormal renal function if one or more of these parameters was above the appropriate discriminatory level. This criterion was used previously by Roels[38].

Like the Prescot data, either the scatter plot of ln(*u_β₂*) against ln(*Cd_b*) or the plot of ln(*u_β₂*) against ln(*Cd_u*) indicates a particular linear relation in some range of either ln(*Cd_b*) or ln(*Cd_u*) and a different linear relation elsewhere. After a similar procedure was adopted as above, it was finally found for the Prayon data that *Cd_u* = 7 µg/g creat and *Cd_b* = 71 n mol/l are possible change points. The corresponding models are:

$$\ln(u\_\beta_2) = -3.1368 + 0.7875(\ln(Cd\_b) - 4.263)a + \varepsilon ,$$

$\ln(u\_\beta_2) = -3.1841 + 0.8208(\ln(Cd\_u) - 1.9459)a + \varepsilon$.

The slope of ln(*Cd_u*) is not significantly different from zero when *Cd_u* is equal to or less than 7 μg/g creat, whereas the slope of ln(*Cd_u*) is 0.8208 when *Cd_u* is larger than 7 μg/g creat. The slope of ln(*Cd_b*) is not significantly different from zero when *Cd_b* is equal to or less than 71 nmol/l, whereas the slope of ln(*Cd_b*) is 0.7875 when *Cd_b* is larger than 71 nmol/l.

2.1.4 Balen

The sample size of the Balen data is 184, also collected in 1978 from male workers exposed to cadmium in northern Belgium. The measurements and the discriminatory levels of renal function were the same as in the Prayon data. The difference in urinary β_2-microglobulin discriminatory level between the Prescot data and the Prayon or the Balen data relates to the fact that the Prescot data set had a significantly higher age distribution than in the Prayon and the Balen data.

In the Balen data, the change point of *Cd_u* is not very clear. The possible change point was assumed to be *Cd_u* = 7 μg/g creat, which is the same as that in the Prayon data, since both scatter plots looked similar. A possible change point of *Cd_b* was found to be 56 n mol/l in the Balen data. The corresponding models for the Balen data are:

$\ln(u\_\beta_2) = -2.8568 + 1.6595(\ln(Cd\_b) - 4.025)a + \varepsilon$,

$\ln(u\_\beta_2) = -2.9556 + 2.6763(\ln(Cd\_u) - 1.9459)a + \varepsilon$.

The slope of ln(*Cd_u*) is not significantly different from zero when *Cd_u* is equal to or less than 7 μg/g creat, whereas the slope of ln(*Cd_u*) is 2.6763 when *Cd_u* is larger than 7 μg/g creat. The slope of ln(*Cd_b*) is not significantly different from zero when *Cd_b* is equal to or less than 56

nmol/l, whereas the slope of ln(Cd_b) is 1.6595 nmol/l when Cd_b is larger than 56 nmol/l.

All three data sets show a similar pattern although the change points are not very close among these data sets. Prior to the change point, the slope of the renal function parameter against the independent variable was close to zero or, at most only marginally significant statistically at 95% level. After the change point, the renal function parameter increased rapidly with increasing values of blood or urine cadmium. By applying Model (2.2), finishing values of urine cadmium and blood cadmium as the change points were obtained, shown in Table 2.1 for each data set. It can be seen from Table 2.1 that the starting and finishing values look fairly close in most of them except urine cadmium in the Balen data. The plots of ln(u_β_2) against ln(Cd_u) and ln(u_β_2) against ln(Cd_b) based on the Prescot data with fitted segmented models are presented in Figure 2.1 and Figure 2.2, respectively.

TABLE 2.1 Estimated change points of urine cadmium and blood cadmium in the three data sets

Data Sources	Urine Cadmium (μg/g creatinine)		Blood Cadmium (n mol/l)	
	Starting Values	Finishing Values	Starting Values	Finishing Values
Prescot	4	4.20±0.33	44	44.43±0.21
Prayon	7	7.43±0.31	71	71.02±42
Balen	7	10.14±0.20	56	56.04±0.44

2.2 Diagnostic Test

2.2.1 Classification

The change points shown in Table 2.1 could then be applied as reference values for a quantitative diagnostic test, such that a value above a reference value was coded as raised and one below the reference value was taken to be not raised. In total, five sets of reference values were examined; three are given in Table 2.1 as appropriate population specific reference values; the other two are 90 n mol/ l for blood cadmium together with 10 μg/g creatinine for urinary cadmium and 50 n mol/l for blood cadmium with 5 μg/g creatinine for urine cadmium as none population specific reference values. The first of these two is based on guidelines used in the United Kindom[26], and the second represents a more conservative approach, each one selected between the highest derived and lowest derived change point as suggested by Chettle. The renal status for each subject was assessed

by the combination of several parameters appropriate to that data set.

The diagnostic multiple tests were constructed in which these five sets of reference values were used to predict renal function in these three data sets, respectively. That is, the two reference values that are not population-specific were applied to each data set, together with the appropriate population specific reference values from Table 2.1. The data sets were classified into subgroups for the multiple test in two ways as follows:

1st way: high *Cd_u* and high *Cd_b* as positive test result,

low *Cd_u* or low *Cd_b* as negative test result.

2nd way: high *Cd_u* or high *Cd_b* as positive test result,

low *Cd_u* and low *Cd_b* as negative test result.

Tables 2.2 - 2.4 show how each of the three data sets was subdivided for the tests.

TABLE 2.2 Classifications of test groups in the Prescot data based on *Cd_u* and *Cd_b* (unit of ug/g creatinine for *Cd_u* and unit of n mol/l for *Cd_b*)

Reference values	Test type	Renal function	
		Abnormal	Normal
Cd_u=10 *Cd_b*=90	Positive test (1^{st})	16	9
	Negative test (1^{st})	23	132
	Positive test (2^{nd})	24	17
	Negative test (2^{nd})	15	124
Cd_u=5 *Cd_b*=50	Positive test (1^{st})	28	19
	Negative test (1^{st})	11	122
	Positive test (2^{nd})	30	29
	Negative test (2^{nd})	9	112
Cd_u=4 *Cd_b*=44	Positive test (1^{st})	28	22
	Negative test (1^{st})	11	119
	Positive test (2^{nd})	31	35
	Negative test (2^{nd})	8	106

TABLE 2.3 Classifications of test groups in the Prayon data based on *Cd_u* and *Cd_b* (unit of ug/g creatinine for *Cd_u* and unit of n mol/l for *Cd_b*)

Reference values	Test type	Renal function	
		Abnormal	Normal
Cd_u=10 *Cd_b*=90	Positive test (1st)	10	35
	Negative test (1st)	11	73
	Positive test (2nd)	11	48
	Negative test (2nd)	10	60
Cd_u=5 *Cd_b*=50	Positive test (1st)	13	51
	Negative test (1st)	8	57
	Positive test (2nd)	15	70
	Negative test (2nd)	6	38
Cd_u=7 *Cd_b*=71	Positive test (1st)	12	45
	Negative test (1st)	9	63
	Positive test (2nd)	13	58
	Negative test (2nd)	8	50

TABLE 2.4 Classifications of test group in the Balen data based on *Cd_u* and *Cd_b* (unit of ug/g creatinine for *Cd_u* and unit of n mol/l for *Cd_b*)

Reference values	Test type	Renal function	
		Abnormal	Normal
Cd_u=10 *Cd_b*=90	Positive test (1^{st})	11	5
	Negative test (1^{st})	47	121
	Positive test (2^{nd})	16	11
	Negative test (2^{nd})	42	115
Cd_u=5 *Cd_b*=50	Positive test (1^{st})	16	10
	Negative test (1^{st})	42	116
	Positive test (2^{nd})	26	31
	Negative test (2^{nd})	32	95
Cd_u=10 *Cd_b*=56	Positive test (1^{st})	14	8
	Negative test (1^{st})	44	118
	Positive test (2^{nd})	21	19
	Negative test (2^{nd})	37	107

2.2.2 Multiple test

The test performance characteristics such as *Sensitivity*, *Specificity*, *Positive predictive value*, *Negative predictive value*, *False positive rate*, *False negative rate* and *Accuracy* are defined as follows:

$$Sensitivity = \frac{Number\ of\ subjects\ with\ abnormal\ renal\ function\ and\ positive\ test\ result}{Total\ number\ of\ subjects\ with\ abnormal\ renal\ function},$$

$$Specificity = \frac{Number\ of\ subjects\ with\ normal\ renal\ function\ and\ negative\ test\ result}{Total\ number\ of\ subjects\ with\ normal\ renal\ function},$$

$$PV^{+} = \frac{Number\ of\ subjects\ with\ abnormal\ renal\ function\ and\ positive\ test\ result}{Total\ number\ of\ subjects\ with\ positive\ test\ result},$$

$$PV^{-} = \frac{Number\ of\ subjects\ with\ normal\ renal\ function\ and\ negative\ test\ result}{Total\ number\ of\ subjects\ with\ negative\ test\ result}.$$

$$False\ negative\ rate = 1 - Sensitivity,$$

$$False\ positive\ rate = 1 - Specificity,$$

$$Accuracy = \frac{Total\ number\ of\ correctly\ assigned\ subjects}{Total\ number\ of\ subjects\ in\ study},$$

where *Positive predictive value* and *Negative predictive value* are denoted as PV^{+} and PV^{-}, respectively.

The results of diagnostic multiple tests based on urine and blood cadmium are given in Tables 2.5 - 2.10. By comparing the results in Tables 2.5 and 2.8, it can be seen that *Sensitivity* is low but *Specificity* is high in the first way; and *Sensitivity* is high but *Specificity* is low in the

second way. The results from Tables 2.6 and 2.9 and from Tables 2.7 and 2.10 show a similar pattern as those from Tables 2.5 and 2.8. It is recommended to use the second way to subdivide the subjects since a *False positive rate* result is far less deleterious than a *False negative rate* result in detecting the cadmium level in the human body.

TABLE 2.5 Frequency with common change points (90 nmol/l for *Cd_b* and 10 μg/g creatinine for *Cd_u*) and combined parameters in the 1st way

Data set	*Sensitivity*	*Specificity*	PV^+	PV^-	*Accuracy*
Prescot	.41	.94	.64	.85	.82
Prayon	.48	.68	.22	.87	.64
Balen	.19	.96	.69	.72	.72
All sets	.31	.87	.43	.80	.74

TABLE 2.6 Frequency with common change points (50 nmol/l for *Cd_b* and 5 μg/g creatinine for *Cd_u*) and combined parameters in the 1st way

Data set	*Sensitivity*	*Specificity*	PV^+	PV^-	*Accuracy*
Prescot	.72	.87	.60	.92	.83
Prayon	.62	.53	.20	.88	.54
Balen	.28	.92	.62	.73	.72
All sets	.48	.79	.42	.83	.71

TABLE 2.7 Frequency with derived change points shown in Table 2.1 for each data set and combined parameters in the 1st way

Data set	*Sensitivity*	*Specificity*	PV^+	PV^-	*Accuracy*
Prescot	.72	.83	.56	.92	.82
Prayon	.57	.58	.21	.88	.58
Balen	.24	.94	.67	.73	.72
All sets	.46	.80	.42	.82	.72

TABLE 2.8 Frequency with common change points (90 nmol/l for *Cd_b* and 10 µg/g creatinine for *Cd_u*) and combined parameters in the 2nd way

Data set	*Sensitivity*	*Specificity*	PV^+	PV^-	*Accuracy*
Prescot	.61	.88	.59	.89	.82
Prayon	.52	.56	.19	.86	.55
Balen	.28	.91	.59	.73	.71
All sets	.43	.80	.40	.82	.71

TABLE 2.9 Frequency with common change points (50 nmol/l for *Cd_b* and 5 µg/g creatinine for *Cd_u*) and combined parameters in the 2nd way

Data set	*Sensitivity*	*Specificity*	PV^+	PV^-	*Accuracy*
Prescot	.77	.79	.51	.93	.79
Prayon	.71	.35	.18	.86	.41
Balen	.45	.75	.46	.75	.66
All sets	.60	.65	.35	.84	.64

TABLE 2.10 Frequency with derived change points shown in Table 2.1 for each data set and combined parameters in the 2nd way

Data set	*Sensitivity*	*Specificity*	PV^+	PV^-	*Accuracy*
Prescot	.79	.75	.47	.93	.76
Prayon	.62	.46	.18	.86	.49
Balen	.36	.85	.53	.74	.70
All sets	.55	.70	.37	.83	.67

By taking a close look at the results in Tables 2.8, 2.9, and 2.10, the following points may be observed:

(1) *Sensitivity* values are quite low but *Specificity* values are quite high if the reference values are based on the U.K. guidelines.

(2) *Sensitivity* in Balen values are low and *Specificity* in Prayon values are low. Even if we use derived reference values from the same data, the results can not be improved significantly.

(3) Derived reference values generated from each data set performs better than guideline reference values. As expected, *Sensitivity* values and PV^- are improved at the cost of *Specificity* values and PV^+, and there is a marginal drop compared to guideline reference values in overall *Accuracy*.

(4) More conservative reference values of 50 n mol/l for blood cadmium and 5 μg/g creatinine for urine cadmium produce slightly different results from derived reference values. By comparing the results from Tables 2.9 and 2.10, *Sensitivity* value in Prescot decreases marginally while *Sensitivity* values in Prayon and Balen increase in the more conservative

approach. In addition, *Specificity* value increases slightly in Prescot but decreases in either Prayon or Balen. *PV⁻* are similar between Tables 2.9 and 2.10. In all sets, *Sensitivity* of 60% and *Specificity* of 65% classified by the conservative approach indicate that the conservative approach gives more effective performance since *Sensitivity* gains without losing much *Specificity*, compared with those in Table 2.10.

The discussion about the effectiveness of both liver and kidney cadmium for monitoring the cadmium level is made now. Table 2.11 indicates the classifications of test groups based on reference values of kidney cadmium and liver cadmium as criteria. These reference values were chosen to be 20 mg for kidney cadmium and 30 ppm for liver cadmium for all three data sets, based on previous studies[40, 18]. A value of kidney cadmium equal or greater than 20 mg or a value of liver cadmium equal or greater than 30 ppm was considered as a positive test result. The value of kidney cadmium less than 20 mg and a value of liver cadmium less than 30 ppm, on the other hand, was considered as a negative test result. Discriminatory levels of 250 mg/g creatinine for total protein and 12 mg/g creatinine for albumin were used, along with 0.2 mg/g creatinine for β_2-microglobulin for the Prayon and Balen data sets, which were the same in the discussion of urine and blood cadmium. If one or more of these parameters were above the appropriate discriminatory level, the kidney status was assumed abnormal. For the Prescot data set, the same procedure as in the discussion of urine and blood cadmium was also adapted.

Table 2.12 gives the results of diagnostic test based on the levels of liver and kidney cadmium as criteria. Comparing the results of Table 2.12 to previous results from Tables 2.5 to

2.10, we observe with interest the following points:

(1) *Sensitivity* values are lower or the same in Table 2.12 compared with those in Tables 2.6, 2.7, 2.8, 2.9 and 2.10, except for the Balen data in Table 2.7 and for the Prayon data in Tables 2.7 and 2.8, but are higher than those in Table 2.5;

(2) *Specificity* values are higher or the same in Table 2.12 compared with those in Tables 2.6, 2.7, 2.8, 2.9 and 2.10, except for the Balen data in Tables 2.6 and 2.7 and for the Prayon data in Table 2.8, but are lower than those in Table 2.5;

(3) PV^+ values are higher or the same in Table 2.12 compared with in Tables 2.5, 2.6, 2.7, 2.8, 2.9 and 2.10, except for the Balen data in Tables 2.5, 2.6 and 2.7 and for the Prescot data in Table 2.5;

(4) PV^- values are higher compared with those in Table 2.5, but lower or the same compared with those for the Balen data in Tables 2.6, 2.7, 2,8, 2.9 and 2.10;

(5) *Accuracy* values are higher or the same in Table 2.12 compared with in Tables 2.5, 2.6, 2.7, 2.8, 2.9 and 2.10, except for the Balen data in Tables 2.5, 2.6 and 2.7 and for the Prayon data in Table 2.5; *Accuracy* value on all data sets in Table 2.12 is highest.

TABLE 2.11 Classifications of test groups based on *Cd_l* and *Cd_k* (unit of ppm for *Cd_l* and unit of mg for *Cd_k*)

Reference values (*Cd_l*=30 & *Cd_k*=20)	Test type	Renal function	
		Abnormal	Normal
Balen	Positive test	16	11
	Negative test	42	115
Prayon	Positive test	13	44
	Negative test	8	64
Prescot	Positive test	22	14
	Negative test	17	127

TABLE 2.12 Frequency with common change points (30 ppm for *Cd_l* and 20 mg for *Cd_k*)

Data set	*Sensitivity*	*Specificity*	PV^+	PV^-	*Accuracy*
Prescot	.56	.90	.61	.88	.83
Prayon	.61	.59	.23	.89	.60
Balen	.28	.91	.59	.73	.71
All sets	.43	.81	.43	.82	.76

The foregoing analysis underlines the difficulty of using blood and urine cadmium data alone to provide effective biological monitoring for cadmium in workplace, which agrees with the results from previous studies.

It has been implicitly assumed that the more recent, highly technical and expensive tests involving the *in vivo* analysis of cadmium in the liver and kidney, are more powerful biological monitors of cadmium exposure than blood or urine measurements. However, the results from Table 2.12 show only slight improvement, based on liver and kidney cadmium as monitoring for cadmium. Among all *Accuracy* tests, *Accuracy* of all sets based on liver and kidney cadmium is marginally the best but does not give a clear answer. By looking at the Prescot data closely, if a reference group of 77 subjects was only considered, none of the tests is higher than 80%, since *Sensitivity* is 69%; *Specificity* is 70%; PV^+ is 61%; PV^- is 76% and *Accuracy* is 69%. All of these might imply a simple test is not good enough to describe cadmium in the human body thoroughly.

In order to get a complete understanding of cadmium, the compartment models, involving measurements of urine and blood cadmium as well as kidney and liver cadmium, are constructed in next two chapters to describe cadmium metabolism in the human body.

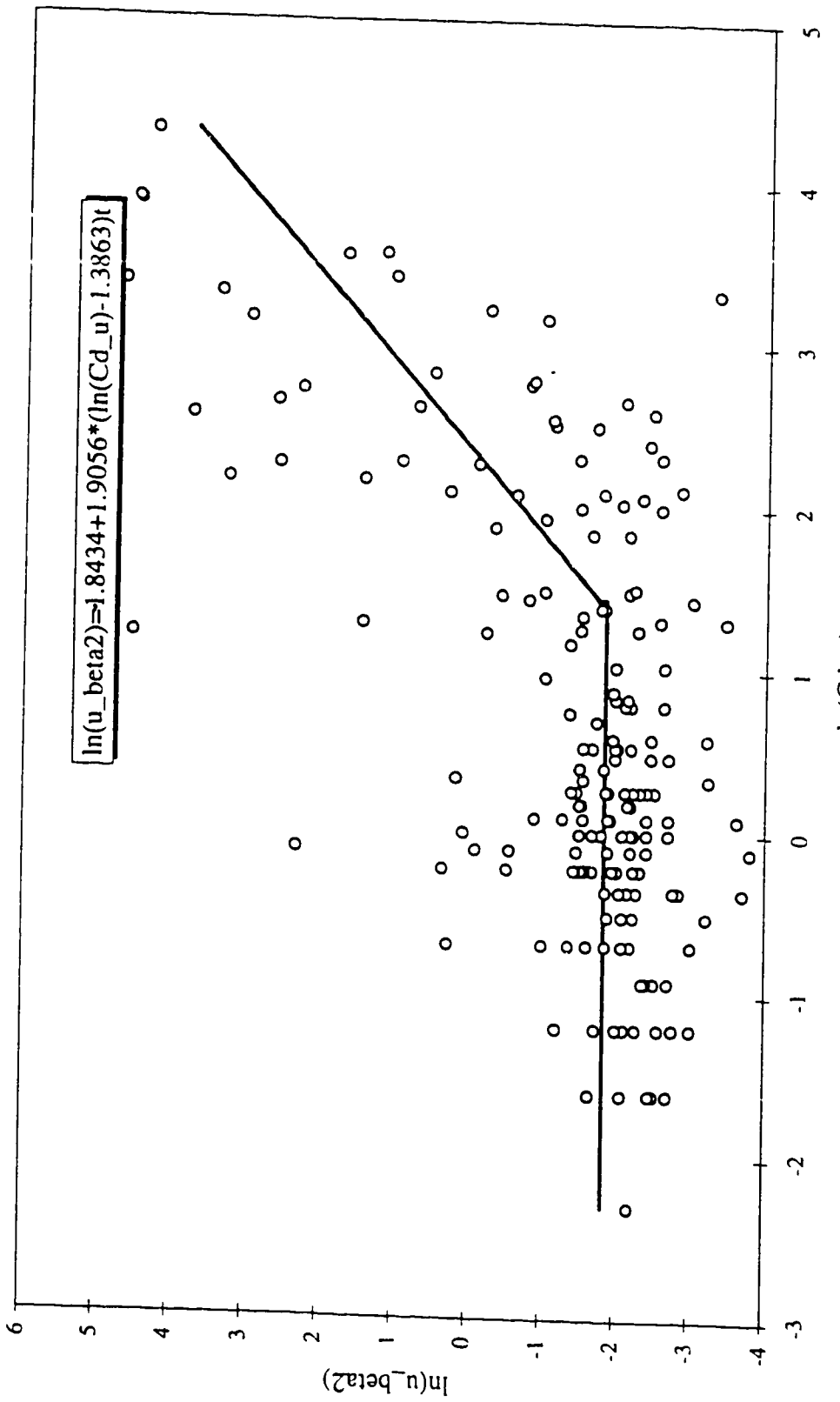


Figure 2.1 Plot of observed Prescot data (u_beta2 versus Cd_u) with fitted segmented model

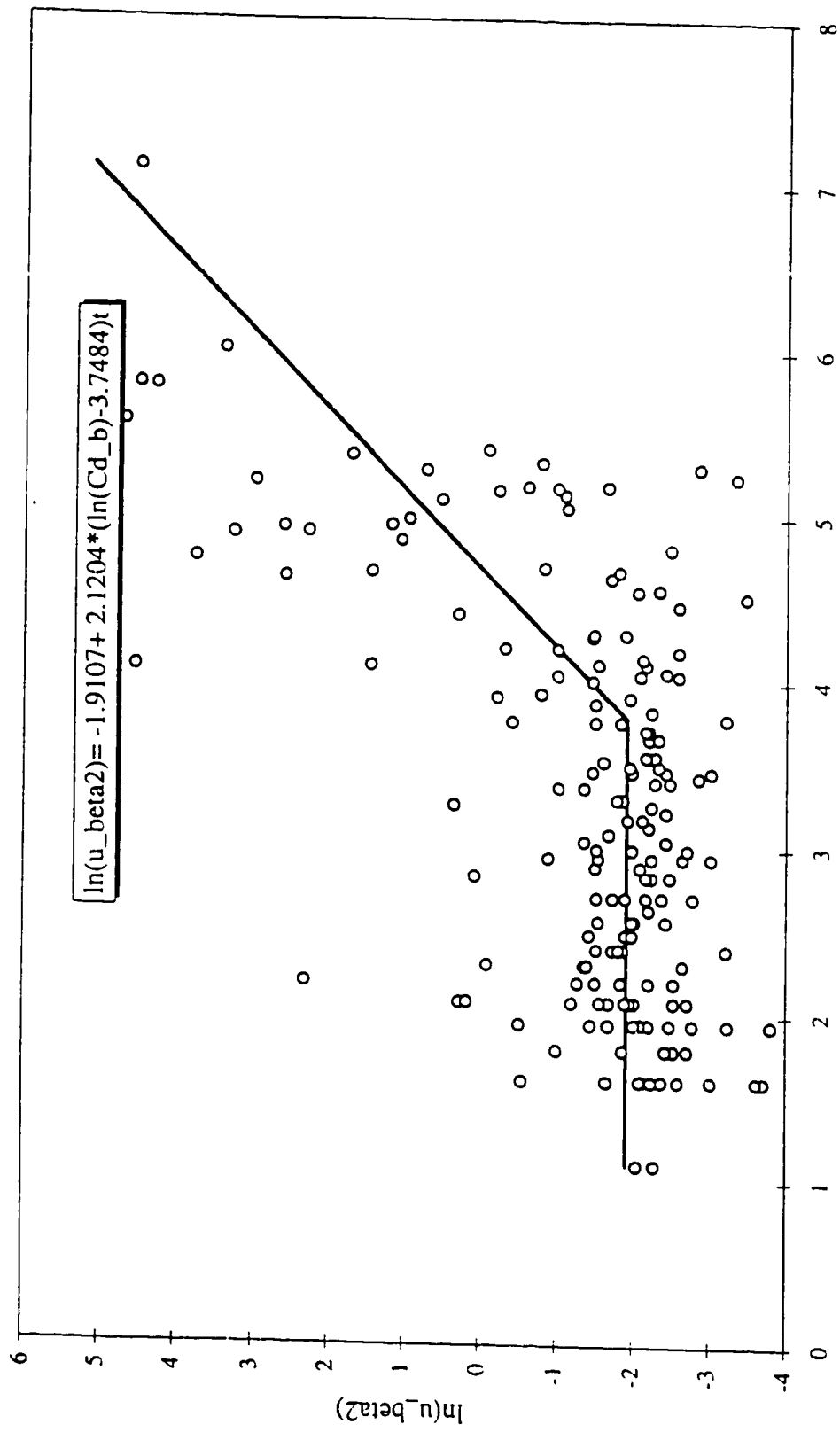


Figure 2.2 Plot of observed Prescot data (u_beta2 versus Cd_b) with fitted segmented model

CHAPTER THREE

TWO-COMPARTMENT MODEL

3.1 Compartmental Analysis

3.1.1 Basic concepts

In this chapter and the next, the analysis of metabolic system of cadmium in the human body will be discussed by means of compartmental modeling.

The use of compartment models is fairly recent. In 1948, Hevesy demonstrated applications of tracer study with some of his work. In his book, he discussed how tracers could be used to determine the distribution and excretion of material in the body. In 1966, Rescigno and Segre wrote a book, which covers many specific cases of compartmental modeling. Sheppard in 1961 addressed the development of more complex compartment models and started to considered general theories[2]. After Atkins published his work in 1969, Jacquez[27] wrote the book entitled Compartmental Analysis in Biology and Medicine. Jacquez's book contains the basic details of linear and nonlinear compartmental systems, radioactive tracers, and related theorems. His book has now become the standard reference on compartmental analysis. The application of this type of modeling is quite

broad; its use is not only in studies of metabolic systems, but also in ecosystems, chemical reactions and drug kinetics in pharmacology.

The fundamental approach of compartmental modeling is to analyze a system by separating it into a finite number of component parts, called compartments or states, which interact through the exchange of material. In biological systems, kinetics is the branch of dynamics that pertains to the turnover of specific particles. A compartment is an amount of material that acts kinetically in a homogeneous, distinct, and well-mixed way[27]. The compartment to which a particle belongs characterizes both its physical-chemical properties and its environment. The particles of each compartment transfer from one compartment to another. Since all particles in a particular compartment are considered indistinguishable, they have the same probability of transition by the system.

The compartments in a compartmental system are interconnected in the way that there is exchange of material among them. Diffusion, radioactive decay, chemical reactions and temperature, etc., cause material exchange among interacting compartments. The compartmental system is primarily modeled in a continuous deterministic manner by a system of several ordinary differential equations. Each ordinary differential equation describes the time rate of change of amount of material in a particular compartment.

There are two types of compartmental systems, open and closed, since there may be inputs from the environment into one or more compartments and may be outputs from one or more compartments into the environment. If there is no exchange of material to the

outside environment, the compartmental system is referred to as a closed system, otherwise it is called an open system. When some material is excreted during analysis, it is obvious that the system is open.

3.1.2 Two-compartment model

The two-compartment model discussed in this chapter is the prelude to the four-compartment model, and constitutes the preliminary work. The complete analysis and discussions are finally achieved by the four compartment model, which will be the subject matter of the next chapter.

Basically, a general compartment model describes the flow and accumulation of cadmium in the human body. A system of equations is formulated to model the rates of absorption, accumulation and elimination with respect to each compartment.

The description for the dynamics of the exchange of cadmium with respect to a particular compartment is based on the mass balance function. Suppose there are n compartments in the system, the mass balance function associated the ith compartment is as follows:

$$\frac{dq_i}{dt} = \textit{rate of inflow - rate of outflow,} \qquad i = 1,2, \ldots, n,$$

where $q_i(t)$ is greater or equal to zero, which is the quantity of cadmium in compartment i at time t.

In the Jaguar data set analyzed in Chapters 3 and 4, the subjects are 14 male workers selected from the workers in British Leyland Jaguar, engaged in brazing and silver soldering. The silver solder contained cadmium and it was the resulting fumes which constituted the exposure[23]. The duration of cadmium exposure ranged from 2 to 34 years. The level of exposure for each subject varied throughout the exposure time according to the work undertaken. The exposure for all but one subject (number 3) was at or above the current U.K. occupational limit for cadmium in air, 0.05 mg/m^3, for at least part of the time.

Longitudinal measurements including biochemical and *in vivo* measurements were made for these 14 male workers. Biochemical measurements consisting of urinary cadmium, blood cadmium and urinary β_2-microglobulin had been made at approximately six monthly to yearly intervals from 1983 to 1990. In addition to the biochemical measurements, all subjects had *in vivo* measurements of liver and kidney cadmium made in December 1983, and eight subjects (number 1, 2, 3, 4, 5, 10, 11, 13) had additional *in vivo* measurements made in March/April 1990. These organ levels were measured by prompt γ-ray neutron activation analysis, using different measurement systems on each occasion. The possibility of significant differences arising solely from the different measurement systems is thought to be negligible[3].

The data set is incomplete or otherwise inconsistent, as shown in Table 4.1. There are some missing points because some subjects had failed to appear for one monitoring session. However, the challenge here is to make the best possible use of the data which are available. The duration of cadmium exposure, the first measurement and last one of β_2-

microglobulin as an indicator of kidney status, the history of smoking and age for each subject are listed in Table 3.1.

FIGURE 3.1 Diagram for the two-compartment model (*Cb_u* and *Cd_k*)

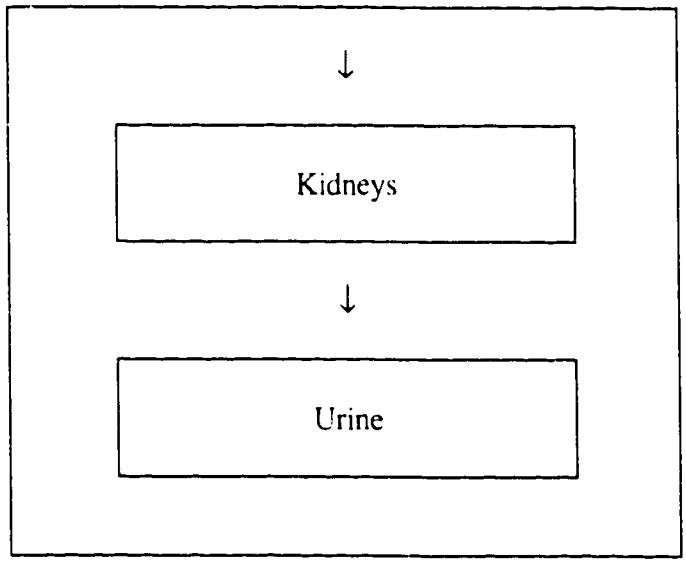


TABLE 3.1 Duration of exposure, age and indicator of kidney status

Subject Number	Cadmium Exposure (years)	Year of Birth	β_2-microglobulin (mg/g creat.)	Smoking Habit
1	2	1964	257/NA	Not Smoking
2	31	1937	90/57	Not Smoking
3	13	1945	58/135	Not smoking
4	33	1930	86/238	Smoking (1948-)
5	20	1928	688/88	Not Smoking
6	9	1923	344/NA	NA
7	3	1961	19/NA	NA
8	2	1925	59/NA	NA
9	24	1928	1667/NA	NA
10	34	1921	3077/84600	Smoking (1939-1958)
11	16	1920	158000/154100	Smoking (1938-1962)
12	22	1927	13400/155800	NA
13	22	1925	1067/NA	Smoking (1941-1975)
14	24	1924	37000/102500	NA

In the "β_2-microglobulin" column, the left side of backslash is for the first measurement and the right side is for the second one.

"NA" is that the information is not available.

In this chapter, only urine and kidney cadmium as two compartments are considered since urine and kidney cadmium are directly related. The major cadmium excretion routes are via feces and urine. Total daily excretion rate is about 0.01-0.02% of the total body burden of cadmium in humans[21]. The average urine cadmium level correlates well with the average kidney cadmium level in current exposure. Urine cadmium level will be expected to increase rapidly both after the high inhaled exposure and after damage to the kidneys.

In previous work of examination of these data, prior to the second set of *in vivo* measurements, the decrease in urinary cadmium excretion followed an exponential function which implied the elimination from kidneys[9]. When the monitoring period was extended further and the second set of *in vivo* measurements were also added into the data, the simple relationships began to break down and it appeared necessary at least to account for continuing input from food or other general environmental sources.

The rate of change of expected kidney cadmium $\eta_k(t)$ at time t can be represented by

$$\frac{d\eta_k(t)}{dt} = -\lambda_k \eta_k(t) + R_k ,$$

where λ_k is the cadmium elimination rate constant from kidney to urine, and R_k is the monthly cadmium input rate. If kidney cadmium at time t=0 is $\eta_k(0)$, then the solution of the above equation is

$$\eta_k(t) = \frac{R_k}{\lambda_k}(1-\exp(-\lambda_k t)) + \eta_k(0)\exp(-\lambda_k t),$$

and

$$R_k = \lambda_k \frac{\eta_k(t) - \eta_k(0)\exp(-\lambda_k t)}{1-\exp(-\lambda_k t)}.$$

Since $\lambda_k \eta_k$ is the urinary output rate and the monthly amount of urine cadmium is linearly related to kidney cadmium, the model for urine cadmium can be simply written as

$$\frac{d\eta_u(t)}{dt} = R_k(1-\exp(-\lambda_k t)) + \lambda_k \eta_k(0)\exp(-\lambda_k t)$$

where η_u is the expected response of urine cadmium.

The diagram of the two-compartment model is illustrated in Figure 3.1. The estimation of parameters will be discussed in the next two sections of this chapter. The classical approach of parameter estimation will be discussed in Section 2, while the Bayesian approach will be presented in Section 3.

3.2 Classical Approach

3.2.1 Least-squares estimation

A nonlinear ordinary least-squares model for two responses can be written as

$$y_{nm} = \eta_{nm} + \varepsilon_{nm},$$

$$h(\theta) = \sum_{m=1}^{2} \sum_{n=1}^{N} (y_{nm} - \eta_{nm})^2,$$

where the expectation function $\eta_{nm} = f_m(x_n, \theta)$, $n = 1, \ldots, N$; $m = 1, 2$; N is the number of measurements; x_n is the independent variable which is time t for case n, ranging from a minimum of -10 to a maximum of most up to 100 on monthly basis, 0 corresponds to December, 1983; y_{nm} represents the mth response for case n, η_{nm} represents the expectation function of the mth response for case n, and θ is a 2×1 vector of the unknown parameters, which is $(\lambda_k, R_k)^T$, $k = 1, \ldots, N$. During the parameter estimation process, the measurement of kidney cadmium at time 0, which is 12/1983, is added to be treated as an unknown parameter. The unit of monthly urine cadmium is the value of μg Cd/g creatine multiplied by 53 on the assumption that a daily output of creatine is of 1.75g.

The following assumptions are now made for the model:

(1) All variances are known;

(2) All variances are assumed equal;

(3) There is no correlation between y_{ui} and y_{uj}, $i \neq j$, $i, j = 1, 2$ and $u = 1,...N$.

Table 3.2 shows the results from nonlinear least-squares estimation. The range of estimate of λ_k from 0.0047 to 0.0537 per month appears to be reasonable, which might imply that it is essential to include the input rate into the model. The range of estimate of R_k is from 18.44 to 1059.4 μg/month except for subject 10 with a negative estimate of R_k that is not realistic. Table 3.2 indicates that standard deviations of most subjects are quite large, although the estimate of kidney cadmium at time 0 and the prediction of kidney cadmium at time 76 are rather close to the measured values. Observed values of kidney cadmium are dominant on the data so that the second assumption of least-squares criterion is violated and weights were considered in the criterion.

3.2.2 Sensitivity of weights

To check the sensitivity of the weights applied to the model, four different ways of implementing weights in the model were used. Tables 3.3, 3.4, 3.5 and 3.6 show the results based on weights 1, 2, 3 and 4, respectively. The different weights were applied to the model are as follows.

Weight 1

Approximately, the measurement error of kidney cadmium can be assumed as 2.5 mg for single kidney, whereas the measurement error of urine cadmium can be assumed to be roughly 0.5 μg/g creatine. These assumptions form the basis of weight 1.

Weight 2

Weight 2 for kidney cadmium is based on the fact that the measurement error of kidney cadmium can be approximately as 6 mg, closing up bound of the measurement error, whereas the weight 2 for urine cadmium is the same as the one in weight 1.

Weight 3

Weight 3 for kidney cadmium varies according to previous recording of measurement error from 2 mg to 8 mg, and weight 3 for urine cadmium is the same as previous weights.

Weight 4

Weight 4 for kidney cadmium is selected as 6 mg which is the same one as given in weight 2, whereas weight 4 for urine cadmium varies from individual to individual according to variation of urine cadmium.

Tables 3.3, 3.4 3.5 and 3.6 show that, after adding weights, the weighted residual sum of squares are dramatically reduced. The range of estimates of λ_k is from 0.0047 to 0.034 with weight 1, from 0.0047 to 0.0486 with weight 2, from 0.0046 to 0.0402 with weight 3 and from 0.0048 to 0.0495 in weight 4. Among the four different weights, it is interesting to see that the estimate of λ_k is not really sensitive to the weights. Largest estimates of λ_k are centralized either in subject 11 or 12 among the different weights. In subject 7, the estimate of λ_k is smallest for each weight. In most of the cases, the estimate of R_k varies significantly from weight to weight. One of the reasons may be that the input rate is not directly related to urine cadmium but connected directly to blood cadmium so that the variation of R_k is rather large. Both the estimates of R_k in subject 13 based on weight 3 and in subject 10 un-weighted are unrealistic.

Since the results based on weight 4 are quite close to the others and derivation of weight 4 is biologically reasonable, the results based on weight 4 were used for the calculation of the half-life time of kidney cadmium at this preliminary stage. Approximately, the half-life time of kidney cadmium based on weight 4 for each subject is estimated as: 99 months for subject 1, 42 months for subject 2, 46 months for subject 3, 100 months for subject 4, 56 months for subject 5, 50 months for subject 6, 144 months for subject 7, 60 months for subject 8, 32 months for subject 9, 53 months for subject 10, 26 months for subject 11, 14 months for subject 12, 46 months for subject 13, and 29 months for subject 14. So the longest half-life time of kidney cadmium is estimated as 144

months in subject 7, the shortest half-life time of kidney cadmium, on the other hand, is estimated as 26 months in subject 11. R_k for the four workers known to be non-smoking is numerically lower than for the four workers known to be smoking.

TABLE 3.2 Results of nonlinear least-squares for the two-compartment model (*Cd_k* & *Cd_u*)

Subject	$\hat{\lambda}_K$ $month^{-1}$	$\hat{R}_K$ µg/month	$\hat{Cd\_k}(0)$ µg	$Cd\_k(0)$ (S.) µg	$\hat{Cd\_k}(76)$ µg	$Cd\_k(76)$ (B.) µg	OFV
1	0.007	18.44	2499.95	2500	4023.9	4000	1872.46
2	0.017	277.00	21000.2	21000	23356	24000	140083
3	0.015	358.80	12002.1	12000	23947	24000	93415.8
4	0.0068	291.50	14000.6	14000	34001	34000	41787.7
5	0.0117	197.80	2501.21	2500	12014	12000	33491.0
6	0.0140	345.71	21000.0	21000	30666		1572482
7	0.0047	95.41	2500.00	2500	9595.6		916.95
8	0.0116	204.29	15000.0	15000	22742		6539.89
9	0.0223	429.61	15000.1	15000	21236		24409.3
10	0.0112	-833.53	77996.2	78000	23942	24000	5.30
11	0.027	1054.4	31001.8	31000	42001	42000	77725
12	0.0537	684.80	10002.5	10000	12875		279763
13	0.0119	1059.4	16018.6	16000	65959	66000	3.3492
14	0.0236	629.84	23999.8	24000	30234		136677

S. refers to single.

B. refers to both.

OFV refers to the objective function value.

TABLE 3.3 Results of nonlinear least-squares for the two-compartment model (*Cd_k* & *Cd_u*) based on weight 1

Subject	$\hat{\lambda}_k$ $month^{-1}$	$\hat{R}_k$ µg/month	$\hat{Cd\_k}(0)$ µg	$Cd\_k(0)$ (S.) µg	$\hat{Cd\_k}(76)$ µg	$Cd\_k(76)$ (B.) µg	OFV
1	0.0075	32.68	2271.33	2500	4473	4000	2.46
2	0.019	271.86	19054.8	21000	19925	24000	189.66
3	0.015	230.72	14229.4	12000	19564	24000	79.64
4	0.0069	193.93	15836.9	14000	30218	34000	47.11
5	0.0126	126.97	3981.23	2500	9265	12000	32.00
6	0.014	343.37	21216.2	21000	30705		220.12
7	0.0047	95.56	2505.9	2500	9613		1.28
8	0.0116	204.23	15006.2	15000	22744		9.16
9	0.0214	421.67	15650.3	15000	21984		33.88
10	0.0160	1238.7	53185.3	78000	86000	24000	1312.63
11	0.034	1013.7	24928.9	31000	31327	42000	1008.55
12	0.032	594.37	17291.4	10000	19981		302.23
13	0.022	165.16	23366.6	16000	14877	66000	826.33
14	0.02	635.29	23439.0	24000	35070		191.13

S. refers to single.

B. refers to both.

OFV refers to the objective function value.

TABLE 3.4 Results of nonlinear least-squares for the two-compartment model (*Cd_k* & *Cd_u*) based on weight 2

Subject	$\hat{\lambda}_K$ month^{-1}	$\hat{R}_K$ µg/month	$\hat{Cd\_k}(0)$ µg	$Cd\_k(0)$ (S.) µg	$\hat{Cd\_k}(76)$ µg	$Cd\_k(76)$ (B.) µg	OFV
1	0.0078	39.13	2124.9	2500	4592.8	4000	2.39
2	0.0459	386.55	7698.4	21000	8634.7	24000	155.63
3	0.0131	196.07	16550	12000	21667	24000	73.41
4	0.0071	146.14	16487	14000	27807	34000	41.84
5	0.0129	113.58	4093.9	2500	8573.2	12000	29.72
6	0.0133	333.06	22159	21000	32057		221.57
7	0.0047	94.77	2492.3	2500	9544.0		1.293
8	0.0115	203.98	15036	15000	22884		9.22
9	0.0188	394.83	17867	15000	24531		33.14
10	0.0168	1423.8	48938	78000	88411	24000	402.27
11	0.0486	1064.3	17339	31000	22217	42000	932.97
12	0.0226	498.83	25138	10000	27135		250.02
13	0.0199	22.70	26750	16000	12680	66000	427.48
14	0.0258	649.33	21937	24000	27801		191.88

S. refers to single.

B. refers to both.

OFV refers to the objective function value.

TABLE 3.5 Results of nonlinear least-squares for the two-compartment model (*Cd_k* & *Cd_u*) based on weight 3

Subject	$\hat{\lambda}_K$ month^{-1}	$\hat{R}_K$ µg/month	$\hat{Cd\_k}(0)$ µg	$Cd\_k(0)$ (S.) µg	$\hat{Cd\_k}(76)$ µg	$Cd\_k(76)$ (B.) µg	OFV
1	0.0085	37.25	1964.73	2500	4145	4000	2.42
2	0.0220	311.18	16031.7	21000	17511	24000	187.95
3	0.0132	209.19	16283.5	12000	21979	24000	77.16
4	0.0064	178.44	17420.4	14000	32160	34000	45.63
5	0.010	119.67	5219.44	2500	11252	12000	30.57
6	0.0133	333.01	22165.4	21000	32059		221.52
7	0.0046	96.02	2523.70	2500	9717		1.29
8	0.0116	204.14	15016.0	15000	22747		9.22
9	0.0203	411.22	16518.6	15000	22989		33.73
10	0.0278	1431.0	29801.8	78000	52458.5	24000	996.31
11	0.0402	1048.0	21155.0	31000	26835	42000	993.8
12	0.0301	577.27	18708.9	10000	21030		291.70
13	0.0109	-174.59	46355.3	16000	31469	66000	970.89
14	0.0257	649.53	21921.3	24000	27907		191.83

S. refers to single.

B. refers to both.

OFV refers to the objective function value.

TABLE 3.6 Results of nonlinear least-squares for the two-compartment model (*Cd_k* & *Cd_u*) based on weight 4

Subject	$\hat{\lambda}_K$ month^{-1}	$\hat{R}_K$ µg/month	$Cd\_\hat{k}(0)$ µg	$Cd\_k(0)$ (S.) µg	$Cd\_\hat{k}(76)$ µg	$Cd\_k(76)$ (B.) µg	OFV
1	0.007	40.09	2303.9	2500	5069.61	4000	6.933
2	0.0167	262.34	20965.8	21000	23079	24000	3.761
3	0.015	254.41	13795.7	12000	20360.6	24000	5.454
4	0.0069	193.22	15846.9	14000	30187.6	34000	8.449
5	0.0124	141.13	3786.7	2500	9897.49	12000	10.743
6	0.014	345.5	21041.6	21000	30684.4		5.506
7	0.0048	94.26	2472.3	2500	9435.7		4.679
8	0.0116	204.19	15012.9	15000	22747.3		3.230
9	0.0220	426.65	15253.9	15000	21481.3		2.206
10	0.0130	286.69	68846.2	78000	65108	24000	119.27
11	0.0271	1028.3	31154.9	31000	41051.3	42000	3.339
12	0.0495	675.8	10966.0	10000	13844.9		3.417
13	0.0150	681.9	24928.9	16000	46866.5	66000	53.046
14	0.0236	630.5	23958.0	24000	30242.9		2.258

S. refers to single.

B. refers to both.

OFV refers to the objective function value.

3.3 Bayesian Approach

3.3.1 Thomas Bayes

The Reverend Thomas Bayes was a Presbyterian minister and mathematician who lived in England in the 1700s (died in 1761). His friend, Richard Price who was interested in Bayes's research, submitted Bayes' manuscript An Essay Toward Solving problem in the Doctrine of Chances, to the professional journal, Philosophical Transactions of the Royal Society, which initially published Bayes'paper posthumously in 1763[37]. Bayes's paper was published again in Biometrika in 1958[45], and has been reprinted at least four times in this century[42].

Bayes's essay has been described as one of the most difficult works to read in the history of statistics[42]. Common interpretation today about Bayes' paper[37] is that his paper proposed a method for making probability inferences about the parameter of binomial distribution conditional on some observations from that distribution. Common belief[37] is that Bayes assumed that the parameter had a uniform distribution on the unit interval. His proposed method for making inferences about the binomial parameter is now called Bayes' theorem and has been generalized to be applicable beyond the binomial distribution, to any sampling distribution. 50 years after Bayes died, Laplace, a mathematician who lived in France, stated the theorem on inverse probability in general form. Stigler pointed out[41] that Laplace probably never saw Bayes' essay and

discovered the theorem independently. Jeffreys rediscovered Laplace's work in 1939 and made his great contribution to Bayes' theorem[28].

3.3.2 Bayes' theorem

Suppose that $Y^T = (y_1, \ldots, y_n)$ is a vector of n observations whose probability distribution depends on the values of k parameters $\theta^T = (\theta_1, \ldots, \theta_k)$, and θ itself has a probability distribution $p(\theta)$. Given the observed data Y, the conditional distribution of θ is

$$p(\theta \mid Y) = \frac{p(\theta, Y)}{p(Y)} = \frac{p(Y \mid \theta)\, p(\theta)}{p(Y)},$$

where

$$p(Y) = \begin{cases} \int p(Y \mid \theta)\, p(\theta)\, d\theta & \text{if } \theta \text{ continuous} \\ \Sigma\, p(Y \mid \theta)\, p(\theta) & \text{if } \theta \text{ discrete} \end{cases}$$

The statement above is usually referred to as Bayes' Theorem. In this statement, $p(\theta)$ is called the prior distribution of θ, since it only tells us what is known about θ without knowledge of the data. Correspondingly, $p(\theta \mid Y)$ is called the posterior distribution of θ given Y, since it tells us what is known about θ given knowledge of the data.

Given data Y, $p(Y \mid \theta)$ in the Bayes' formula above may be regarded as a function not of Y but of θ, and can be called likelihood function of θ for given Y[17]. The

expression of likelihood function is usually denoted as $l(\theta \mid Y)$. Bayes' formula can thus be written as

$$p(\theta \mid Y) \propto l(\theta \mid Y)\, p(\theta).$$

The likelihood function plays a very important rule in Bayes' formula.

3.3.3 Jeffreys' rule

Generally speaking, locally uniform prior means that a prior is dominated by the likelihood, and does not change very much within the appreciable region of the likelihood and not have large values outside of the corresponding region. A locally uniform prior can be regarded as non-informative about parameters in the sense that only little prior knowledge is provided by an experiment.

In some dispute of Bayes' postulate, it has been argued that, if the distribution of a continuous parameter θ were taken to be locally uniform, then the distribution of $1/\theta$, $log\theta$ or some other transformation would not be locally uniform. Therefore, the application of Bayes' postulate to different transformations of θ would lead to inconsistent posterior distributions from the same data.

Jeffreys[28] solved the problem mentioned above on the basis of invariance under parameter transformations. The rule named as Jeffreys' rule for the choice of a noninformative prior distribution was first given by Jeffreys. In the single-parameter model, his rule states that the prior distribution for a single parameter θ is

approximately non-informative if it is taken to be proportional to the square root of Fisher's information measure.

Jeffreys' rule for multi-parameter problems is that the prior distribution for a set of parameters is taken to be proportional to the square root of the determinant of the information matrix so that

$$p(\theta) \propto \left|I(\theta)\right|^{1/2}$$

where $I(\theta)$ is the information matrix of θ.

To show that, let $\ln p$ be the logarithm of the likelihood function with k parameters

Since

$$\left(\frac{\partial \ln p}{\partial \theta}\right)^T = \left(\frac{\partial \ln p}{\partial \phi}\right)^T \left(\frac{\partial \phi}{\partial \theta}\right)^T,$$

$$I(\theta) = E\left\{\left(\frac{\partial \ln p}{\partial \theta}\right)\left(\frac{\partial \ln p}{\partial \theta}\right)^T\right\}$$

$$= E\left\{\left(\frac{\partial \phi}{\partial \theta}\right)\left(\frac{\partial \ln p}{\partial \phi}\right)\left(\frac{\partial \ln p}{\partial \phi}\right)^T\left(\frac{\partial \phi}{\partial \theta}\right)^T\right\}$$

$$= \left(\frac{\partial \phi}{\partial \theta}\right) E\left\{\left(\frac{\partial \ln p}{\partial \phi}\right)\left(\frac{\partial \ln p}{\partial \phi}\right)^T\right\}\left(\frac{\partial \phi}{\partial \theta}\right)^T$$

$$= \left(\frac{\partial \phi}{\partial \theta}\right) \mathrm{I}(\phi) \left(\frac{\partial \phi}{\partial \theta}\right)^{T}$$

where

$\left(\frac{\partial \ln p}{\partial \theta}\right)^{T} = \left(\frac{\partial \ln p}{\partial \theta_1}, \frac{\partial \ln p}{\partial \theta_2}, \ldots, \frac{\partial \ln p}{\partial \theta_k}\right)$ is a vector with dimension of $k \times 1$, and

$\frac{\partial \phi}{\partial \theta} = \frac{\partial (\phi_1, \phi_2, \ldots, \phi_k)}{\partial (\theta_1, \theta_2, \ldots, \theta_k)}$ is a matrix with dimension of $k \times k$.

It directly follows that

$$\left|\mathrm{I}(\theta)\right| = \left|\mathrm{I}(\phi)\right| \times 2\left|\frac{\partial \phi}{\partial \theta}\right|^{2}, \quad \text{or} \quad \left|\mathrm{I}(\phi)\right|^{1/2} = \left|\mathrm{I}(\theta)\right|^{1/2} \times \left|\frac{\partial \theta}{\partial \phi}\right|.$$

Hence, if the parameter vector ϕ can be chosen such that

$$\left|\frac{\partial \theta}{\partial \phi}\right| \propto \left|\mathrm{I}(\theta)\right|^{-1/2},$$

then $\left|\mathrm{I}(\phi)\right|$ will be constant independent of ϕ and the likelihood will be approximately data translated in terms of ϕ.

The determinant of the information matrix is a nonnegative value. In addition to that, the expression for the determinant matrices mentioned above satisfies the transformation formula

$$p(\phi) = p(\theta) \left|\frac{\partial \phi}{\partial \theta}\right|.$$

Therefore, the square root of the information matrix can be selected to be proportional to the density function p(θ). The non-informative prior for θ should be chosen locally as,

$$p(\theta) \propto \left|I(\theta)\right|^{1/2}, \quad \text{or} \quad p(\theta) \propto \left|\frac{\partial \phi}{\partial \theta}\right|.$$

It is obviously inapplicable when the information measure does not exist. Further more, when more than one parameter in involved, careful consideration must be given to transformation implications and to knowledge of prior independence.

3.3.4 Multivariate analysis

Assumption

In the Bayesian approach, consider m output responses which is m-variate observation $y^T_{(u)} = (y_{u1}, \ldots, y_{ui}, \ldots, y_{um})$, $u = 1,2, \ldots, n$, obtained at the uth time. There would be m expectation functions $E(y_{(u)}) = \eta_{(u)} = (\eta_{u1}, \ldots, \eta_{um})^T$ at each time, where

$E(y_{u1}) = \eta_{u1} = \eta_1(\xi_{u1}, \theta_1)$,

.
.
.

$E(y_{ui}) = \eta_{ui} = \eta_i(\xi_{ui}, \theta_i)$,

.
.
.

$E(y_{um}) = \eta_{um} = \eta_m(\xi_{um}, \theta_m)$,

where ξ_{ui} would contain $p_{(i)}$ elements (ξ_{u1i}, ... $\xi_{up(i)i}$), θ_i would contain $k_{(i)}$ elements (θ_{1i}, ... , $\theta_{k(i)i}$) and the number of unknown parameters is p. A given output would involve certain inputs and certain parameters which might or might not be shared by other outputs, depending on what the real problem is. Furthermore, the expectation function η_{ui} might be linear or nonlinear both in the parameters θ_i and inputs ξ_{ui}.

Assume that the error function $\varepsilon_{(u)} = (\varepsilon_{u1}, \ldots, \varepsilon_{um}) = y_{(u)} - \eta_{(u)}$, $u = 1, 2, \ldots n$, for given θ and Σ, distributed as the m-variate Normal N (0, Σ). The error terms in different responses but in the same measurements may not identical and may correlated to each other.

By using matrix notation, Y, H and E can be expressed respectively as

$$Y = \begin{bmatrix} y_{11} \cdots y_{1i} \cdots y_{1m} \\ \vdots \\ y_{u1} \cdots y_{ui} \cdots y_{um} \\ \vdots \\ y_{n1} \cdots y_{ni} \cdots y_{nm} \end{bmatrix} = [\, y_1, \ldots, y_i, \ldots, y_m \,] = \begin{bmatrix} y_{(1)}^T \\ \vdots \\ y_{(u)}^T \\ \vdots \\ y_{(n)}^T \end{bmatrix},$$

$$H = \begin{bmatrix} \eta_{11} \cdots \eta_{1i} \cdots \eta_{1m} \\ \vdots \\ \eta_{u1} \cdots \eta_{ui} \cdots \eta_{um} \\ \vdots \\ \eta_{n1} \cdots \eta_{ni} \cdots \eta_{nm} \end{bmatrix} = [\, \eta_1, \ldots, \eta_i, \ldots, \eta_m \,] = \begin{bmatrix} \eta_{(1)}^T \\ \vdots \\ \eta_{(u)}^T \\ \vdots \\ \eta_{(n)}^T \end{bmatrix}, \text{ and}$$

$$E = \begin{bmatrix} \varepsilon_{11} \ldots \varepsilon_{1i} \ldots \varepsilon_{1m} \\ \vdots \\ \varepsilon_{u1} \ldots \varepsilon_{ui} \ldots \varepsilon_{um} \\ \vdots \\ \varepsilon_{n1} \ldots \varepsilon_{ni} \ldots \varepsilon_{nm} \end{bmatrix} = [\varepsilon_1, \ldots, \varepsilon_i, \ldots, \varepsilon_m] = \begin{bmatrix} \varepsilon_{(1)}^T \\ \vdots \\ \varepsilon_{(u)}^T \\ \vdots \\ \varepsilon_{(n)}^T \end{bmatrix}.$$

Likelihood Function of (θ, Σ)

The joint distribution of the n vectors of errors E can be expressed as

$$p(E \mid \Sigma, \theta) = \prod_{u=1}^{n} p(\varepsilon_{(u)} \mid \Sigma, \theta)$$

$$= (2\pi)^{-mn/2} |\Sigma|^{-n/2} \exp\left(-\frac{1}{2} \sum_{u=1}^{n} \varepsilon_{(u)}^T \Sigma^{-1} \varepsilon_{(u)}\right),$$

$$-\infty < \varepsilon_{ui} < \infty, \qquad i = 1, \ldots, m, \quad u = 1, \ldots, n,$$

where $\Sigma = \{\sigma_{ij}\}$ is the $m \times m$ covariance matrix, $\Sigma^{-1} = \{\sigma^{ij}\}$ is the inverse matrix of Σ, and θ refers to the full set of all parameters $\theta_1, \ldots, \theta_m$ with $k = k_1 + k_2 + \ldots + k_m$ elements.

By using Theorem 3.1 in the Appendix, the exponent in the joint function above can be given as

$$\sum_{u=1}^{n} \varepsilon_{(u)}^T \Sigma^{-1} \varepsilon_{(u)} = tr[\sum_{u=1}^{n} \varepsilon_{(u)}^T \Sigma^{-1} \varepsilon_{(u)}]$$

$$= \sum_{u=1}^{n} tr[\varepsilon_{(u)}^T \Sigma^{-1} \varepsilon_{(u)}]$$

$$= \sum_{u=1}^{n} tr[\Sigma^{-1} \varepsilon_{(u)} \varepsilon_{(u)}^T]$$

$$= tr[\Sigma^{-1} (\sum_{u=1}^{n} \varepsilon_{(u)} \varepsilon_{(u)}^T)]$$

$$= tr[\Sigma^{-1} S(\theta)],$$

where tr B refers to the trace of the matrix B, and $S(\theta) = \{S_{ij}(\theta_i, \theta_j)\}$ with dimension $m \times m$, and

$$S_{ij}(\theta_i, \theta_j) = \sum_{u=1}^{n} \varepsilon_{ui} \varepsilon_{uj} = \sum_{u=1}^{n} [y_{ui} - \eta_i(\xi_{ui}, \theta_i)][y_{uj} - \eta_j(\xi_{uj}, \theta_j)] = \varepsilon_i^T \varepsilon_j, \quad j = 1, \ldots, m.$$

Then, the likelihood function, given observations Y, can be expressed as

$$l(\theta, \Sigma \mid Y) \propto p(E \mid \Sigma, \theta)$$

$$\propto |\Sigma|^{-n/2} \exp[-\frac{1}{2} tr \Sigma^{-1} S(\theta)].$$

Prior Distribution of (θ, Σ)

In particular, it is usually appropriate to take location parameters to be distributed independently of scale parameters. This is because any prior idea one might have about the location parameters θ of a distribution would usually not be much influenced by one's idea about the scale parameters Σ of distribution. Thus $p(\theta \mid \Sigma) \doteq p(\theta)$. Assume that θ and Σ are approximately independent, so that the prior distribution of the parameters (θ, Σ) can be written as

$p(\theta, \Sigma) \doteq p(\theta)\, p(\Sigma)$.

It is appropriate to take θ as locally uniform such that $p(\theta) \propto$ constant. For the prior distribution of Σ, Jeffreys' principle leads to non-informative reference prior as

$$p(\Sigma) \propto \left| I(\Sigma) \right|^{1/2},$$

where $\left| I(\Sigma) \right|$ is the determinant of the information matrix of Σ. Derivation of the prior distribution of Σ is as follows.

First, consider the expression of the information matrix of Σ. By using Theorem 3.3 in the Appendix, it directly follows that

$$\left| \frac{\partial\, \Sigma}{\partial\, \Sigma^{-1}} \right| = \left| \frac{\partial\, \Sigma^{-1}}{\partial\, \Sigma} \right|^{-1};$$

Hence

$$\left| I(\Sigma) \right| = \left| I(\Sigma^{-1}) \right| \times \left| \frac{\partial\, \Sigma^{-1}}{\partial\, \Sigma} \right|^{2} = \left| I(\Sigma^{-1}) \right| \times \left| \frac{\partial\, \Sigma}{\partial\, \Sigma^{-1}} \right|^{-2},$$

where

$$\left| \frac{\partial\, \Sigma}{\partial\, \Sigma^{-1}} \right| = \left| \frac{\partial\, (\sigma_{11}, \sigma_{12}, \ldots, \sigma_{mm})}{\partial\, (\sigma^{11}, \sigma^{12}, \ldots, \sigma^{mm})} \right|$$

is the Jacobian of the transformation from the elements σ_{ij} of Σ to the elements of σ^{ij} of Σ^{-1}.

Next, consider the expression of the determinant of the information matrix of Σ^{-1}. It can be shown that $\left|I(\Sigma^{-1})\right| \propto \left|\frac{\partial \Sigma}{\partial \Sigma^{-1}}\right|$ as follows. The density of the m-dimensional normal distribution mentioned above is

$$p(\varepsilon_{(u)} | \Sigma, \theta) = (2\pi)^{-m/2} \left|\Sigma^{-1}\right|^{1/2} \exp[-\frac{1}{2} tr\ \Sigma^{-1} \varepsilon_{(u)}\ \varepsilon^{T}_{(u)})], -\infty < \varepsilon_{(u)} < \infty,$$

where

$$\varepsilon_{(u)} = (\varepsilon_{u1}, \ldots, \varepsilon_{um}) = y_{(u)} - \eta_{(u)} = (y_{u1} - \eta_{u1}, \ldots, y_{um} - \eta_{u1}), \qquad u = 1, 2, \ldots n.$$

Assume $\Sigma=\{\sigma_{ij}\}$ and $\Sigma^{-1}=\{\sigma^{ij}\}$ $(i, j = 1,2, \ldots, m)$ and that they both consist of $m(1+m)/2$ distinct elements. Taking logarithms of the density function, it follows that

$$\log p = -\frac{m}{2} \log(2\pi) + \frac{1}{2} \log\left|\Sigma^{-1}\right| - \frac{1}{2} tr\, \Sigma^{-1} \varepsilon_{(u)} \varepsilon^{T}_{(u)}.$$

Differentiating log p with respect to σ^{ij} $(i, j = 1,2, \ldots, m, i \geq j)$,

$$\frac{\partial \log p}{\partial \sigma^{ij}} = -\frac{1}{2} \frac{1}{\left|\Sigma^{-1}\right|} \frac{\partial \left|\Sigma^{-1}\right|}{\partial \sigma^{ij}} - (y_{ui} - \eta_{ui})(y_{uj} - \mu_{uj}).$$

Since

$$\{\sigma_{ij}\} = \Sigma = (\Sigma^{-1})^{-1} = \frac{1}{\left|\Sigma^{-1}\right|} \begin{bmatrix} \Sigma^{-1}_{11} \ldots \Sigma^{-1}_{i1} \ldots \Sigma^{-1}_{m1} \\ \vdots \\ \Sigma^{-1}_{1u} \ldots \Sigma^{-1}_{iu} \ldots \Sigma^{-1}_{mu} \\ \vdots \\ \Sigma^{-1}_{1m} \ldots \Sigma^{-1}_{im} \ldots \Sigma^{-1}_{mm} \end{bmatrix}$$

where Σ^{-1}_{ij} is a cofactor of σ_{ij} $(i, j = 1, \ldots, m)$.

The derivatives of the determinant of Σ^{-1} with respect to σ_{ij} can be given as

$$\frac{\partial \left| \Sigma^{-1} \right|}{\partial \sigma^{ij}} = \frac{\partial \left(\sum_{j=1}^{m} \sigma^{ij} \Sigma^{-1}{}_{ij} \right)}{\partial \sigma^{ij}} = \Sigma^{-1}{}_{ij} = \left| \Sigma^{-1} \right| \sigma_{ji}, \qquad i, j = 1, \ldots, m, \quad i \geq j,$$

and the first derivatives are

$$\frac{\partial \log p}{\partial \sigma^{ij}} = -\frac{1}{2} \frac{1}{\left| \Sigma^{-1} \right|} \left| \Sigma^{-1} \right| \sigma_{ji} - (y_i - \eta_i)(y_j - \eta_j), \qquad i, j = 1, \ldots, m, \quad i \geq j.$$

Thus, the second derivatives are

$$\frac{\partial^2 \log p}{\partial \sigma^{ij} \partial \sigma^{kl}} = -\frac{1}{2} \frac{\partial \sigma_{ji}}{\partial \sigma^{kl}} \qquad \begin{pmatrix} i, j = 1, \ldots, m, & i \geq j \\ k, l = 1, \ldots, m, & k \geq l \end{pmatrix}.$$

Therefore, the determinant of the information matrix Σ^{-1} is proportional to

$$\left| I(\Sigma^{-1}) \right| = \left| -E\left\{ \frac{\partial^2 \log p}{\partial \sigma^{ij} \partial \sigma^{ij}} \right\} \right| \propto \left| \frac{\partial \Sigma}{\partial \Sigma^{-1}} \right|.$$

Finally, consider the Jacobian of the transformation from the elements σ_{ij} of Σ to the elements of σ^{ij} of Σ^{-1}. It can be shown that $\left| \frac{\partial \Sigma}{\partial \Sigma^{-1}} \right| = \left| \Sigma \right|^{m+1}$ as follows.

We can write: $\Sigma = \Sigma \Sigma^{-1} \Sigma$.

Since Σ^{-1} is symmetric and it consists of $m(m+1)/2$ distinct random variables, then the result that $\left| \frac{\partial \Sigma}{\partial \Sigma^{-1}} \right| = \left| \Sigma \right|^{m+1}$ follows directly from Theorem 3.6g provided in the Appendix.

It is straight forward to combine the three steps mentioned above in order to get the non-informative reference prior as

$$p(\Sigma) \propto \left| I(\Sigma) \right|^{1/2}$$

$$= \left[\left| I(\Sigma^{-1}) \right| \times \left| \frac{\partial \Sigma}{\partial \Sigma^{-1}} \right|^{-2} \right]^{1/2}$$

$$\propto \left[\left| \frac{\partial \Sigma}{\partial \Sigma^{-1}} \right| \times \left| \frac{\partial \Sigma}{\partial \Sigma^{-1}} \right|^{-2} \right]^{1/2}$$

$$= \left| \frac{\partial \Sigma}{\partial \Sigma^{-1}} \right|^{-1/2}$$

$$= \left(\left| \Sigma \right|^{m+1} \right)^{-1/2}$$

$$= \left| \Sigma \right|^{-(m+1)/2}.$$

Consequently, the prior distribution of (θ, Σ) is

$$p(\theta, \Sigma) \doteq p(\theta)\, p(\Sigma) \propto |\Sigma|^{-(m+1)/2}.$$

Posterior Distribution of (θ, Σ^{-1})

The joint posterior distribution of the parameters (θ, Σ), which can be expressed as

$$p(\theta, \Sigma | Y) \propto p(\theta, \Sigma)\, l(\theta, \Sigma)$$

$$\propto \left| \Sigma \right|^{-(n+m+1)/2} \exp\left[-\frac{1}{2} tr\, \Sigma^{-1} S(\theta) \right], \qquad -\infty < \theta < \infty, \quad \Sigma > 0,$$

where $-\infty < \theta < \infty$ means that each element of θ can vary from $-\infty$ to ∞, and $\Sigma > 0$ means that matrix Σ is positive definite.

Since

$$p(\theta, \Sigma^{-1}|Y) = p(\theta, \Sigma|Y)\left|\frac{\partial \Sigma}{\partial \Sigma^{-1}}\right|, \text{ and } \left|\frac{\partial \Sigma}{\partial \Sigma^{-1}}\right| = |\Sigma|^{m+1},$$

it follows that the joint posterior distribution of the parameters (θ, Σ^{-1}) is

$$p(\theta, \Sigma^{-1}|Y) \propto |\Sigma|^{\frac{1}{2}(n-m-1)} \exp[-\frac{1}{2} tr\ \Sigma^{-1} S(\theta)], \qquad -\infty < \theta < \infty, \quad \Sigma > 0.$$

Marginal Distribution of θ

The Wishart distribution can be used for deriving the marginal distribution of θ. In 1928, Wishart proposed the Wishart distribution as multivariate generalization of the χ^2 distribution[44]. By using $W_m(B^{-1}, q)$ as notation of the Wishart distribution, Z is distributed as Wishart with q degrees of freedom and parameter matrix B^{-1}, which can be given as

$$W_m(B^{-1}, q) = p(Z) = k|Z|^{1/2(q-1)} \exp(-\frac{1}{2} tr\, ZB), \qquad Z > 0,$$

where Z is a $m \times m$ positive definite symmetric random matrix which consists of $m(1+m)/2$ distinct random variables z_{ij} $(i,j = 1,2, \ldots, m;\ i \geq j)$, $q > 0$, and B is a $m \times m$ positive definite symmetric matrix with elements of fixed constants. Since

$$\int_{z>0} |Z|^{1/2q-1} \exp(-\frac{1}{2} tr\, ZB)\, dZ = |B|^{-1/2(q+m-1)}\, 2^{1/2m(q+m-1)}\, \Gamma_m(\frac{q+m-1}{2}),$$

where $\Gamma_m(q+m+1/2)$ is the generalized gamma function defined as

$$\Gamma_p(b) = [\Gamma(\frac{1}{2})]^{1/2p(p-1)} \prod_{\alpha=1}^{p} \Gamma(b + \frac{\alpha - p}{2}), \qquad b > \frac{p-1}{2},$$

The right side of the integral equation above is a constant as reciprocal coefficient ($1/k$) for the Wishart distribution.

Comparing the Wishart distribution to the posterior distribution of (θ, Σ^{-1}), S(θ) in the posterior distribution of the (θ, Σ^{-1}) corresponds to B in the Wishart distribution with elements of the fixed constants, whereas Σ^{-1} in the posterior distribution of (θ, Σ^{-1}) is corresponding to Z in the Wishart distribution. Furthermore, the degrees of freedom for the posterior distribution of the (θ, Σ^{-1}) is n-m+1. The posterior distribution of (θ, Σ^{-1}) can be denoted as W($S(\theta)$, (n-m+1)).

By integrating out Σ^{-1} in the posterior distribution of (θ, Σ^{-1}), we can be simply obtain[8]

$$p(\theta \mid Y) \propto \left| S(\theta) \right|^{-n/2} = \left| Z^T Z \right|^{-n/2}, \qquad -\infty < \theta < \infty, \quad \text{provided } n \geq m.$$

The marginal distribution of θ, $p(\theta \mid Y)$, plays a very important rule in the following analysis. The parameter estimates are to be chosen so as to minimize the Bayesian determinant $d(\theta)$ which is given by

$$d(\theta) = \left| Z^T Z \right|.$$

The Bayesian determinant criterion involves constraints on the number of observations, N, the number of responses, M, and the number of parameters, P. We need to have $N>P$ and $N \geq M$ in order to carry out the necessary computation[5].

3.3.5 Bayesian approach

In the cadmium data, the number of responses M is 2 for the two-compartment model and 4 for the four-compartment model, while the number of the unknown parameters P is 3 for the two-compartment model and 6 for the four-compartment model. Furthermore, the number of observations N varies from 9 to 12.

The third assumption in the least-squares model is that there is no correlation between y_{ui} and y_{uj}, $i \neq j$ and $i, j = 1,...,M$ and $u = 1,...N$. Since the monthly amount of urine cadmium is linearly related to kidney cadmium[4], the third assumption might be violated. Multivariate analysis in the Bayesian approach might be more appropriate to apply to cadmium analysis.

An effort is made below to demonstrate the Bayesian approach to the model, although the incomplete cadmium data pose some difficulty in the application. Table 3.7 shows the results of the Bayesian approach based on a combination of simulated and real data.

It is reasonable to believe that the measurement errors are normally distributed. The generated variable of kidney cadmium at time t is provided by

$$Cd\_k(t) = n\sigma + E(Cd\_k(t)),$$

where n was generated so that it is normally distributed with mean zero and standard deviation one; the initial time t_0 is set at 0 and the unit of time is one month; μ is the prediction of kidney cadmium at time t, derived from the measurements of kidney cadmium at time t=0 and t=76; and σ is the standard deviation of measurement error in kidney cadmium, which is assumed as 6000 μg. Therefore, the simulation is based on the measurements of kidney cadmium at time 0

and 76, standard normal variables n, the standard deviation of measurement error in kidney cadmium σ, and the prediction of kidney cadmium μ. After the variable of kidney cadmium is simulated, the second way in the Bayesian approach described earlier is ready to be applied.

Working on this simulated and real data, it was failed to estimate the parameters with only one measurement of kidney cadmium, but the method is more stable to obtain the results during the convergence procedure. Table 3.7 presents the results of the two-compartment model from the Bayesian approach with the combination of simulated and real data. The estimated λ_k for each subject seems to fall in a reasonable range, which is not much different from the nonlinear least-squares results. The half-life time of kidney cadmium based on the Bayesian method for each subject is estimated as 116 months for subject 1, 39 months for subject 2, 36 months for subject 3, 87 months for subject 4, 46 months for subject 5, 58 months for subject 10, 26 months for subject 11 and 25 months for subject 13.

Highest posterior density (HPD) regions of content $1-\alpha$ is defined by Box and Tiao[8] as a region R in the parameter space such that $\Pr\{\beta \in R\} = 1-\alpha$ and, for $\beta_1 \in R$ and $\beta_2 \notin R$, the density $p(\beta_1 | y) \geq p(\beta_2 | y)$[5]. The general form of HPD in this case can be written as either

$$\frac{|Z^T Z| - |\hat{Z}^T \hat{Z}| / P}{s^2} < F(P, N-P; \alpha)$$

or

$$\ln[p(\hat{\theta} | Y)] - \ln[p(\theta | Y) < \frac{1}{2}\chi^2(P; \alpha),$$

where s^2 is $\left|\hat{Z}^T \hat{Z}\right| / (N - P)$ and $\chi^2 (P; \alpha)$ is the upper α percentile of the χ^2 distribution with P degrees of freedom.

In order to display the results graphically, three dimensional plots and the contour plots of logarithm of the objective function of (R_k, λ_k) from simulation results were generated for eight subjects, shown in Figures 3.2-3.17, where in Figures 3.2 and 3.3 are for subject 1, Figures 3.4 and 3.5 for subject 2 and Figures 3.6 and 3.7 for subject 3, Figures 3.8 and 3.9 for subject 4, Figures 3.10 and 3.11 for subject 5, Figures 3.12 and 3.13 for subject 10, Figures 3.14 and 3.15 for subject 11, Figures 3.16 and 3.17 for subject 13. Figures 3.2, 3.4, 3.6, 3.8, 3.10, 3.12, 3.14 and 3.16 are contour plots of logarithm of the objective function of (R_k, λ_k), while Figures 3.3, 3.5, 3.7, 3.9, 3.11, 3.13, 3.15 and 3.17 are three dimensional plots of logarithm of the objective function of (R_k, λ_k).

The contour plots follow patterns in the way that the largest value refers to 95% HPD and the second largest value refers to 90% HPD, while the smallest value refers to 50% HPD and the second smallest value refers to 75% HPD in each plot. The different values of HPD come from the different number of measurements among these 8 subjects and the minimum in the optimization.

In contour plots, 50%, 75%, 90% and 95% HPD are 3.28, 3.48, 3.71 and 3.89 for subject 1, 3.86, 4.00, 4.18 and 4.31 for subject 2, 4.41, 4.59, 4.80 and 4.96 for subject 3, 4.53, 4.71, 4.92 and 5.08 for subject 4, 5.85, 6.01, 6.21 and 6.35 for subject 5, 8.18, 8.35, 8.57 and

8.72 for subject 10, 3.33, 3.52, 3.76 and 3.93 for subject 11 and 6.47, 6.74, 6.83 and 6.97 for subject 13.

From the contour plots and three dimensional plots, the shape of the objective function and wide range of values for the parameter R_k can be seen for each subject. It should be pointed that the large measurement error for kidney cadmium distorted the interpretation of true relationship between kidney and urine cadmium. Moreover, there might be some linear relationship between urine cadmium and kidney cadmium. Some other factors might influence their relationship. One of those factors might be the saturation of cadmium in kidney. The relationship might depend on the conditions of kidneys in the possible situation damaged and saturated, neither damaged nor saturated, and not damaged but saturated.

The results for R_k in the subgroup with normal kidney status are close for the two estimation methods, but not so in the group with abnormal kidney status. The plots clearly display a wide range of R_k for each subject. It might imply the indirect relationship between the input rate and urine cadmium, and suggest that the blood cadmium which is connected much more directly with the input rate from outside should be included into the model.

It is noted among the results from the two estimation methods, least-squares and Bayesian approach, that the estimated R_k with low β_2-microglobulin is lower than that with high β_2-microglobulin except for subject 13. These consistent results provide possible regions for initial values for some unknown parameters, at the next step of estimation in the four-compartment model. Furthermore, incorporating blood cadmium into the model is of

importance due to the fact that the input rate from outside the human body is not directly related to urine cadmium but connected directly to blood cadmium.

TABLE 3.7 Results of the two-compartment model from the Bayesian approach with the combination of simulated and real data

Subject	$\hat{\lambda}_K$ $month^{-1}$	$\hat{R}_K$ μg/month	$\hat{Cd\_k(0)}$ μg	$Cd\_k(0)$ (S.) μg	$\hat{Cd\_k(76)}$ μg	$Cd\_k(76)$ (B.) μg	OFV
1	0.006	54.50	2759.63	2500	6824.4	4000	20.49
2	0.018	276.50	19169	21000	21211	24000	38.82
3	0.019	235.82	11520	12000	14920	24000	65.22
4	0.008	170.22	14754	14000	25759	34000	77.76
5	0.015	105.64	36780	2500	28316	12000	280.93
10	0.012	516.62	71838	78000	83474	24000	2009.22
11	0.027	990.71	31958	31000	40191	42000	21.4776
13	0.027	275.53	19518	16000	13909	66000	525.02

OFV refers to the objective function value.

Figure 3.2 3-D plot of logarithm of the objective function for subject 1 based on λ_k and R_k in the two-compartment model by Bayesian criterion

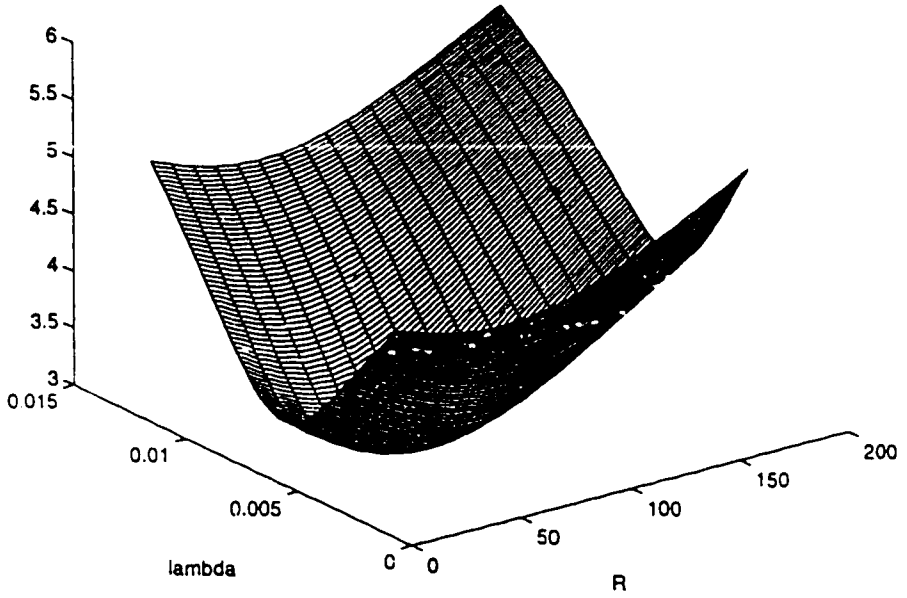


Figure 3.3 Contour plot of logarithm of the objective function for subject 1 based on λ_k and R_k in the two-compartment model by Bayesian criterion

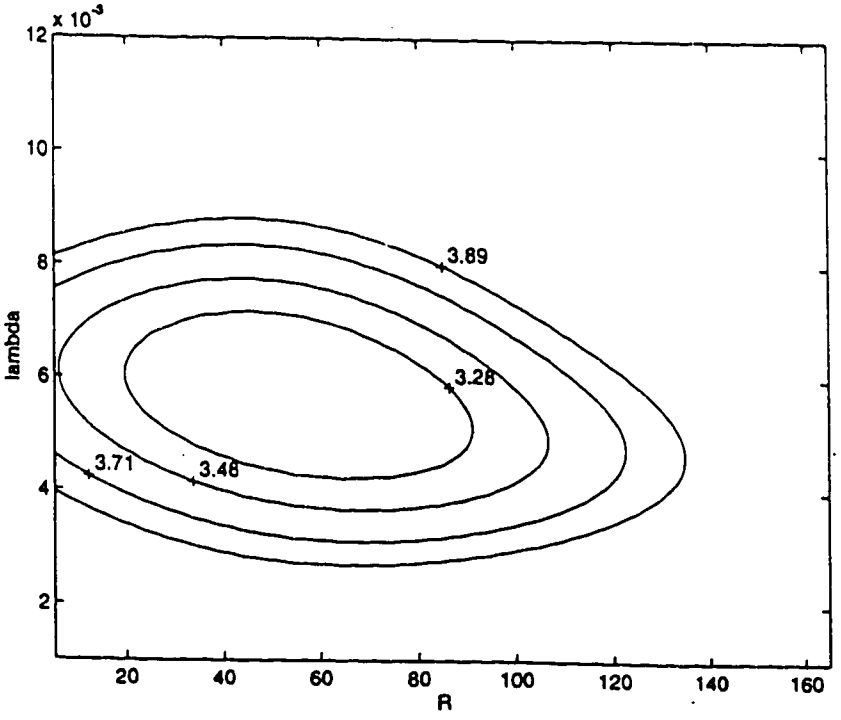


Figure 3.4 3-D plot of logarithm of the objective function for subject 2 based on λ_k and R_k in the two-compartment model by Bayesian criterion

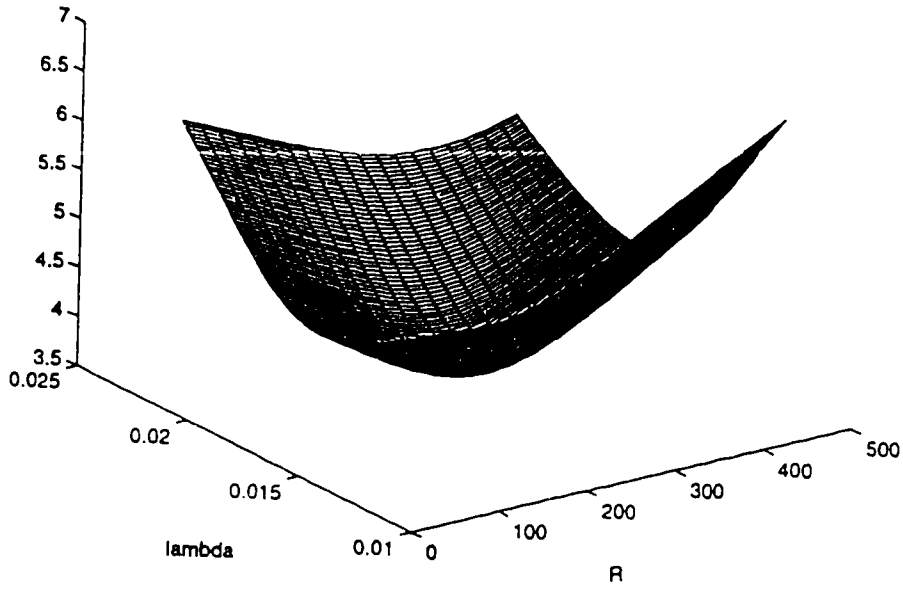


Figure 3.5 Contour plot of logarithm of the objective function for subject 2 based on λ_k and R_k in the two-compartment model by Bayesian criterion

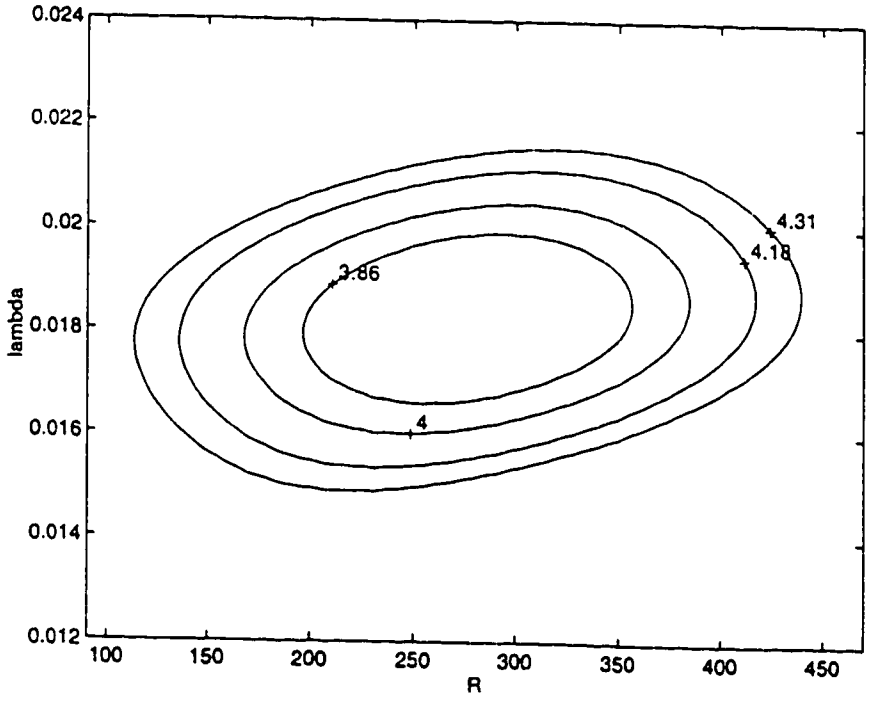


Figure 3.6 3-D plot of logarithm of the objective function for subject 3 based on λ_k and R_k in the two-compartment model by Bayesian criterion

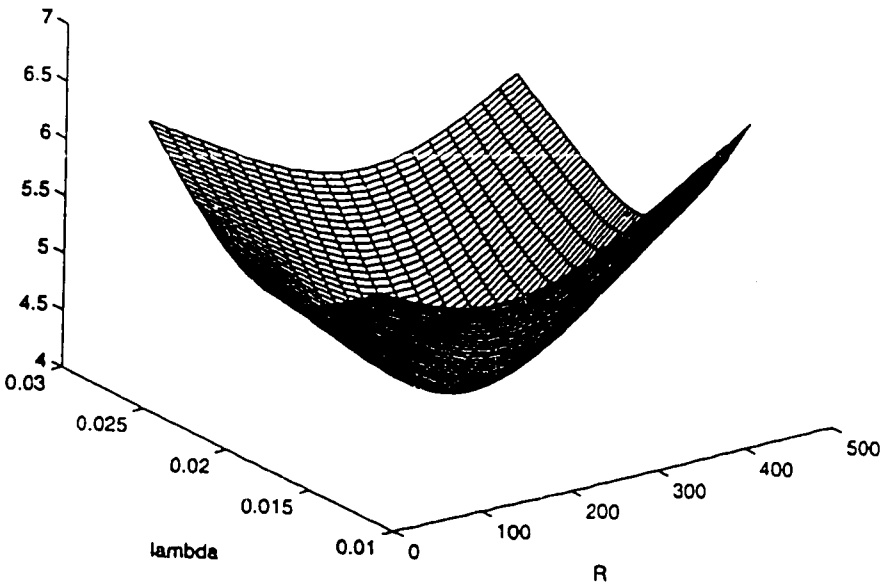


Figure 3.7 Contour plot of logarithm of the objective function for subject 3 based on λ_k and R_k in the two-compartment model by Bayesian criterion

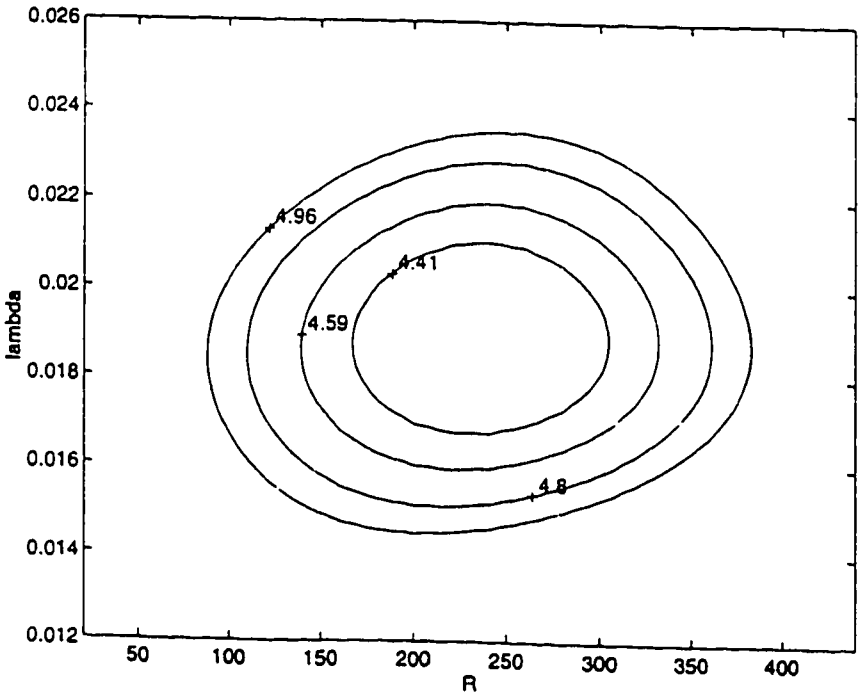


Figure 3.8 3-D plot of logarithm of the objective function for subject 4 based on λ_k and R_k in the two-compartment model by Bayesian criterion

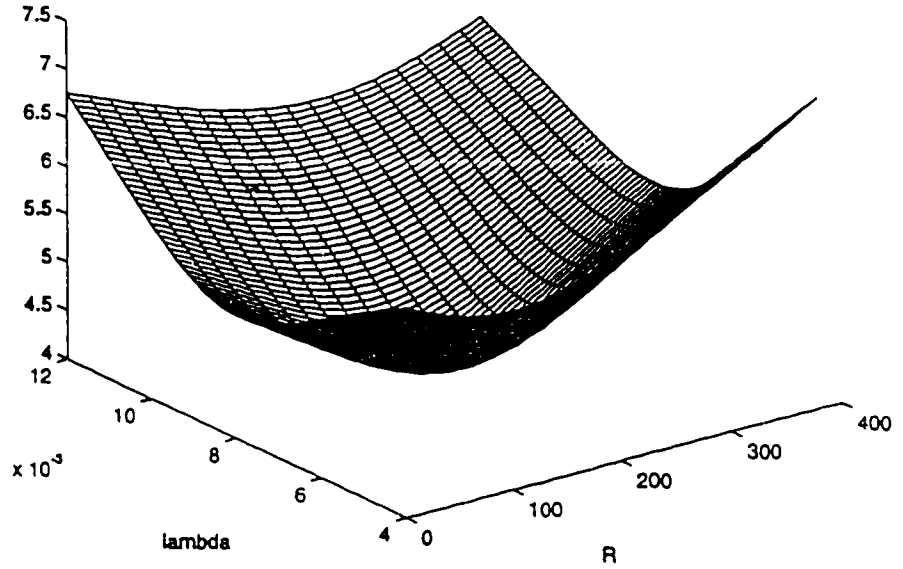


Figure 3.9 Contour plot of logarithm of the objective function for subject 4 based on λ_k and R_k in the two-compartment model by Bayesian criterion

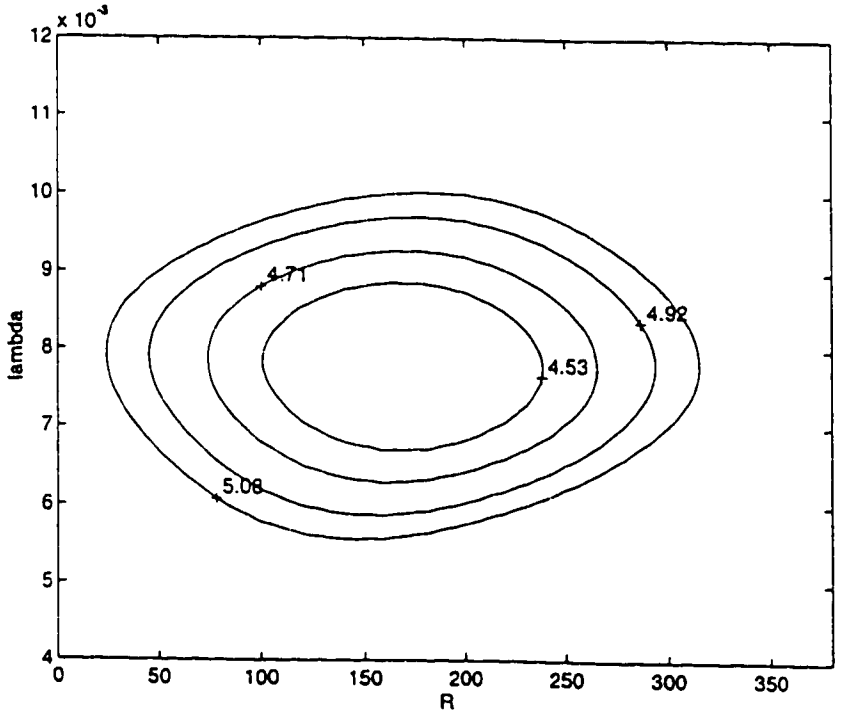


Figure 3.10 3-D plot of logarithm of the objective function for subject 5 based on λ_k and R_k in the two-compartment model by Bayesian criterion

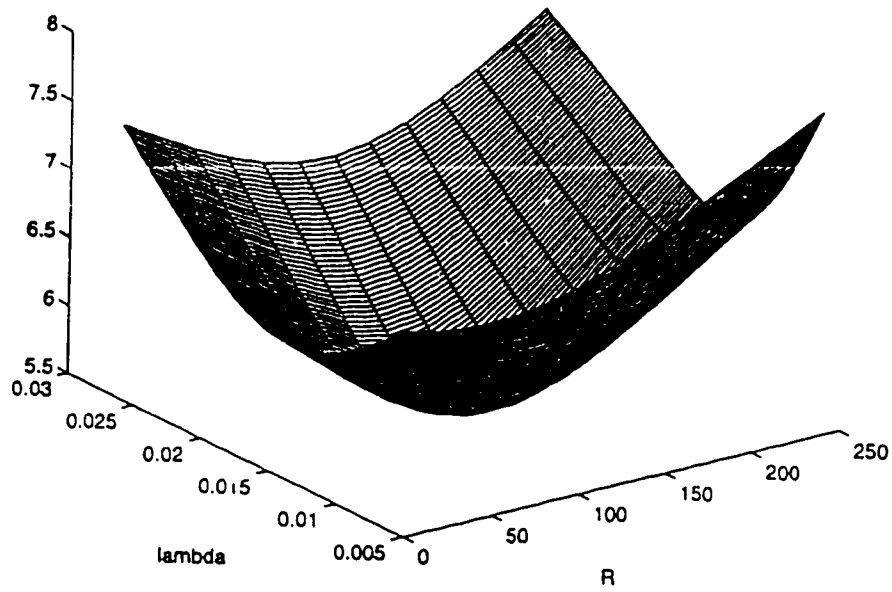


Figure 3.11 Contour plot of logarithm of the objective function for subject 5 based on λ_k and R_k in the two-compartment model by Bayesian criterion

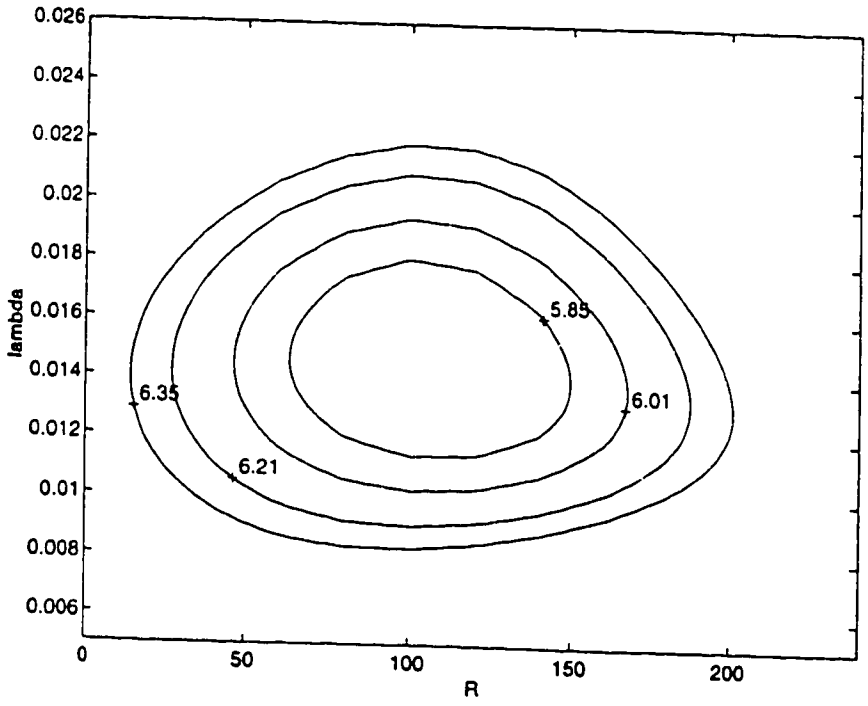


Figure 3.12 3-D plot of logarithm of the objective function for subject 10 based on λ_k and R_k in the two-compartment model by Bayesian criterion

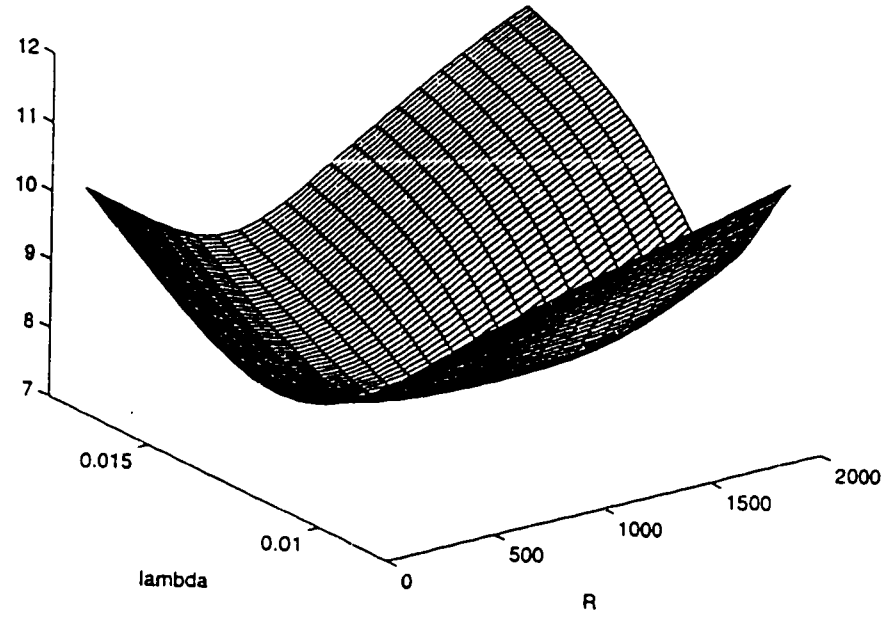


Figure 3.13 Contour plot of logarithm of the objective function for subject 10 based on λ_k and R_k in the two-compartment model by Bayesian criterion

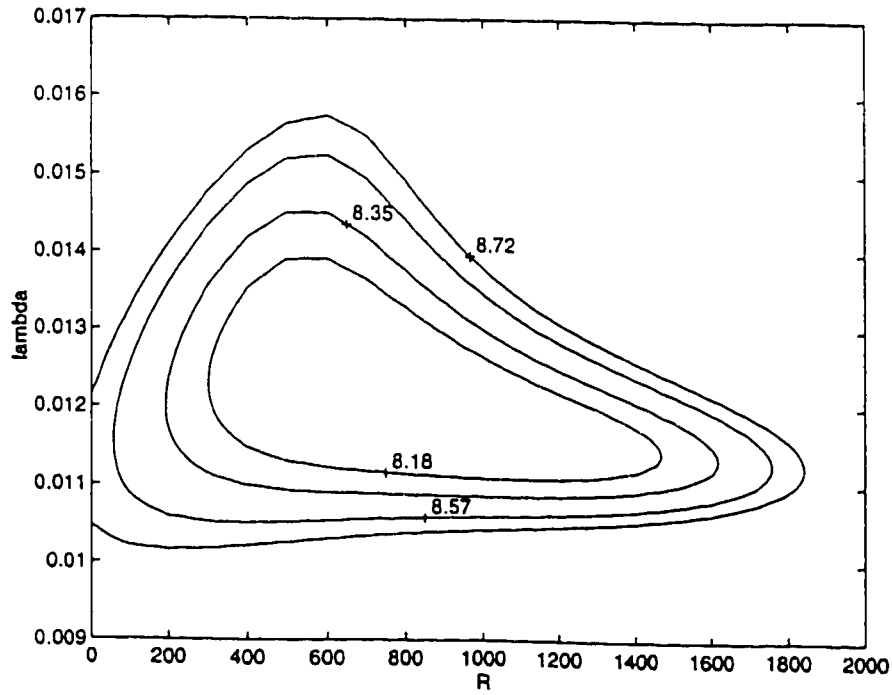


Figure 3.14 3-D plot of logarithm of the objective function for subject 11 based on λ_k and R_k in the two-compartment model by Bayesian criterion

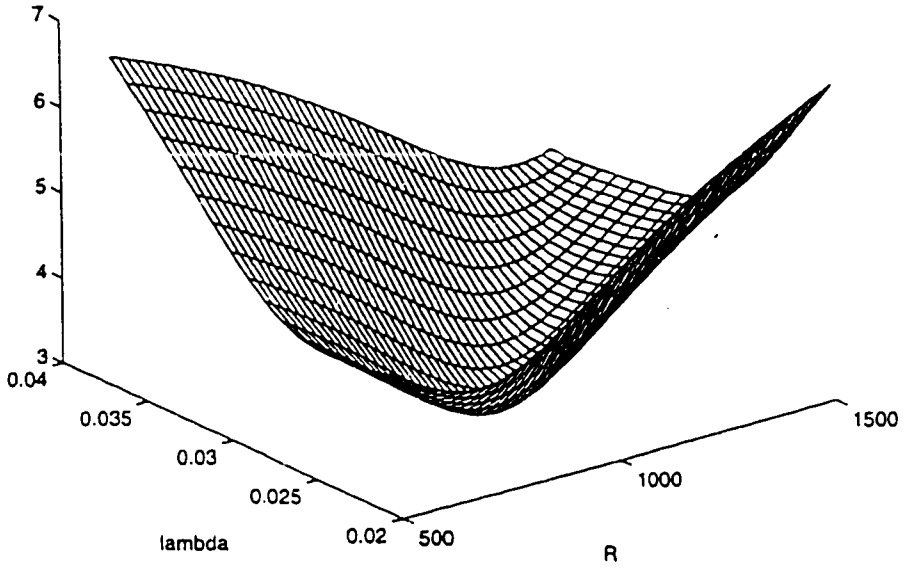


Figure 3.15 Contour plot of logarithm of the objective function for subject 11 based on λ_k and R_k in the two-compartment model by Bayesian criterion

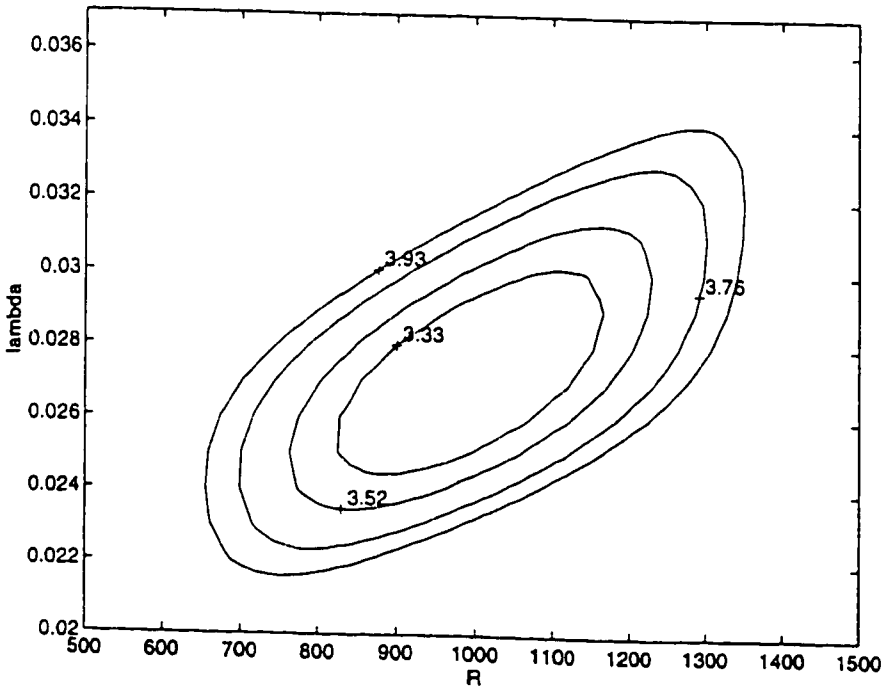


Figure 3.16 3-D plot of logarithm of the objective function for subject 13 based on λ_k and R_k in the two-compartment model by Bayesian criterion

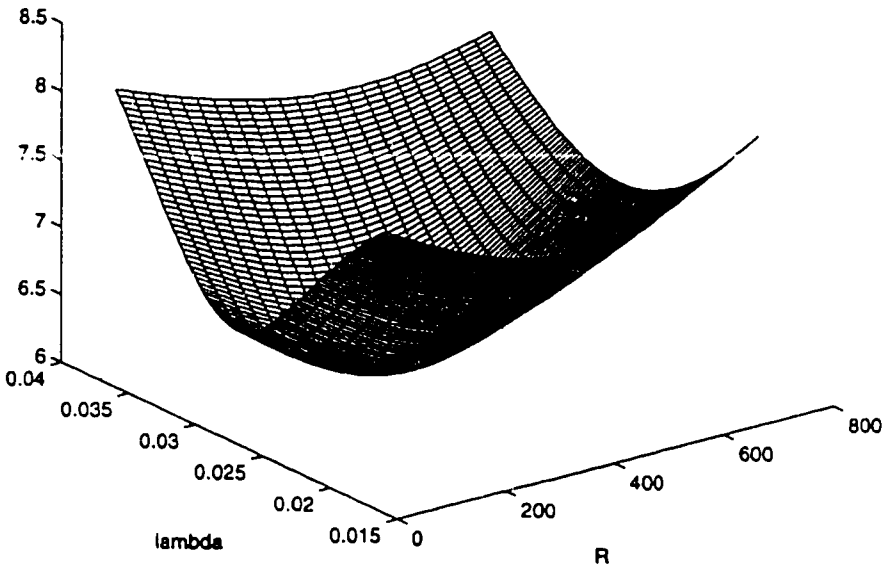
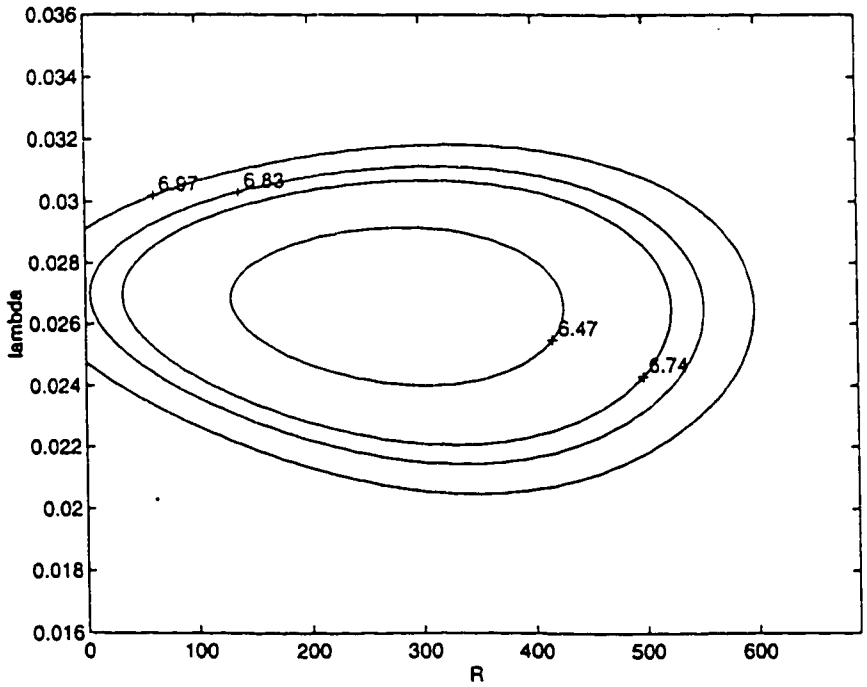


Figure 3.17 Contour plot of logarithm of the objective function for subject 13 based on λ_k and R_k in the two-compartment model by Bayesian criterion



CHAPTER FOUR

FOUR-COMPARTMENT MODEL

4.1 Expectation Functions

This chapter is composed of five sections. In Section 4.1, a four-compartment model, in the form of a linear non-homogeneous system of ordinary differential equations, is given, both analytically and graphically. Four compartments are cadmium in blood, cadmium in urine, cadmium in kidney, and cadmium in liver. Moreover, the expectation functions of four-compartment model are derived analytically in term of eigenvalues and corresponding eigenvectors of a matrix of transfer rates.

In Section 4.2, blood cadmium and the total body burden defined as total amount of cadmium in the body as the additional preliminary work are discussed briefly.

In Section 4.3, the discussion is about obtaining the starting values of the unknown parameters in two ways, based on graphical search and grid search.

In Section 4.4, the discussions and conclusions are about the estimation of parameters, by classical and Bayesian approaches. Two numerical methods, namely, Gauss-Newton and

Newton-Raphson methods, are described specifically, for the optimization problem required for the estimation methods.

In the last section, the comparison between the model developed and Kjellström's model has been made and discussed .

4.1.1 Four-compartment model

In this section, derivation of the solution of the four-compartment model, in the form of a linear system of ordinary differential equations, is discussed, in which the four compartments are cadmium in blood, cadmium in urine, cadmium in kidney, and cadmium in liver. It is assumed that the rates of flow of cadmium follow the first order kinetics, in which the mass balance equations are required for the description of dynamics of the exchange of cadmium among the compartments. The transfer coefficient is assumed to be a constant with respect to time. The model can then be described analytically in the form of linear system of ordinary differential equations as follows:

$$\begin{cases} \dfrac{d\mathrm{H}}{dt} = A\mathrm{H} + B \quad (t \geq 0) \\ \mathrm{H}(0) = \mathrm{H}_0 \end{cases}$$

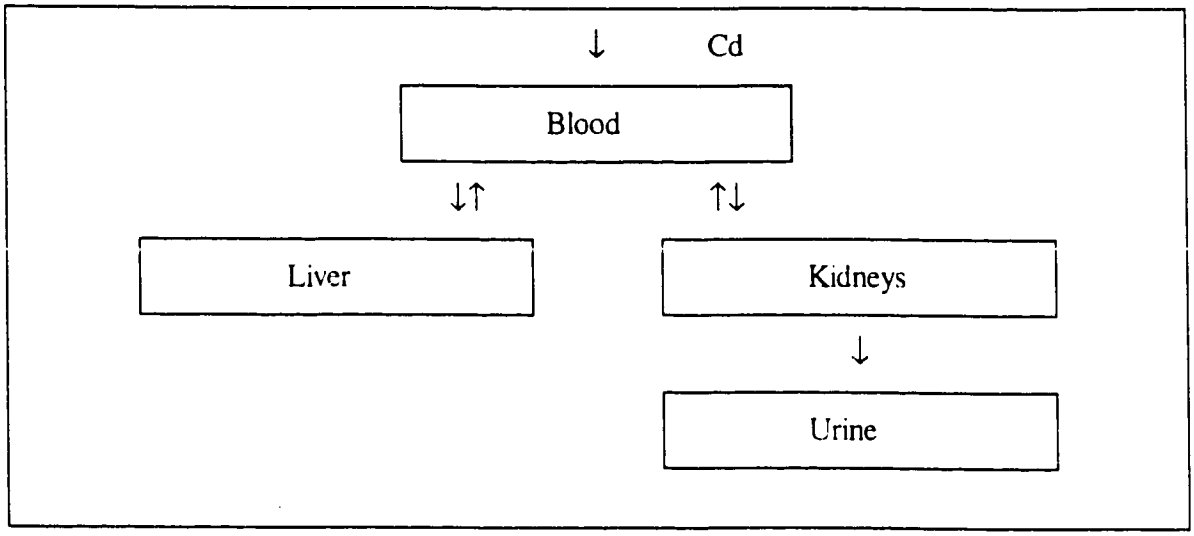
where

$$H=\begin{bmatrix}\eta_b\\ \eta_l\\ \eta_k\\ \eta_u\end{bmatrix};\quad A=\begin{bmatrix}-(C_{bl}+C_{bk}) & C_{lb} & C_{kb} & 0\\ C_{bl} & -C_{lb} & 0 & 0\\ C_{bk} & 0 & -(C_{kb}+C_{ku}) & 0\\ 0 & 0 & C_{ku} & 0\end{bmatrix};\quad B=\begin{bmatrix}R\\ 0\\ 0\\ 0\end{bmatrix}$$

where the five parameters C_{bl}, C_{lb}, C_{bk}, C_{kb} and C_{ku} in matrix A denote the transfer rates of cadmium from blood to liver, from liver to blood, from blood to kidney, from kidney to blood, and from kidney to urine, respectively; R in vector B stands for monthly intake of cadmium absorbed into the blood from the environment; the elements of H such as η_b, η_l, η_k, and η_u are the expected responses of cadmium in blood, liver, kidney and urine, respectively; t is time in monthly unit; and H_0 denotes the initial value of H at time 0.

The compartment system can also be represented graphically, in which the boxes represent compartments and where the arrows labeled with transfer coefficients represent transfers of material into or out of compartments. The compartment diagram for the model described above is shown below in Figure 4.1.

Figure 4.1 Diagram for the four-compartment model (*Cd_b, Cd_l, Cd_k* and *Cd_u*)



Since the measurements of the amount of cadmium in the urine per month are available and urine cadmium has little feedback to the kidney, the dimension can be reduced to take the first three ordinary differential equations into consideration at the initial stage of deriving equations for the expected responses. For simplicity in computation, we shall rewrite the model as

$$\begin{cases} \dfrac{d\mathrm{H}_1}{dt} = A_1\mathrm{H}_1 + B_1 \quad (t \geq 0) \\ \mathrm{H}_1(0) = \mathrm{H}_{10} \\ \dfrac{d\eta_u}{dt} = C_{ku}\eta_k, \end{cases}$$

where

$$H_1 = \begin{bmatrix} \eta_b \\ \eta_l \\ \eta_k \end{bmatrix}; \quad A_1 = \begin{bmatrix} -(C_{bl} + C_{bk}) & C_{lb} & C_{kb} \\ C_{bl} & -C_{lb} & 0 \\ C_{bk} & 0 & -(C_{kb} + C_{ku}) \end{bmatrix}; \quad B_1 = \begin{bmatrix} R \\ 0 \\ 0 \end{bmatrix}.$$

In the cadmium data, the number of measurements for each subject is at most 12 which is not large and the data structure is irregular with some missing values, which poses some difficulty in the analysis. The data set for the analysis is presented in Table 4.1.

The common approach for constructing the expectation functions is to establish the weighted sums-of-exponential model in which the expected responses can be expressed as combinations of weighted-sums-of-exponentials and constants due to the special form of the ordinary differential equations, without solving them.

From this approach, one can not directly estimate the parameters in the generating system since the number of exponential parameters may exceed the number of system parameters.

If there are only a few missing values in the data and the number of measurements are reasonably large, these missing data can be estimated as the unknown parameters and the weighted sums-of-exponentials model can be applied. However, it is certainly not the case that we have in this thesis. The number of observations is at most 12, but the number of the unknown parameters in the weighted sums-of-exponentials turns out to be 15. It is, therefore, not practical to use this approach for setting the functions of expected responses.

The way we approach this problem is a combination of an analytical approach and an exponential matrix approach. With this approach, the expectation functions for the blood, liver and kidney cadmium can be expressed by elements in A_1, the elements in B_1, the eigenvalues of A_1, and elements of the corresponding eigenvectors.

Before the expectation functions are derived, we present a brief introduction to eigenvalues and eigenvectors relating to a linear system of ordinary differential equations.

4.1.2 Eigenvalues and eigenvectors

The general form of a linear system with a constant matrix of n ordinary differential equations can be written as

$$\dot{X}(t) = CX(t) + D \qquad (LN)$$
$$\dot{X}(t) = CX(t) \qquad (LH)$$

where C is a constant matrix and D is a constant vector; LH denotes a linear homogeneous system while LN denotes a linear non-homogeneous system.

If $\Phi(t)$ is any fundamental matrix of a linear homogeneous system and $r(t)$ is any solution of a corresponding linear non-homogeneous system, then the general solution of the linear non-homogeneous system can be given as

$\Phi(t)S + r(t)$,

where S is an arbitrary constant vector, fundamental matrix is defined as a set of n linearly independent solutions of a linear homogeneous system.

Theorem 4.4, proved in the appendix, states that the vector function of $r(t)$ is as follows:

$$r(t)=\Phi(t)\int_0^t \Phi(\eta)^{-1} D\, d\eta,$$

where $\Phi(t)$ is a fundamental matrix.

The general form of a linear non-homogeneous system with an initial value problem, denoted by *LNH with IVP*, can be written as

$$\dot{X}(t)=CX(t)+D, \quad t\geq 0$$
$$X(0)=X_0 \qquad\qquad (LNH\ with\ IVP)$$

where $\exp(Ct)$ is a principal matrix for a linear homogeneous system with initial value problem and can be written as

$$\exp(Ct)=\sum_{k=0}^{\infty}\frac{C^k t^k}{k!}.$$

It can also be shown[32] that for some nonsigular matrix Q, if A and Q are similar, then the following equation holds:

$$\exp(Ct)=Q\exp(Jt)Q^{-1},$$

where matrices A and Q are similar, meaning that there is a nonsingular matrix P such that

$$A = P^{-1}QP;$$

J is a Jordan canonical form given by

$$J=\begin{bmatrix} J_1 & 0 & \cdots & 0 \\ 0 & J_2 & \vdots & \vdots \\ \vdots & \vdots & \ddots & 0 \\ 0 & \cdots & 0 & J_n \end{bmatrix};$$

elements of the Jordan Canonical Form, J_k, $k = 1,2,\ldots, n$, are block diagonal submatrices given by

$$J_k=\begin{bmatrix} \lambda_k & 1 & 0 & 0 \\ 0 & \lambda_k & 1 & 0 \\ \vdots & \vdots & \ddots & 1 \\ 0 & \cdots & 0 & \lambda_k \end{bmatrix};$$

λ_k is a general eigenvalue of the matrix C. In the special case, the general eigenvalue simply becomes an eigenvalue when the grade is 1. Furthermore, the columns corresponding to the first column of each of the Jordan block J_k are the eigenvectors of matrix C corresponding to the eigenvalues λ_k.

Therefore, the unique solution of a linear non-homogeneous system with initial value problem is given by

$$X(t) = \Phi(t)\,X_0 + \Phi(t)\int_0^t \Phi^{-1}(\eta)D\,d\eta$$

$$= \exp(Ct)X_0 + \exp(Ct)\int_0^t \exp^{-1}(C\eta)\,D\,d\eta$$

$$= Q\exp(Jt)Q^{-1}X_0 + Q\exp(Jt)Q^{-1}(I - Q\exp(-Jt)Q^{-1})\,C^{-1}D \qquad (4.1)$$

4.1.3 Expectation functions

In order to find all the eigenvalues of A_1 and the corresponding eigenvectors of A_1, consider the characteristic polynomial of A_1 given by

$$p(\lambda) = \det(A_1 - \lambda I_3),$$

where det $(A_1-\lambda I_3)$ denotes determinant of matrix of $A_1-\lambda I_3$ and I_3 denotes a 3×3 identity matrix and λ is a scalar.

The characteristic polynomial can be simplified as

$$\lambda^3 + m_1\lambda^2 + m_2\lambda + m_3 = 0$$

where

$$\begin{cases} m_1 = C_{bl} + C_{lb} + C_{bk} + C_{kb} + C_{ku} \\ m_2 = C_{bl}\,C_{kb} + C_{bl}\,C_{ku} + C_{bk}\,C_{kb} + C_{bk}\,C_{ku} + C_{lb}\,C_{ku} + C_{lb}\,C_{bk} \\ m_3 = C_{lb}\,C_{bk}\,C_{ku}. \end{cases}$$

To solve the equations easily, we make the change $\lambda = x - m_1/3$. It then turns out that

$$x^3 + f_1 x + f_2 = 0,$$

where

$$\begin{cases} f_1 = -\dfrac{m_1^2}{3} + m_2 \\ f_2 = \dfrac{2}{27}m_1^2 - \dfrac{m_1 m_2}{3} + m_3. \end{cases}$$

By applying Cardan's formula[33], the discriminant Δ for the equation is given by

$$\Delta = \frac{1}{9}f_1^3 + \frac{1}{4}f_2^2.$$

There are four types of eigenvalues of A_1, depending on what the discriminant Δ is.

Type 1:

If Δ is greater than zero, only one eigenvalue is real and the other two are complex conjugate values. The expressions of eigenvalues in this case are given by

$$\lambda_1 = \alpha + \beta - \frac{m_1}{3},$$

$$\lambda_2 = -\frac{1}{2}(\alpha + \beta) + \frac{\sqrt{3}}{2} i(\alpha - \beta) - \frac{m_1}{3},$$

$$\lambda_3 = -\frac{1}{2}(\alpha + \beta) - \frac{\sqrt{3}}{2} i(\alpha - \beta) - \frac{m_1}{3},$$

$$\alpha = \sqrt[3]{-\frac{f_2}{2} + \sqrt{\Delta}}; \quad \beta = \sqrt[3]{-\frac{f_2}{2} - \sqrt{\Delta}},$$

where
$i = \sqrt{-1}$.

Type 2:

If Δ is equal to zero, one of the possibilities is that $f_1 = f_2 = 0$. All eigenvalues are the same and real in this case. They are given by

$$\lambda_1 = \lambda_2 = \lambda_3 = -\frac{m_1}{3}.$$

Type 3:

If Δ is equal to zero, another possibility is that $f_1^2/9 = -f_2^2/4$. In this case, two eigenvalues are the same and all of them are real. They are given by

$$\lambda_1 = \alpha + \beta - \frac{m_1}{3},$$

$$\lambda_2 = \lambda_3 = -\frac{(\alpha + \beta)}{2} - \frac{m_1}{3}.$$

Type 4:

If Δ is less than zero, the eigenvalues are all distinct. These eigenvalues and the corresponding eigenvectors in expectation equation functions are given by

$$\lambda_j = 2\sqrt{-\frac{f_1}{3}}\cos[\frac{1}{3}\cos^{-1}(-\frac{f_2}{2}\sqrt{-\frac{27}{f_1^3}}) + 2j\pi] - \frac{m_1}{3}, \qquad j = 1,2,3;$$

$$U = \begin{bmatrix} \frac{1}{\sqrt{1+n_1^2+p_1^2}} & \frac{1}{\sqrt{1+n_2^2+p_2^2}} & \frac{1}{\sqrt{1+n_3^2+p_3^2}} \\ \frac{n_1}{\sqrt{1+n_1^2+p_1^2}} & \frac{n_2}{\sqrt{1+n_2^2+p_2^2}} & \frac{n_3}{\sqrt{1+n_3^2+p_3^2}} \\ \frac{p_1}{\sqrt{1+n_1^2+p_1^2}} & \frac{p_2}{\sqrt{1+n_2^2+p_2^2}} & \frac{p_3}{\sqrt{1+n_3^2+p_3^2}} \end{bmatrix};$$

where

$$n_i = \frac{C_{bl}}{\lambda_i + C_{lb}}, \qquad p_i = \frac{C_{bk}}{\lambda_i + C_{kb} + C_{ku}}, \qquad i = 1,2,3.$$

Biologically, it will not be meaningful in the first type since it will not be meaningful for the eigenvalues, associated with the half-life time of cadmium in blood, kidney and liver, to be complex values. We can rule out the second type as well, since it is not realistic that all three eigenvalues are the same because the half-life time of blood cadmium can not be the same as

the half-life time of either liver cadmium or kidney cadmium. There is a diminutive possibility of having type 3 due to the uncertainty in the parameter estimation and the possible similarity between the half-life time of kidney cadmium and that of liver cadmium. Therefore, it is most likely to be of the 4th type for all subjects since the three eigenvalues derived from matrix A_1 are all distinct.

The solutions of linear systems of ordinary differential equations with initial values exist in the defined region and can be formed in terms of the matrix exponential as mentioned above. The matrix exponential can be written as

$$\exp(A_1 t) = U \exp(Jt) U^{-1},$$

where λ_i (i=1,...,n) are the eigenvalues of A_1; U is non-singular and the columns of U are the corresponding eigenvectors of A; and $\exp(Jt)$ is a diag$\{\exp(\lambda_1 t),...,\exp(\lambda_n t)\}$ matrix.

It is assumed that the three eigenvalues λ_i (i=1,2,3) of A_1 are dissimilar in each subject. According to (4.1), the solutions of the compartment model as the expectation functions can then be derived as

$$\mathrm{H}_1 = U \exp(Jt) U^{-1} (\mathrm{H}_{10} + A_1^{-1} B_1) - A_1^{-1} B_1,$$

where

$$\exp(Jt) = \begin{bmatrix} e^{\lambda_1 t'} & 0 & 0 \\ 0 & e^{\lambda_2 t'} & 0 \\ 0 & 0 & e^{\lambda_3 t'} \end{bmatrix}, \quad t' = \begin{cases} t & (t \geq 0) \\ 0 & (t < 0) \end{cases}$$

The columns of U are the corresponding eigenvectors of A_1. The eigenvalues of A_1, λ_i (i=1,2,3), and the corresponding eigenvectors in the expectation functions which have been presented corresponding to Type 4.

If the situation in Type 3 takes place, the matrix diag{exp($\lambda_1 t$),...,exp($\lambda_n t$)} should be replaced by a general form, namely, the Jordan canonical form. The corresponding eigenvectors should be the generalized eigenvectors. This situation will not be discussed here.

Comparing the expectation functions to ordinary differential equations, it can be seen that the expectation functions have been modified when the time is less than 0. There are two possible reasons for this modification of the model:

(1) Since the cadmium exposure to the workers ceased at time t_0 and the first measurement was made when there was still some cadmium exposure, the level of cadmium in the blood was not a dramatic change from the first measurement to time 0 and it would decrease right after the exposure stopped until it reached another steady state.

(2) There is no direct relationship between the intake of cadmium and liver cadmium, or kidney cadmium. The intake of cadmium has direct contact with blood cadmium through the respiratory system and blood circulation system.

TABLE 4.1 Jaguar Data

	Month	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14
Cd_u	-10	14.37													
	-9	35.66	851.67	330.25	191.76	95.88	665.82	10.65	344.63	633.86	1464.8	1763.09	1038.68	1065.31	1171.84
	-4	23.42	819.73			53.27	303.61	42.61			1683.2	2167.91	1411.54	1523.40	1225.11
	2	37.26	686.66	537.98	266.33	133.16	761.70	26.63	404.82	756.37	1880.3	1715.15	1075.97	942.80	1054.66
	7		548.26	372.86	255.68		681.80	21.31	287.63	644.51			1155.86	751.05	1273.05
	15	58.55	601.49	474.06	255.68	101.20	564.62	21.31	335.57	628.53	1523.4	1278.38	1012.05	889.54	
	27		484.39	415.47	245.02	213.06	580.60	21.31	303.61	596.58			788.33	687.13	761.70
	40		212.92			95.88	362.21					937.48	692.45	500.70	772.35
	48											814.96			
	54	53.23	479.06	372.86	213.06	133.16		53.27		431.45			820.29	378.19	878.88
	64	26.62	511.00	266.33	79.90	37.29		37.29			1470.1		687.13	229.04	564.62
	76	21.29	314.05	223.72	154.47						1400.9	974.76	553.96	234.37	
	100		479.06	229.04	266.33	106.53					1598.0	1597.97	479.39		798.98
Cd_b	-10	32.24													
	-9		36.92	29.64	26.00	24.96	44.72	28.60	35.36	52.00	29.64	131.04	56.68	49.40	88.92
	-4	40.56	41.60			21.84	35.88	35.88			77.48	84.76	61.36	54.60	76.96
	2	37.44	45.24	27.04	22.36	20.28	49.92	30.16	33.28	47.84	72.80	82.16	62.92	45.76	68.64
	7		37.44	31.72	30.68		33.28	28.08	32.24	46.80			49.92	44.72	67.60
	15	35.36	14.04	28.08	24.44	16.12	31.20	11.44	30.68	43.68	76.44	89.96	50.96	52.00	
	27		22.88	16.64	22.88	7.80	32.24	13.00	13.52	39.52			42.64	68.64	55.64
	40		25.48			6.24	27.04				79.56	88.92	41.60	48.88	54.60
	50										82.68				
	54	2.60	32.76	19.76	20.28	5.72		8.32		35.88			49.40	51.48	56.16
	64	2.60	24.44	8.84	18.72	5.72		5.72			104.52		39.52	42.12	48.36
	76	5.20	29.12	18.20	31.72	7.80		8.84			98.80	95.68	43.68	47.32	
	100		26.00	10.40	21.32	7.28					83.20	88.40	38.48		48.88
Cd_l	0	8500	37400	11900	11900	4200	28900	8500	10200	20400	119000	86700	39100	34000	39100
	76	37500	44200	13600	35700	4200					153000	107100		61200	
Cd_k	0	5000	42000	24000	28000	5000	4200	5000	30000	30000	156000	62000	20000	32000	48000
	76	4000	24000	24000	34000	12000					24000	42000		66000	

4.2 Additional Preliminary Work

In addition to the discussions in Chapter 3 about the kidney and urine cadmium in the two-compartment model as preliminary work, the following discussions about blood cadmium and the body burden are needed to form the additional preliminary work for the four-compartment model.

4.2.1 Blood model

To reduce the dimensions of the parameters and the responses, only the level of blood cadmium of each subject after one hundred months has been examined. Table 4.2 shows the results of an exponential model for blood cadmium with the parameter R_b of cadmium intake, while Table 4.3 shows the corresponding results without the parameter R_b of monthly cadmium intake. In both models, λ_b is a decay rate which is related to the half-life time of blood cadmium and R_b stands for the monthly intake from environment.

The model with the intake parameter R_b is more general and seems to be more suitable since estimates of R_b for some subjects are significantly different from zero. Under both models, the initial values of blood cadmium for all subjects were treated as unknown parameters. The estimated initial values of the blood cadmium under both models are not significantly different for all subjects except 8 and 10. Although the estimated half-life time of blood cadmium in the model with the intake parameter R_b seems a little shorter than the one

without the intake parameter R_b, the results from both models reveal that the levels of blood cadmium fall off very slowly and reach a steady-state in a few months after the exposure ceased. This agrees with previous studies in that the level of blood cadmium reflects recent exposure more than the body burden[3]. The estimates of R_b are quite small and have unexpected signs, which suggests that more compartments need to be incorporated into the model.

4.2.2 The total body burden

The relationship of urine cadmium with the total body burden of cadmium was examined. Since the accumulation of liver cadmium is approximately 16% of the total body burden and that of kidney cadmium is about 53% of the body burden, the body burden can be expressed as

$$Total\ Body\ burden\ =\ \frac{1.8\,Cd\_l\ +\ 2\,Cd\_k}{0.16\ +\ .53}\ mg\ .$$

The results of an exponential model with observations of urine cadmium and the body burden of cadmium are shown in Table 4.4 where in λ_{total} indicates the monthly rate from urine cadmium to the total body burden, and R_{total} indicates the cadmium intake.

It should be observed that the rates λ_{total} are not significantly different from zero for all subjects, which might suggest that the influence of blood cadmium be incorporated into the model. Negative values of estimates implies once again that more compartments are needed to describe the metabolism of cadmium in the human body.

TABLE 4.2 Results of eponential model for blood cadmium with $\hat{R}_b$

	$\hat{R}_b$	$\hat{\lambda}_b$	$\hat{Cd\_b}(0)$
Subject 1	-.5	-.0015	35.53
Subject 2	1.5263	.0592	35.66
Subject 3	.0076	.0102	28.88
Subject 4	.7449	.0335	25.5748
Subject 5	.2187	.0404	19.69
Subject 6	.0980	.0127	40.01
Subject 7	.0989	.029	27.6107
Subject 8	-4.3715	-.1258	34.05
Subject 9	.5294	.0188	48.55
Subject 10	22.9448	.2652	81.3828
Subject 11	17.14	.18	98.9613
Subject 12	1.0500	.0270	56.38
Subject 13	2.5751	.05	51.0677
Subject 14	2.7946	.0551	51.0677

TABLE 4.3 Results of exponential model for blood cadmium without R_b

	$\hat{\lambda}_b$	$\hat{Cd\_b}(0)$
Subject 1	.0219	33.9256
Subject 2	.0044	35.0410
Subject 3	.0099	28.8690
Subject 4	.0012	25.3109
Subject 5	.0203	20.2263
Subject 6	.0099	40.0524
Subject 7	.0229	27.7909
Subject 8	.0176	32.9852
Subject 9	.0062	48.5424
Subject 10	-.0042	66.2756
Subject 11	.0012	97.7855
Subject 12	.0042	55.8213
Subject 13	.0008	51.5645
Subject 14	.0059	74.0414

TABLE 4.4 Results of the model with total body burden and urinary cadmium

	$\hat{\lambda}_{total}$	$\hat{R}_{total}$
Subject 1	.0003	-729.2054
Subject 2	.005	345.03
Subject 3	.0041	-458.827
Subject 4	.002	29.1473
Subject 5	.0011	-1213.54
Subject 6	.0050	-52.56
Subject 7	.0002	1505.17
Subject 8	.0030	-170.95
Subject 9	.006	-77.46
Subject 10	.0074	3284.80
Subject 11	.0075	2615.14
Subject 12	.0099	97.58
Subject 13	.0045	1588.62
Subject 14	.0098	319.93

4.3 Starting Values

The optimization required to be performed is very complicated in the four-compartment model, since the number of responses and the number of unknown parameters are rather large. One of the most important things to ensure a successful nonlinear analysis is to obtain good starting values for the unknown parameters, before implementing the estimation procedure.

There are two techniques used here for determining the starting values of this four-compartment model.

4.3.1 Graphical analysis

Since all the parameters in the expectation functions are meaningful to cadmium researchers, this meaning can be interpreted graphically to describe the behavior of the expectation functions in terms of the parameters. There are four sources for interpreting the unknown parameters, namely, the elements of the vector, $(C_{bl}, C_{lb}, C_{bk}, C_{kb}, C_{ku}, R)^T$, in the model. First, the assumptions of 6 to 38 year half-life time with kidney cadmium and 4 to 19 year half life time with liver cadmium[29] were used as reference for selecting starting values of C_{lb} and C_{kb}; next, the starting values of C_{bl} and C_{bk} were chosen much larger than those of C_{lb} and C_{kb} since it is assumed that blood compartment has a rapid turnover without accumulation; next, the portions of body burden of kidney cadmium and liver cadmium were

selected as a reference for starting values of C_{bl} and C_{bk}; finally, the estimates of excretion rate and cadmium intake from urine and kidney cadmium model, in the two-compartment model, were adopted as reference for starting values of C_{ku} and R.

This method of estimating starting values of the unknown parameters is a graphical analysis. The required steps are then as follows:

(1) solve the expectation functions numerically after fixing the parameters within reasonable ranges based on the meaning of the parameters just mentioned above, for which the Matlab software package was used for obtaining the numerical solutions, using the Runge-Kutta-Fehlberg iteration method;

(2) draw the sketches of both fitted values derived from numerical solution and observed values of blood cadmium against time, liver cadmium against time, kidney cadmium against time, and urine cadmium against time, simultaneously, and visualize them;

(3) change the values of fixed parameters and repeat steps (1), (2), and (3) until the fitted and observed values of blood cadmium, liver cadmium, kidney cadmium and urine cadmium are reasonably close.

4.3.2 Grid search

The second method of estimating starting values of the unknown parameters is a grid search. A combination of results of several resources, for example, from which of the two-compartment model in Chapter 3, the graphical analysis mentioned above, and some

previous results, were used as references for setting the range of starting values of parameters.

In attempting to find proper starting values in a grid search, there are many steps involved. At the beginning, the increments are quite large for a rough search, then the increment becomes smaller and smaller for a finer search each time. The program written in C is not intended to give the final results automatically but to provide intermediate results step by step. During the search, it can be visualized on a screen in order to get an idea which part of the range is most likely to be selected. Furthermore, the program can be paused at any time in the middle of searching if it is necessary, in order to adjust the increments or even change the range of parameters.

The results of the grid search for estimating starting values of the parameters are shown in Table 4.5. Although this type of search is very time consuming, it provides a general idea about where the location of a local minimum might be obtained within a reasonable range of the parameters. Furthermore, it certainly accelerates the convergence of the solution of the nonlinear optimization problem.

TABLE 4.5 Results of the starting values of parameters from grid search for the four-compartment model

	$\hat{C}_{bl}$	$\hat{C}_{lb}$	$\hat{C}_{bk}$	$\hat{C}_{kb}$	$\hat{C}_{ku}$	$\hat{R}$	OFV
Subject 1	22	.002	7	.017	.007	414	30.5
Subject 2	7.8	.0033	13.1	.0045	.017	330	17.83
Subject 3	17	.043	18.4	.0092	.018	141	25
Subject 4	13	.0001	12	.0038	.008	512.5	19.96
Subject 5	0.2	.0019	14.2	.0001	.0105	121.1	36.6327
Subject 10	17	.007	1.8	.0004	.0116	530	154.81
Subject 11	9.6	.0059	19.2	.015	.027	1265	9.3449
Subject 13	8.4	.0013	11.2	.0035	.03	840.7	100.9133

OFV refers to the objective function value.

4.4 Classical and Bayesian Approach

4.4.1 Classical approach

In the two-compartment model, there are only the three unknown parameters involved in the expectations so that the optimization was not so difficult to carry out. Even though the starting values of the unknown parameters are sometimes selected not near the real optimized values, there is no difficulty in reaching the real optimized values ultimately.

However, the optimization becomes complicated in the four-compartment model as the number of compartments increases to four and the number of the unknown parameters becomes six.

Two common methods for nonlinear least-squares parameter estimation are the Gauss-Newton method and the Newton-Raphson method. The difference between them is in expanding the expectation functions or objective functions for the linear approximation. Compared to Gauss-Newton approach, Newton-Raphson is a more general approach. Under certain conditions, they are equivalent.

In a linear least-squares problem, an important characteristic of a linear model is that the sum of squares function is quadratic. Because of this, contours of constant sums of squares are well-behaved regular surfaces, and all quantities related to the minimum values can be determined analytically.

For the nonlinear model, the sum of squares function is not regular, and so it is difficult to obtain the optimized values exactly. Linear approximations of the expectation functions are used to determine increments while seeking the estimates, and to determine approximate inference regions when convergence has been achieved. The linear approximation to expectation function based on the starting values of the unknown parameters, produces a linear approximation to the sum of squares function. The Gauss-Newton method is then as follows:

$$H(\theta) \approx H(\theta^0) + V^0(\theta - \theta^0),$$

$$V^0 = \frac{\partial H}{\partial \theta}\Big|_{\theta^0}, \text{ and}$$

$$(Y - H(\theta))^T (Y - H(\theta))$$

$$= [Y - (H(\theta^0) - V^0(\theta - \theta^0))]^T [Y - (H(\theta^0) - V^0(\theta - \theta^0))]$$

$$= [(Y - (H(\theta^0)) - V^0(\theta - \theta^0)]^T [(Y - (H(\theta^0)) - V^0(\theta - \theta^0)]$$

The location of the minimum at the first iteration is

$$\theta^1 = \theta^0 + (V^{0T} V^0)^{-1} V^{0T} (Y - H(\theta^0))$$

which gives the Gauss-Newton increment $\delta_0 = \theta_0 - \theta_1$. The approximation is updated at each iteration to improve the estimates until the final results are obtained.

In Newton-Raphson method, the local quadratic approximation is used to the objective function, instead of the expectation functions. Assume the objective function is the nonlinear sum of squares, $S(\theta)$, then approximated $S(\theta)$ by

$$S(\theta) \approx S(\theta^0) + \omega^{0T}(\theta - \theta^0) + (\theta - \theta^0)^T \frac{\Omega^0}{2}(\theta - \theta^0),$$

where

$\omega^0 = \frac{\partial S(\theta)}{\partial \theta}\Big|_{\theta^0}$ is the gradient of $S(\theta)$ with dimension of $p \times 1$ evaluated at θ^0;

and

$\Omega^0 = \frac{\partial^2 S(\theta)}{\partial \theta \partial \theta^T}\Big|_{\theta^0}$ is the Hessian of $S(\theta)$with dimension of $p \times p$ evaluated at θ^0.

When

$$\omega^0 + \Omega^{0-1}(\theta - \theta^0) = 0,$$

the approximating sum of squares function will have a stationary point. If Ω is positive definite this point will be a minimum, and the Newton-Raphson step is

$$\delta^0 = (\theta - \theta^0) = -\Omega^{0-1}\omega^0.$$

Since the gradient of the objective function $S(\theta)$ is

$$\omega^0 = -2V^T(Y - \mathrm{H})\Big|_{\theta^0},$$

and the Hessian of the objective function $S(\theta)$ is

$$\Omega^0 = 2V^TV - 2\frac{\partial V^T}{\partial \theta^T}(Y - \mathrm{H})\Big|_{\theta^0},$$

the Newton-Raphson step is given as

$$\delta^0 = (\theta - \theta^0) = -\Omega^{0-1}\omega^0 = -(V^{0T}V^0 - \frac{\partial V^T}{\partial \theta^T}\Big|_{\theta^0}(Y - \mathrm{H}(\theta_0))^{-1}V^{0T}(Y - \mathrm{H}(\theta_0)))$$

The Gauss-Newton increment is therefore equivalent to the Newton-Raphson increment with the second derivative term $\frac{\partial V^T}{\partial \theta^T}\Big|_{\theta^0}$ set to zero. If the weight matrix W is considered, W can be simply inserted into the increment right after V^T.

A condition that can cause erratic behavior of the Gauss-Newton iterations is the singularity of the derivative matrix caused by collinearity of the columns. This is possible in the cadmium analysis, since there is a relationship between urine and kidney cadmium. When the derivative matrix is near-singular, the inverse of the Hessian matrix becomes

very large and then the Gauss-Newton increment can also be very large, causing the parameters to go into undesirable regions of the parameter space. The general method for dealing with near-singularity is to modify the Gauss-Newton increment to

$$\theta^1=\theta^0+(V^{0T}V^0+kI)^{-1}V^{0T}(Y-\mathrm{H}(\theta^0))$$

as suggested in Levenberg, or to

$$\theta^1=\theta^0+(V^{0T}V^0+kD)^{-1}V^{0T}(Y-\mathrm{H}(\theta^0))$$

as suggested in Marquardt, where k is a conditioning factor and D is the diagonal matrix with entries equal to the diagonal elements of $V^{0T}V^0$.

During the optimization procedure, it is very helpful to check the contour plots and 3-dimensional plots of two parameters with other parameters fixed, in order to observe the convergence and the location of optima. According to values of urinary β_2-microglobumin, subjects can be divided into two subgroups, one with normal kidney condition and the other one with abnormal condition. Subjects 1, 2, 3, 4, and 5 belong to the subgroup with normal kidney condition, whereas subjects 10, 11 and 13 belong to the subgroup with abnormal kidney condition. Subject 2 was selected as an example from subgroup with normal kidney condition, while subject 11 was selected as an example from subgroup with abnormal kidney condition. The contour plots or 3-dimensional plots of two parameters with other parameters fixed are given from Figures 4-10 to 4-24 for subject 2, whereas the contour plots or 3-dimensional plots of two parameters with other parameters fixed are given in Figures 4-25 to 4-39 for subject 11.

Table 4.6 shows the results of the four-compartment model based on nonlinear least-squares estimation. Estimates of C_{bl}, C_{lb}, C_{bk} and C_{kb} in Table 4.6 provide some information about blood distribution of cadmium to liver and kidney and the cadmium elimination rate from blood either to liver or kidney, which the two-compartment model considered earlier in Chapter 3 was unable to provide. By comparing the estimate of C_{ku} in Table 4.6 and the estimate of λ_k in the tables presented in Chapter 3, it can be noticed that the results from the two-compartment model to the four-compartment model remain close. However, the estimate of R in Table 4.6 differ from the estimate of R_k in the tables presented in Chapter 3 greatly. The convergence procedure here for obtaining the optimization values goes smoothly due to the fact that the grid search provides good starting values of the unknown parameters. The results of subjects 1, 4, 10 and 13 in Table 4.6 are rather close to the starting values obtained from the grid search and presented in Table 4.5.

TABLE 4.6 Results of the four-compartment model by nonlinear least-squares estimation

Subject	C_{bl}	C_{lb}	C_{bk}	C_{kb}	C_{ku}	R	OFV
1	21.98	.00001	6.993	.0164	.0067	414.0	27.7
2	8.68	.0039	21.32	.013	.0169	325.03	16.7581
3	14.30	.0568	15.70	.0037	.0177	141.00	24.20
4	13.39	.00001	12.24	.0038	.0079	510.09	19.86
5	6.74	.0705	10.82	.0001	.0107	62.10	12.0684
10	17.25	.0075	1.15	.0002	.0116	530.0	154.11
11	12.02	.008	17.98	.013	.0273	1259.9	9.22
13	9.15	.0021	11.55	.0045	.0304	837.21	100.82

OFV refers to the objective function value.

4.4.2 Bayesian approach

As it was mentioned earlier in Chapter 3 for the two-compartment model, the assumptions leading to the classical approach may also be not realistic for the four-compartment model. It might be reasonable to assume that the variances for different measurements on the same response are constant, but certainly not that variances for different measurements are equal. Furthermore, the assumption of independent disturbances for different measurements at the same time may not be justified. In real

situations, blood, liver and kidney cadmium may be correlated, and kidney and urine cadmium may also be correlated.

In the optimization procedure, the Gauss-Newton method can be generalized for the objective function $|Z^T Z|$ once two key factors, the gradient and the Hessian matrix of the objective function, are determined[5].

Setting

$$\frac{\partial Z}{\partial \theta_p} = Z_{(p)},$$

$$\frac{\partial |Z^T Z|}{\partial \theta_p} = |Z^T Z| \, tr\left[(Z^T Z)^{-1} \frac{\partial (Z^T Z)}{\partial \theta_p} \right],$$

since

$$\frac{\partial (Z^T Z)}{\partial \theta_p} = Z^T Z_{(p)} + Z_{(p)}^T Z .$$

$$\begin{aligned} \{\omega\}_p &= 2|Z^T Z| \, tr\left[(Z^T Z)^{-1} Z^T Z_{(p)} \right] \\ &= 2|Z^T Z| \, tr\left[Z^+ Z_{(p)} \right] \end{aligned}$$

where $Z^+ = R_1^{-1} Q_1^T$ is the pseudo-inverse of Z.

Setting

$$g = \ln |Z^T Z|,$$

$$|Z^T Z| = e^g ,$$

$$\frac{\partial g}{\partial \theta_p} = g_{(p)} = 2\,tr[Z^* Z_{(p)}],$$

$$\frac{\partial^2 g}{\partial \theta_p \partial \theta_q} = g_{(pq)} = 2\{-tr[Z^* Z_{(p)} Z^* Z_{(q)}] + tr[Z^* (Z^*)^T Z_{(p)}^T (I - ZZ^*) Z_{(q)}] + tr[Z^* Z_{(pq)}]\},$$

$$\frac{\partial^2 |Z^T Z|}{\partial \theta_p \partial \theta_q} = e^g (g_{(p)} g_{(q)} + g_{(pq)}).$$

Assuming $Z_{(pq)} = 0$,

$$\{\Omega\}_{pq} = 4|Z^T Z| tr[Z^* Z_{(p)}] tr[Z^* Z_{(q)}] + 2|Z^T Z|\{-tr[Z^* Z_{(p)} Z^* Z_{(q)}] + tr[Z^* (Z^*)^T Z_{(p)}^T (I - ZZ^*) Z_{(q)}]\}.$$

Therefore, the generalized Gauss-Newton increment for determining the objective function is

$$\delta'' = (\theta - \theta^0) = -\Omega^{-1}\omega.$$

In contrast to the generalized nonlinear least-squares criterion, the Bayesian approach is more general because it takes the dependence of different responses into account in the same case, and also because variances are seldom known in applications. Although the incomplete cadmium data restrains us from illustrating the merit and beauty of the Bayesian approach in the estimation of parameters, it can still be demonstrated as a good method through statistical analysis in this thesis.

The expression[8]

$$p(\theta \mid Y) \propto |S(\theta)|^{-n/2} = |Z^T Z|^{-n/2} \qquad -\infty < \theta < \infty, \quad \text{provided } n \geq m$$

makes it possible to compute the posterior density for the parameters, assuming observations are available on some or all of the responses.

Since blood cadmium is connected with liver cadmium, kidney cadmium and the outside environment directly, the statistical analysis based on blood cadmium can provide useful information for cadmium metabolism in the human body. Because a blood cadmium sample can be more economically and conveniently collected and a Bayesian approach makes the analysis based on limited responses, it will be of interest to discuss the estimation of all the parameters using only the blood cadmium response.

The following expression represents a vector of the expectation functions for blood cadmium, liver cadmium and kidney cadmium derived in the first section of this chapter:

$$\mathrm{H}_1 = U\exp(Jt)U^{-1}(\mathrm{H}_{1_0} + A_1^{-1}B_1) - A_1^{-1}B_1,$$

where

$$\exp(Jt) = \begin{bmatrix} e^{\lambda_1 t} & 0 & 0 \\ 0 & e^{\lambda_2 t} & 0 \\ 0 & 0 & e^{\lambda_3 t} \end{bmatrix}, \quad t = \begin{cases} t & (t \geq 0) \\ 0 & (t < 0) \end{cases}.$$

The first element of a vector H_1 as the expectation function of blood cadmium can be selected for the use of calculation. Consider the posterior distribution of $\theta = (C_{bl}, C_{lb}, C_{bk}, C_{kb}$ and $C_{ku})^T$ given by

$$p(\theta \mid Y) \propto \left| S(\theta) \right|^{-n/2} = \begin{vmatrix} S_{11}(\theta) & S_{12}(\theta) & S_{13}(\theta) \\ S_{12}(\theta) & S_{22}(\theta) & S_{23}(\theta) \\ S_{13}(\theta) & S_{23}(\theta) & S_{33}(\theta) \end{vmatrix}^{-n/2}, \quad -\infty < \theta < \infty,$$

which yields $p(\theta \mid Cd\_b) \propto \left[S_{11}(\theta) \right]^{-n/2}$ when blood cadmium is the only response and

$p(\theta \mid Cd\_u \& Cd\_b) \propto \begin{vmatrix} S_{11}(\theta) & S_{12}(\theta) \\ S_{21}(\theta) & S_{22}(\theta) \end{vmatrix}^{-n/2}$ when urine and blood cadmium as two responses that can be measured.

Table 4.7 shows the results of the four-compartment model from the Bayesian approach based on simulated and observed data. The steps of generating the simulated data are similar to those described for the two-compartment model. Whenever the multi-response cadmium data is available, the approach is more appropriate to the analysis. Table 4.8 gives the results of the four-compartment model from the Bayesian analysis based on blood cadmium observations alone. It should be noticed that the results derived for blood cadmium alone are based on good starting values provided by the graphical analysis and grid search, and the method of obtaining good starting values by the graphical analysis and grid search is based on all responses. It is noticed that estimates of C_{bl}, C_{bk} and R are rather close to the results in Table 4.6 except the estimate of C_{bl} for subject 11, the estimate of C_{bk} for subject 2, and the estimate R for subject 10. Since using only one response (blood cadmium) from the four-compartment model might cause more variation and that the estimates of C_{lb} and C_{kb} are very small, the results of C_{lb} and C_{kb} can be used

as reference but should be treated with caution because they may not be very reliable. Furthermore, it is not suggested to estimate C_{ku} by using blood cadmium alone because there is more direct relationship from kidney and urine cadmium. Table 4.9 shows the results of the four-compartment model from the Bayesian approach based on blood and urine cadmium observed data. The convergent process for obtaining the results in Table 4.9 is smoother than in Table 4.8. Furthermore, the results based on urine and blood cadmium are much reliable than based on blood only. Some unrealistic estimates in Table 4.8 were changed to meaningful values in Table 4.9. C_{kb} for subject 10 is one of these values.

TABLE 4.7 Results of the four-compartment model from the Bayesian approach based on simulated and observed data

Subject	$\hat{C}_{bl}$	$\hat{C}_{lb}$	$\hat{C}_{bk}$	$\hat{C}_{kb}$	$\hat{C}_{ku}$	$\hat{R}$	OFV
2	10.33	.0054	19.67	0.0116	0.0171	294.82	3216.74
4	14.05	0.000004	11.89	0.0033	0.0078	523.5	5668.0
11	11.46	0.0085	18.54	0.0166	0.0253	1174.09	79.44

OFV refers to the objective function value.

TABLE 4.8 Results of the four-compartment model from the Bayesian approach based on blood cadmium observations only

Subject	$\hat{C}_{bl}$	$\hat{C}_{lb}$	$\hat{C}_{bk}$	$\hat{C}_{kb}$	$\hat{C}_{ku}$	$\hat{R}$	OFV
1	22.0	.000003	7.00	.0177	.0071	414.0	4.24
2	7.8	.0039	13.10	.0070	.0531	330.0	6.29
3	14.3	.052	15.70	.0064	.0375	140.99	7.48
4	14.0	.000006	12.00	.0054	.0105	500	2.04
5	6.70	.0704	11.00	.0002	.000008	60	1.19
10	16.98	.006	1.79	0	.007	739	6.88
11	9.40	.013	16.79	.00001	.816	1265.0	1.77
13	8.40	.000004	11.2	.0051	.018	840.70	9.93

OFV refers to the objective function value.

TABLE 4.9 Results of the four-compartment model from the Bayesian approach based on blood and urine cadmium observations

Subject	$\hat{C}_{bl}$	$\hat{C}_{lb}$	$\hat{C}_{bk}$	$\hat{C}_{kb}$	$\hat{C}_{ku}$	$\hat{R}$	OFV
1	25.2	.00031	4.8	.0031	.0061	413.9	22.57
2	9.42	.0034	20.5	.0131	.0169	345.7	23.87
3	10.8	.0544	19.1	.0062	.0181	138.7	6.16
4	14.6	.00044	11.7	.0052	.0084	499.8	54.6
5	6.54	.0694	10.61	.0001	.0106	59.9	8.89
10	16.8	.0064	2.11	.00025	.0113	530.0	341.4
11	12.3	.0072	17.7	.0156	.0279	1265.1	9.18
13	9.27	.0017	10.6	.0058	.0336	840.7	85.9

OFV refers to the objective function value.

The probability plots for subject 2 and 11 were represented in this thesis. Figure 4.40 and 4. 42 illustrate the confidence region with 75%, 90% and 95% between C_{bl} and C_{bk} as the other parameters fixed, respectively. In addition to that, Figure 4.41 and 4.43 illustrate the confidence region with 75%, 90% and 95% between C_{lb} and C_{kb} as the other parameters fixed, respectively. Comparing the plot for subject 2 and the corresponding one for subject 11, the distinction is not visible between them. It might imply that the difference in the system of the body between two subjects, from different kidney status, is not obvious. It is also possible the real difference is hidden because of the measurement

error and insufficient data. However, the cadmium input from outside appears to be distinct based on the results.

The programs for the grid search and the optimization of the four-compartment model are presented in this thesis. At the beginning of each program, there is a short description about the program.

4.4.3 Discussions

Figures 4.2-4.9 show the diagrams of observed data with the fitted four-compartment model for each subject, illustrating the fitted data from the present model agree reasonably well with the observed data for each subject except subject 13. β_2-microglobulin for subject 13 is very high, which indicates that the kidney function for this subject was damaged. Some irregular and unpredicted pattern could have taken place in subject 13.

Large estimate of C_{bl} and estimate of C_{bk} reflect that there is no cadmium accumulation in blood with rapid turnover of cadmium.

A combination of C_{kb} and C_{ku} reflects the half-life time in the kidney. Absence of feces cadmium variable might cause the estimate of the half-life time in kidney to be too small. It is probable that missing observations of feces cadmium leads C_{ku} have been overestimated.

It is noticed from the results that estimates of C_{lb}, C_{bl}, C_{bk}, C_{ku} and R might be affected by the absence of observations of tissue cadmium and feces cadmium. The estimate of C_{lb} indicates that the half-life time in liver. Some estimates of C_{lb} seem mall, which might be influenced by the lack of a tissue cadmium variable in the model. It might affect the estimate of C_{lb} that cadmium may be transported back from tissue to liver via the blood, and missing observations of tissue cadmium might lead both C_{bl} and C_{bk} to be overestimated and C_{lb} to be underestimated. Unfortunately, there is no non-invasive method to measure tissue cadmium yet. Therefore, when each half-life time of blood, liver and kidney cadmium is derived from each of these estimates, the influence of absent tissue cadmium should be taken into account.

For a further model, since the tissue cadmium is assumed to be about 31% of the total body burden, it should be included in the model, despite the unavailable observation on tissue cadmium. When the number of measurements of blood cadmium and others increases to a certain extent, the variable of tissue cadmium can be involved in the model, and the half-life time of tissue cadmium and the relationship with the other compartments can be estimated through blood (or blood and urine) cadmium and other observations without tissue cadmium, based on the Bayesian approach, in a similar way as shown in Table 4.8 (or 4.9).

The estimate of R is quite reasonable. It is found from the estimation results, that the subjects with high β_2-microglobulin have higher estimate of intake cadmium, R, than those with low β_2-microglobulin of the four-compartment model. The interpretation could be that the

environment is not the only sources for cadmium intake, and the cadmium released from the other tissues might contribute to the intake of cadmium as well.

From Table 4.6, the estimate of R for the four workers (subjects 1, 2, 3 & 5) is 236± 162ug/month; for the four workers (subjects 4, 10, 11 & 13) the estimates of R is higher at 784±351 ug/month. The difference is 548±193ug/month. These is reasonable since tobacco contains some cadmium. Also, the estimates of the rate constant for the transfer of cadmium from kidney to urine are somewhat higher in these subjects with raised β_2 microglobulin (subjects 10, 11 & 13) than those with normal kidney function (subjects 1, 2, 3, 4 & 5). This is reasonable since cadmium induced kidney damage is known to give rise to increased excretion of cadmium in urine. In this case, raised β_2 microglobulin is associated with a fall in kidney half life to 30 months from a normal value of 58 months.

The differences in other estimates such as those of C_{bl}, C_{lb}, C_{bk}, C_{kb} and C_{ku} between the two subgroups are not obvious. It is not conclusive because of the small and insufficient data set and the uncertainty in observations, and perhaps implies that the distribution of cadmium in the body depends on the absorption and the metabolism of cadmium in the body which varies from individual to individual, but is not statistically different between a worker with an abnormal kidney condition and one with a normal kidney condition.

4.4.4. Conclusions

When appropriate data are available, it may be possible to investigate the cadmium metabolism in the human body in stratified subgroups with kidney conditions. Furthermore, there might be several statistical analyses needed based on different time intervals. The model should be formulated on the data with shorter time intervals at first, and then designed for the data with longer and longer time intervals.

In order to formulate further refined models and prepare more powerful statistical analyses of these models, as the cadmium research progresses, there are two suggestions which could be made.

First and importantly, the number of subjects and the number of measurements should be increased for appropriate statistical analyses, which was mentioned several times in this thesis even though the difficulty of conducting the *in vivo* measurements is present.

Secondly, since blood and urine cadmium samples are more economic to collect from workers exposed to cadmium than liver and kidney cadmium *in vivo* measurements, blood and urine samples should be gathered more often if the cost and difficulty do not allow the *in vivo* measurements to be collected as frequently as blood and urine cadmium. A series of blood variables can be used for rough estimation of C_{bl}, C_{bk} and R by the four-compartment model. Even though the other three parameters, C_{lb}, C_{kb} and C_{ku} can also be estimated through blood cadmium, the estimation might be poor due to C_{lb} and C_{kb} being very small values and C_{ku} with no direct connection to blood cadmium. The estimation of

C_{bl}, C_{bk}, C_{ku} and R might have large variation, but can still be a reference for researchers. In the meantime, a series of urine cadmium variables and a few kidney cadmium variables can be used to estimate R and C_{ku} by the two-compartment model. Besides these, the tissue cadmium variable can also be incorporated into the model in order to estimate some rates relating to tissue cadmium. Further more, the combination of urine and blood cadmium should provide more stable estimates than blood cadmium along. After the completion of the *in vivo* measurements, the entire analysis can be done by the four-compartment model developed in this thesis using the Bayesian approach. It is strongly recommended that the Bayesian determinant minimization technique be used for the cadmium analysis whenever appropriate sets of multi-response data are available.

In order to analyze the metabolism of cadmium in the human body, both Kjellström's model and the four-compartment model developed in this thesis are applied in an attempt to adhere to physiological mechanisms for absorption, distribution and excretion of cadmium.

Since it was expensive to perform the *in vivo* measurements and difficult to collect the data over a period of decade, the data used in Chapters 3 and 4 are quite precious and one of a very few such data sets existing in the cadmium research area, even though they are noisy and sparse. The cadmium researchers are very much interested in drawing as much information as possible from these data to describe the dynamics of cadmium in the human body. However, the difficulties in fitting Kjellström's model based on the present

human data are assisted with insufficient times of measurements, deficient number of observations, and the complication in Kjellström's model itself.

In Kjellström's model, the unknown parameters are fixed by means of prior experience and knowledge based on different sources and different animal and autopsy data sets obtained earlier. To examine the choice of parameters, the model is run with some parameters fixed while others are changed so that the sensitivity of the ranges of parameters can be checked. During the analysis, the numerical solution of only one compartment of the model can be derived when unknown parameters are fixed. Thus, the relationship between one compartment and time is established. Then the average values of this compartment at different age based on the different sources are calculated. It confirms a right choice made from fixed parameters if the values derived from the numerical solution and the observed mean values are in close agreement.

In contrasting Kjellström's model with the four-compartment model developed in this thesis, it is noticeable there are two major differences as follows.

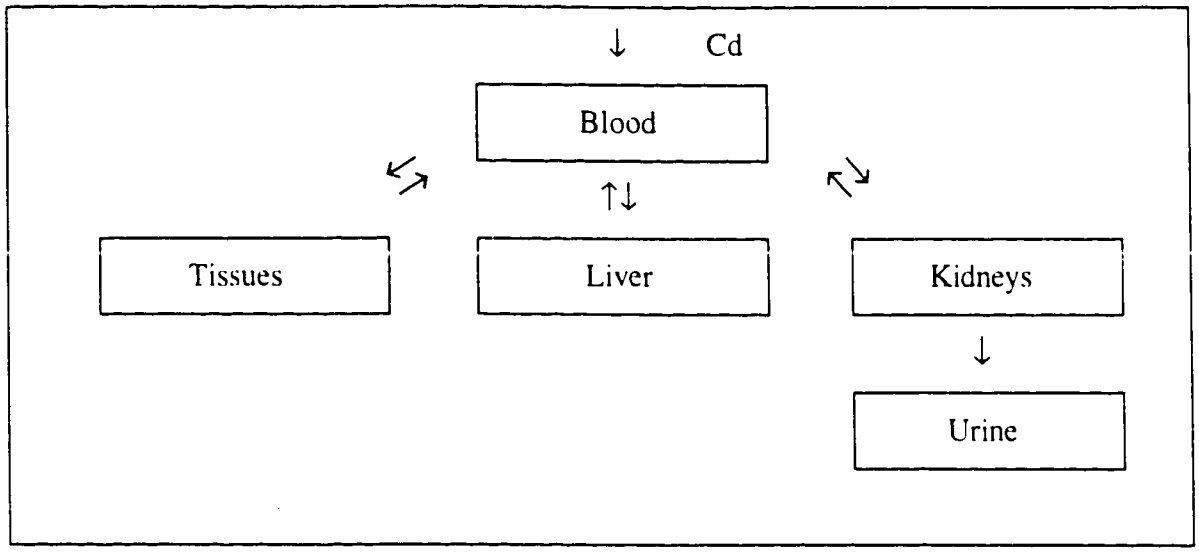
(1) The four-compartment model is used for analyzing a whole system **simultaneously** instead of discussing each compartment separately.

(2) Unlike Kjellström's model with a large number of assumptions about unknown parameters, there is no additional assumptions made about the unknown parameters in the four-compartment model. All the parameters are estimated from the observed human data.

Moreover, the four-compartment models are simpler and more direct to use in order to explain the biological phenomenon. Although some measurements of compartments are not available in the data, the major part of the system such as the measurements of the liver, kidney, blood and urine cadmium are present.

Although there is a limitation of application of Kjellström's model in the present human data, Kjellström's model provides a biological basis for the four-compartment model since some ranges of starting values in four compartments were derived based sources from coefficients in Kjellström's model. The four-compartment model achieves the parameter estimation mathematically in an inverse way, compared with Kjellström's model. The results from the four-compartment model discussed in this thesis show a great consistency with Kjellström's model.

FIGURE 4.44 Diagram for further compartment model (*Cd_b*, *Cd_l*, *Cd_k*, *Cd_u* and *Cd_t*)



Cd_t refers to tissue cadmium.

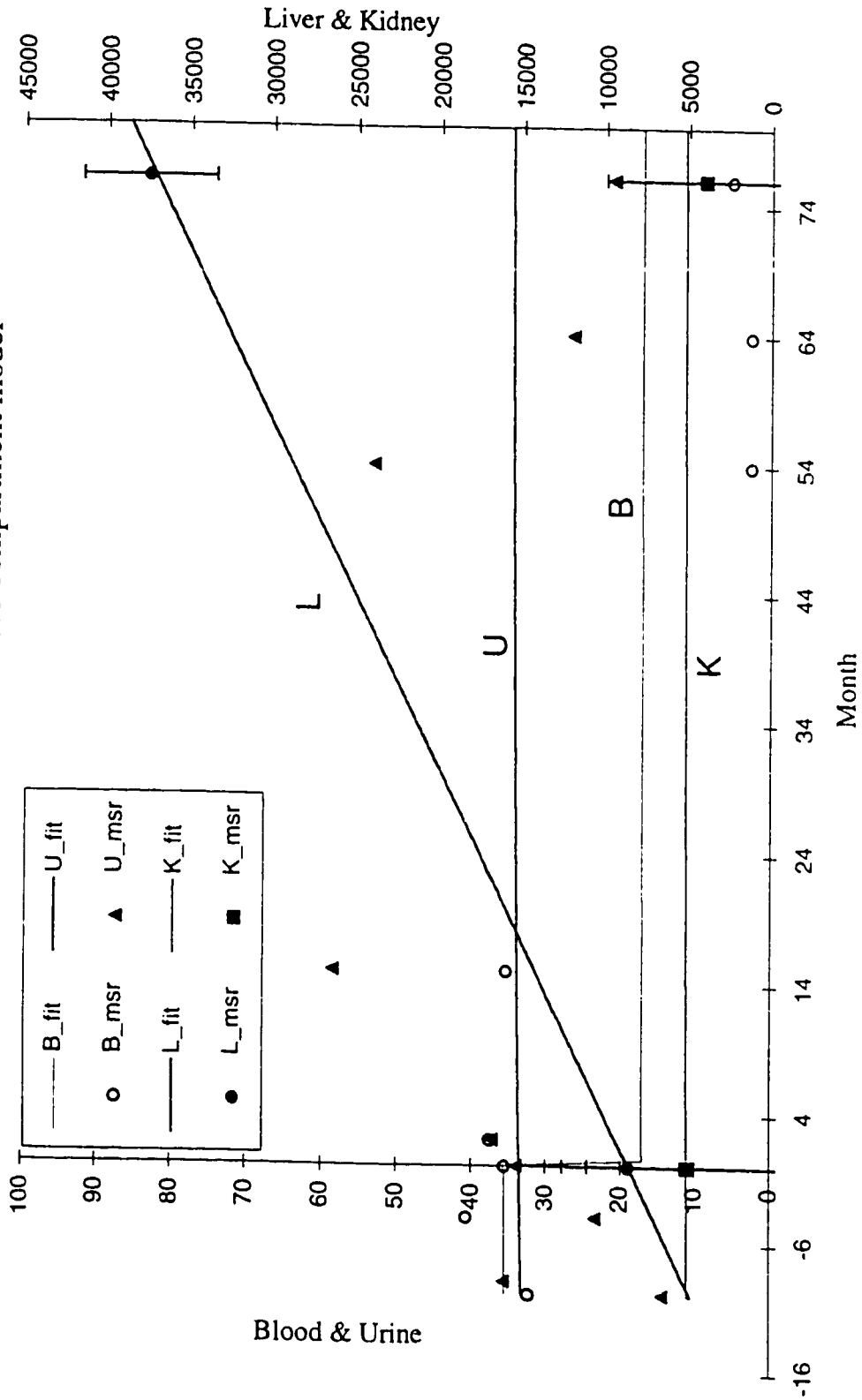


Figure 4.2 Plot of observed data for subject 1 with fitted four-compartment model

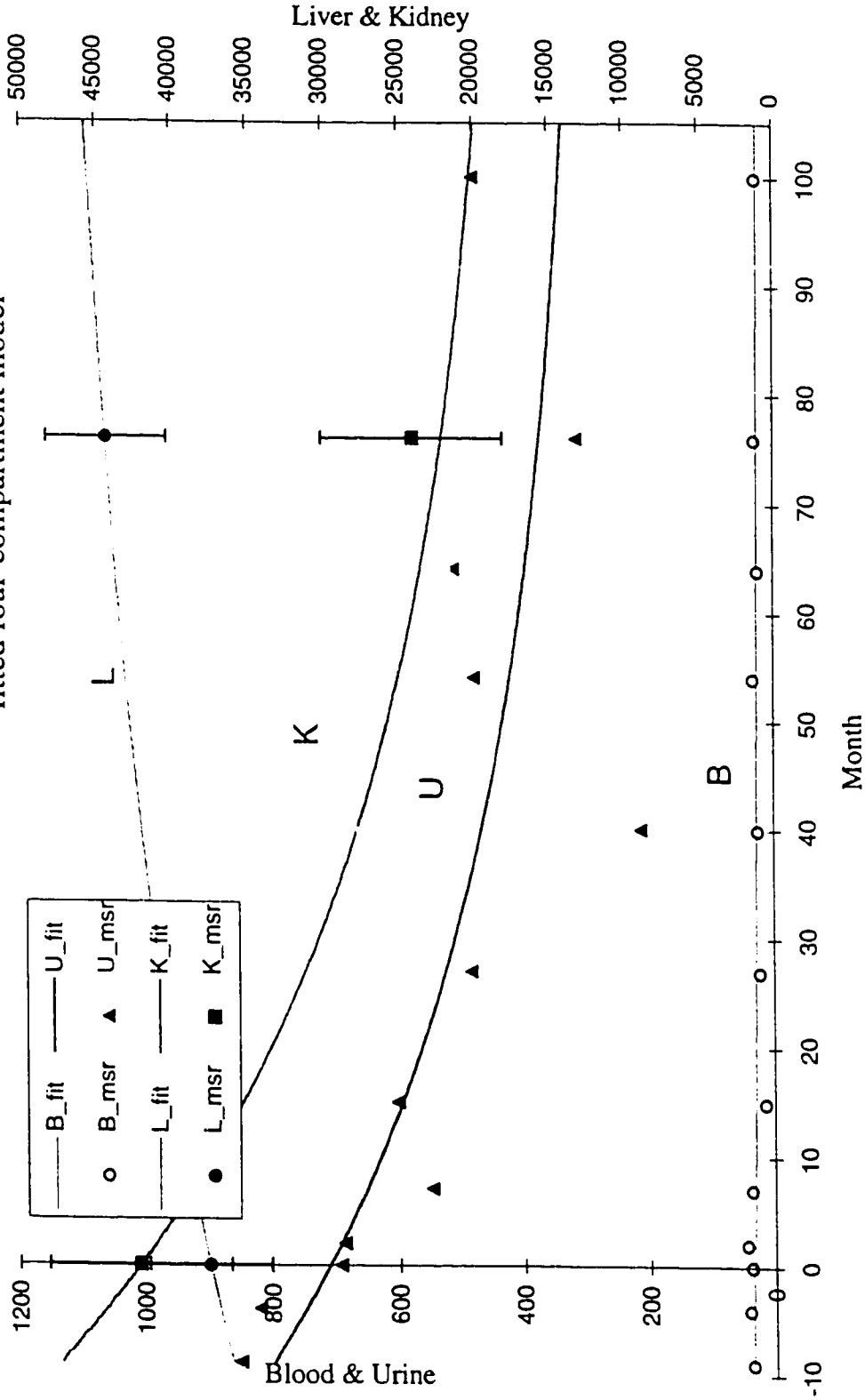


Figure 4.3 Plot of observed data for subject 2 with fitted four-compartment model

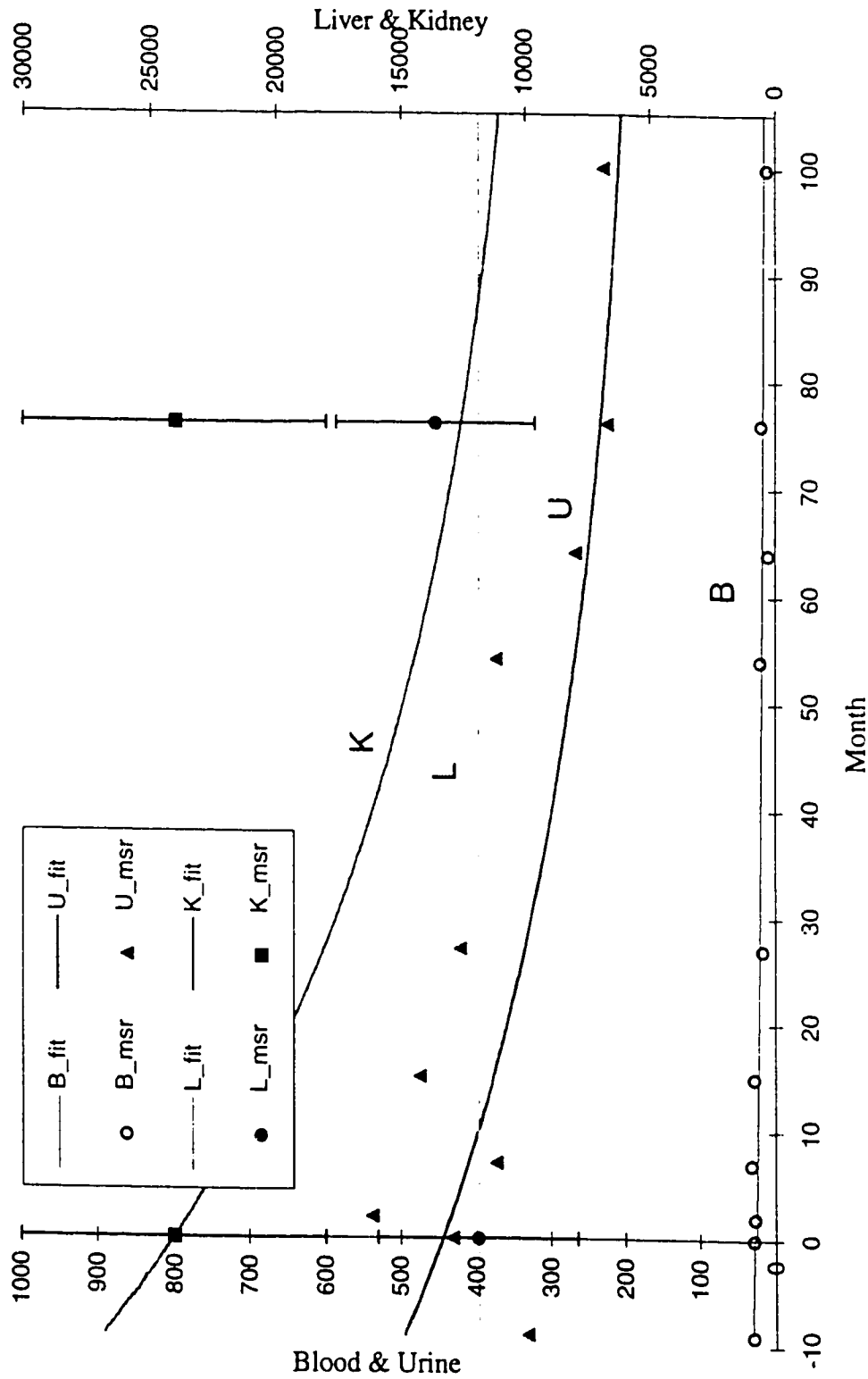


Figure 4.4 Plot of observed data for subject 3 with fitted four-compartment model

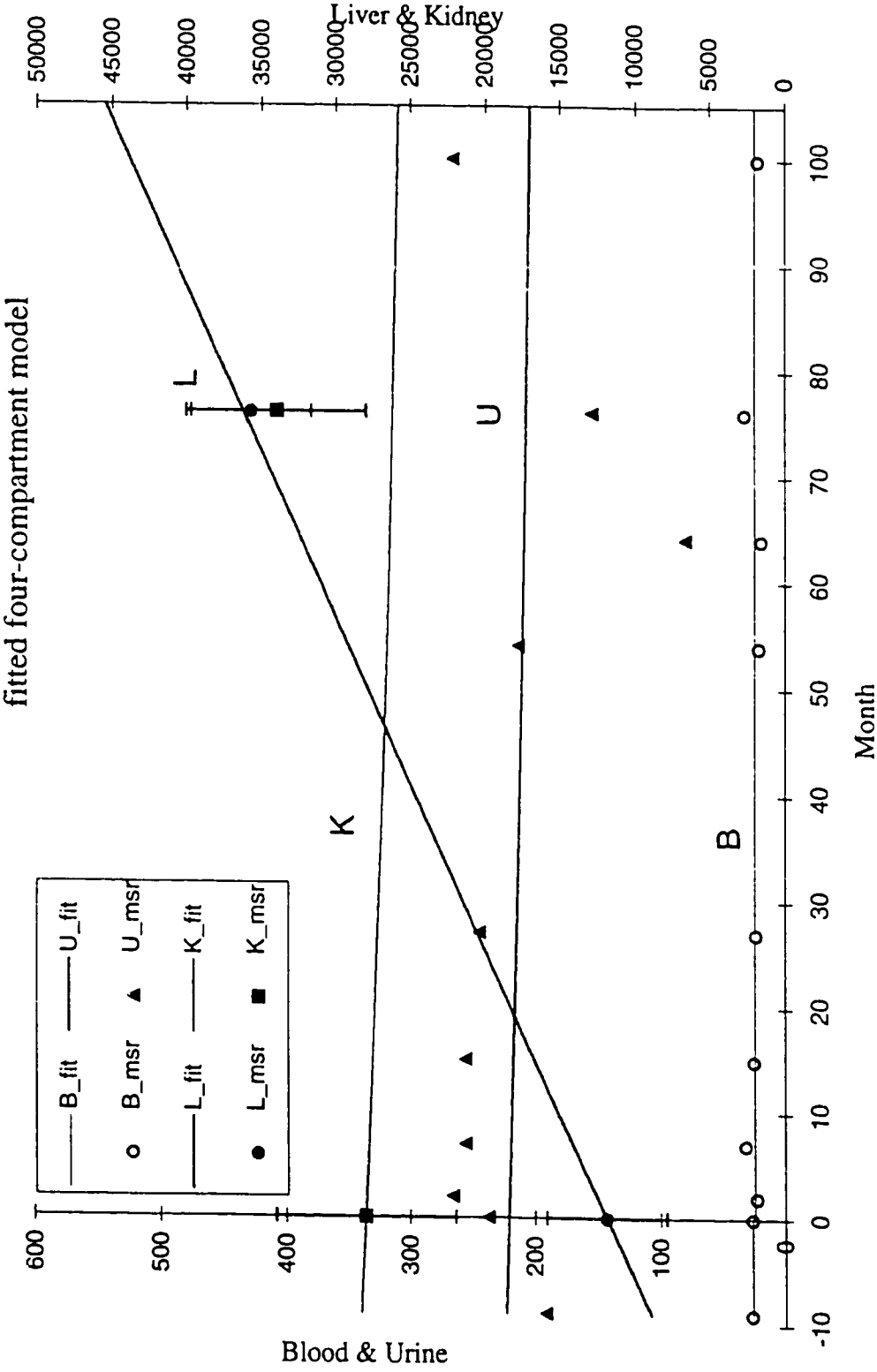


Figure 4.5 Plot of observed data for subject 4 with fitted four-compartment model

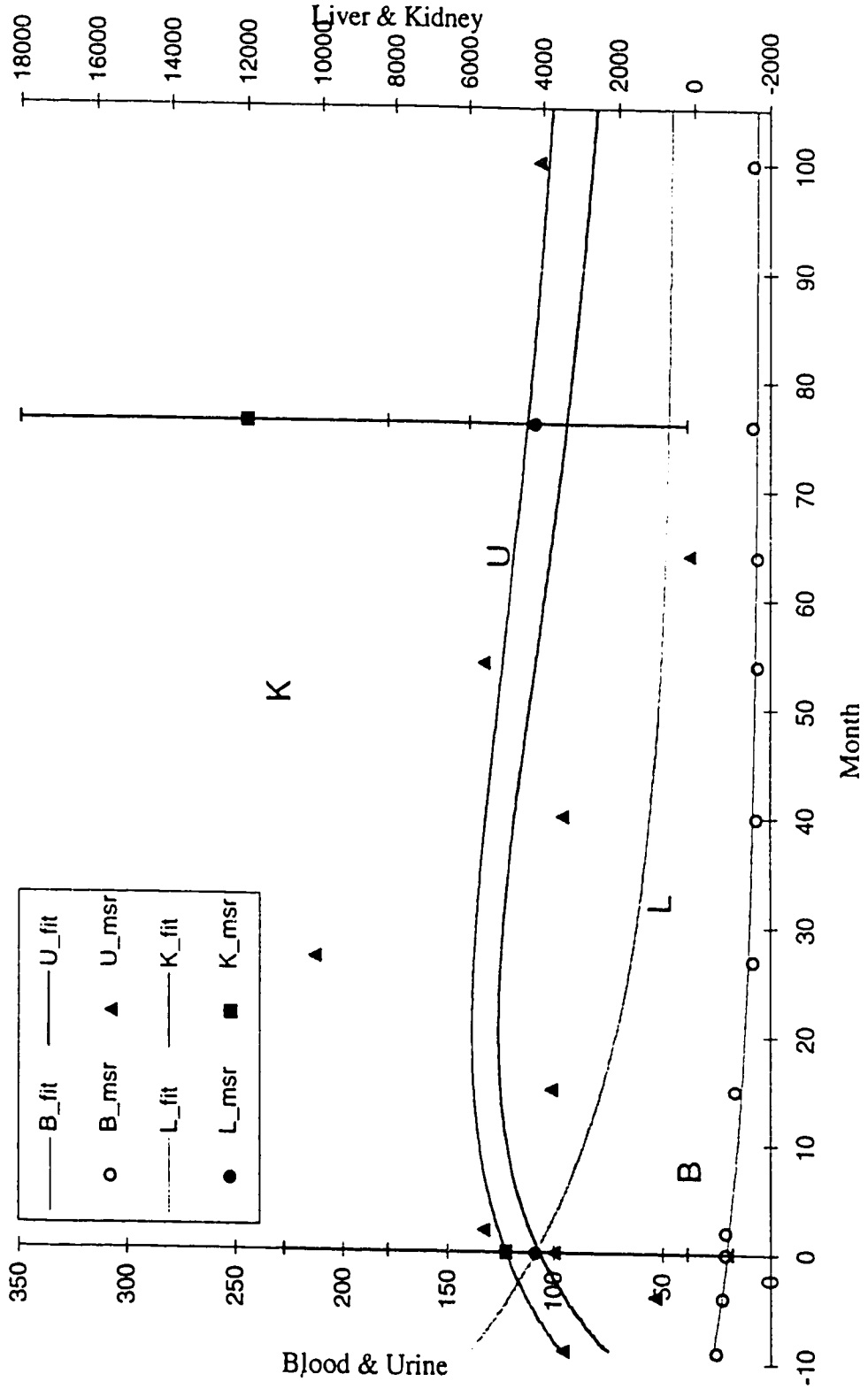


Figure 4.6 Plot of observed data for subject 5 with fitted four-compartment model

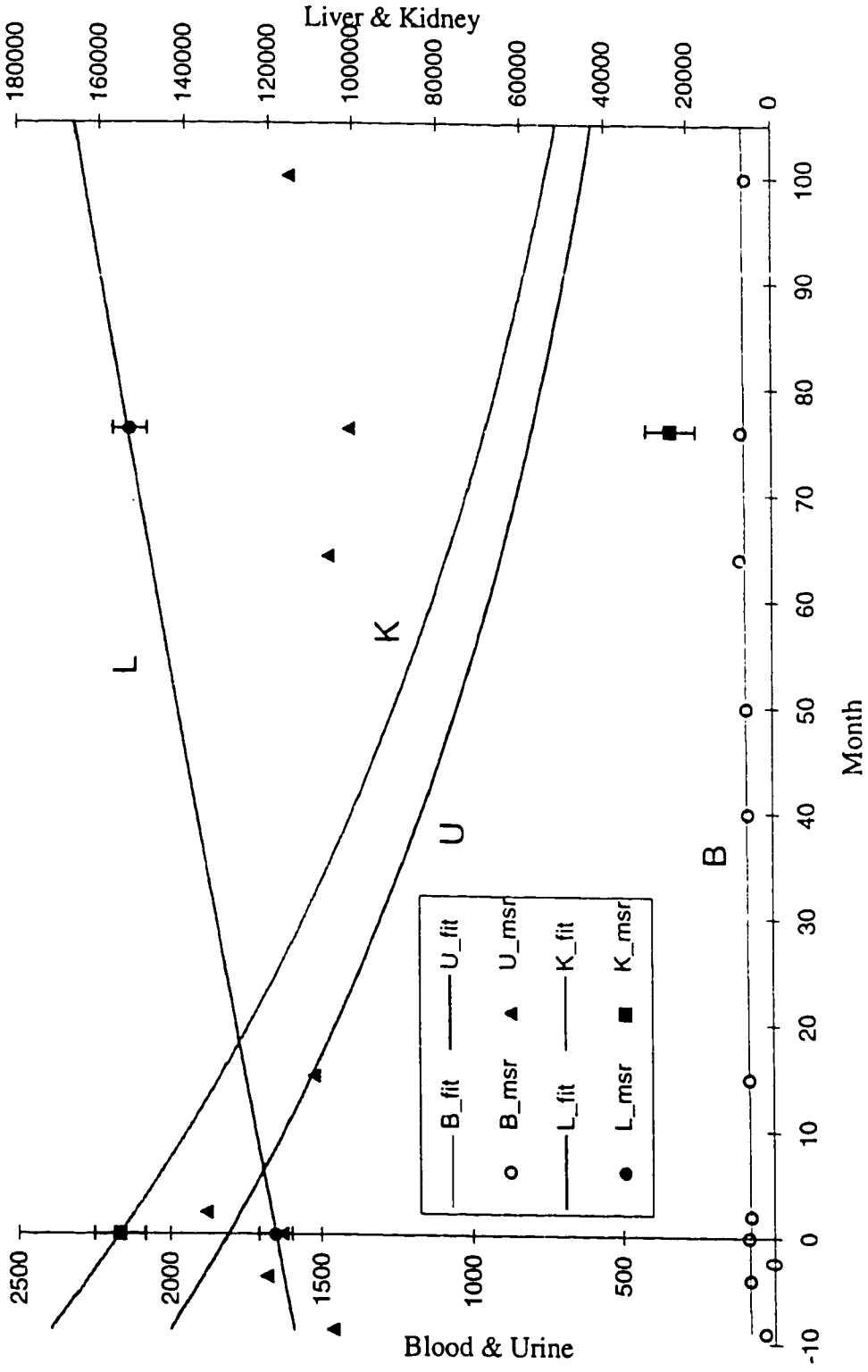


Figure 4.7 Plot of observed data for subject 10 with fitted four-compartment model

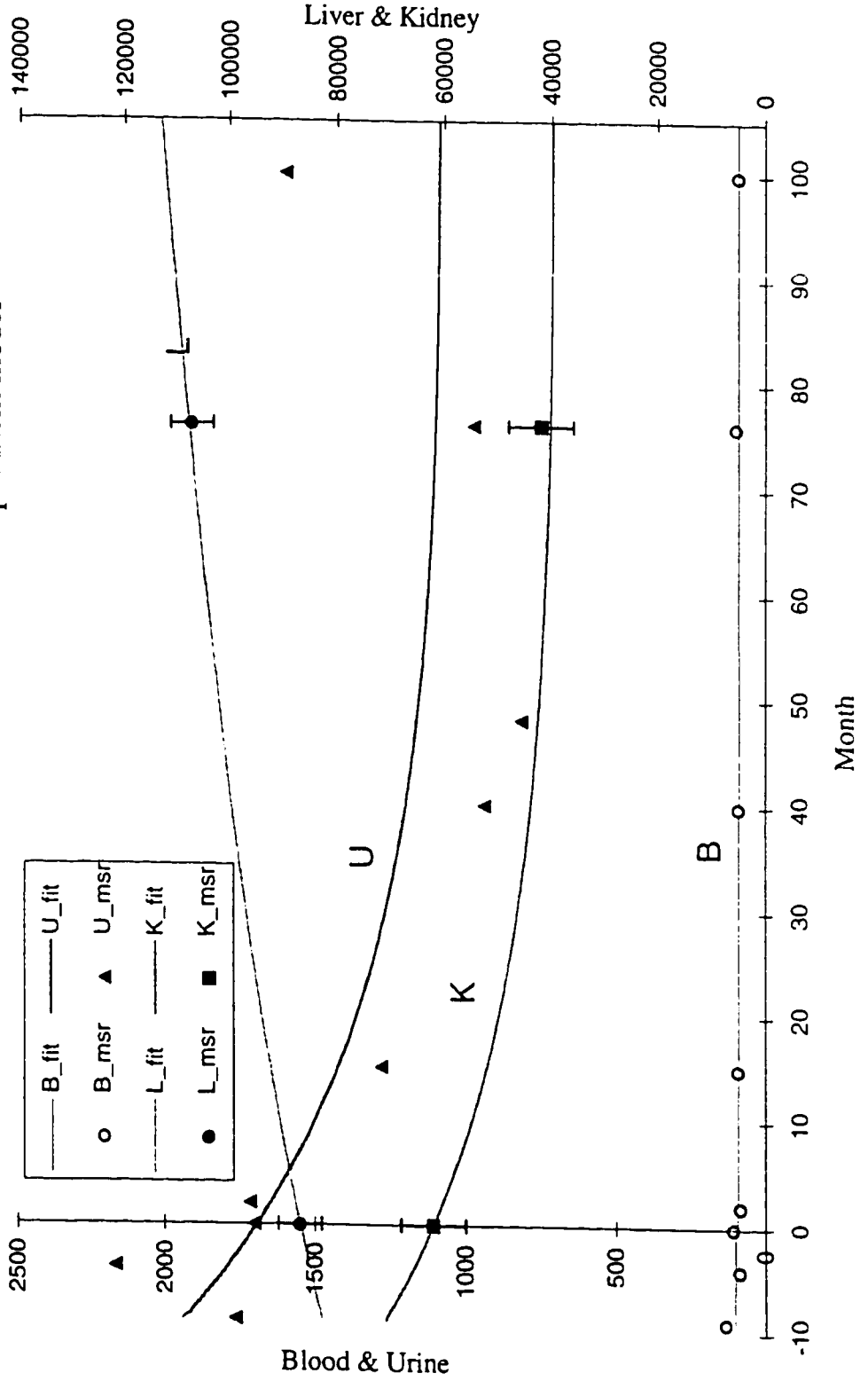


Figure 4.8 Plot of observed data for subject 11 with fitted four-compartment model

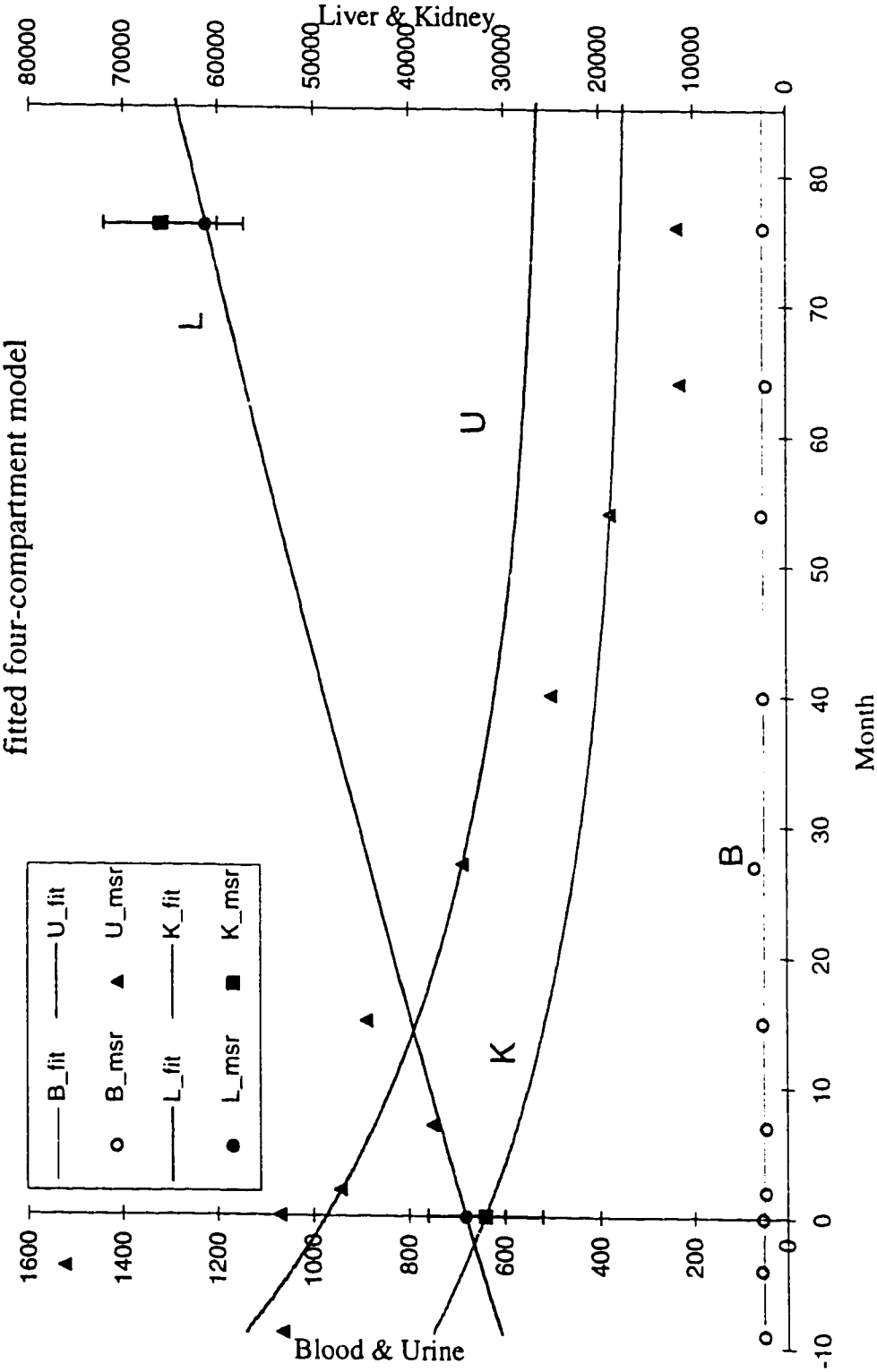


Figure 4.9 Plot of observed data for subject 13 with fitted four-compartment model

Figure 4.10 3-D Plot of a(1) and a(2) with other parameters fixed for subject 2

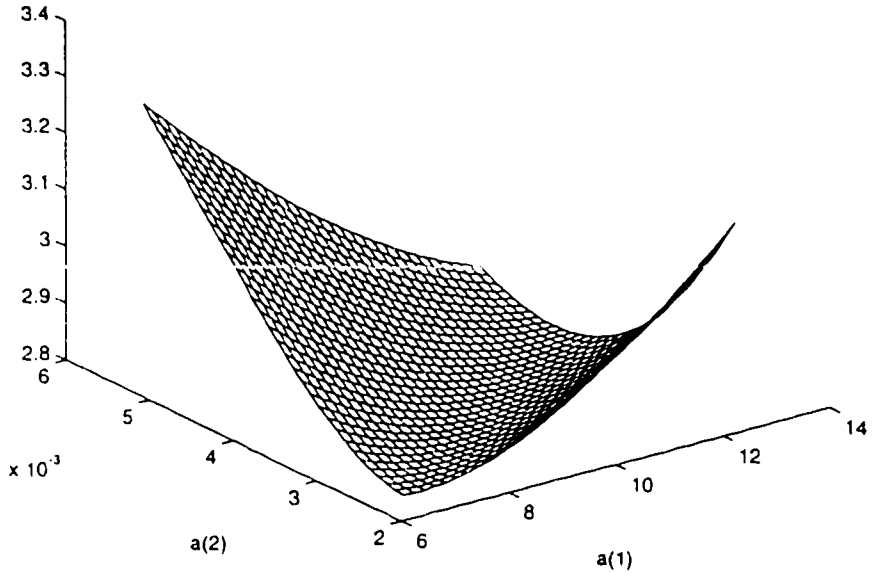


Figure 4.11 Contour Plot of a(1) and a(3) with other parameters fixed for subject 2

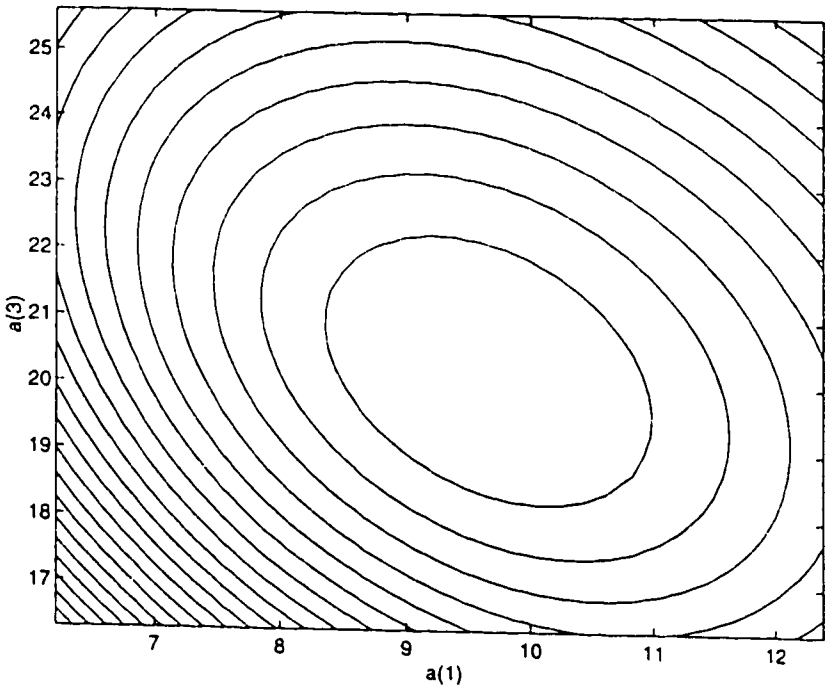


Figure 4.12 Contour Plot of a(1) and a(4) with other parameters fixed for subject 2

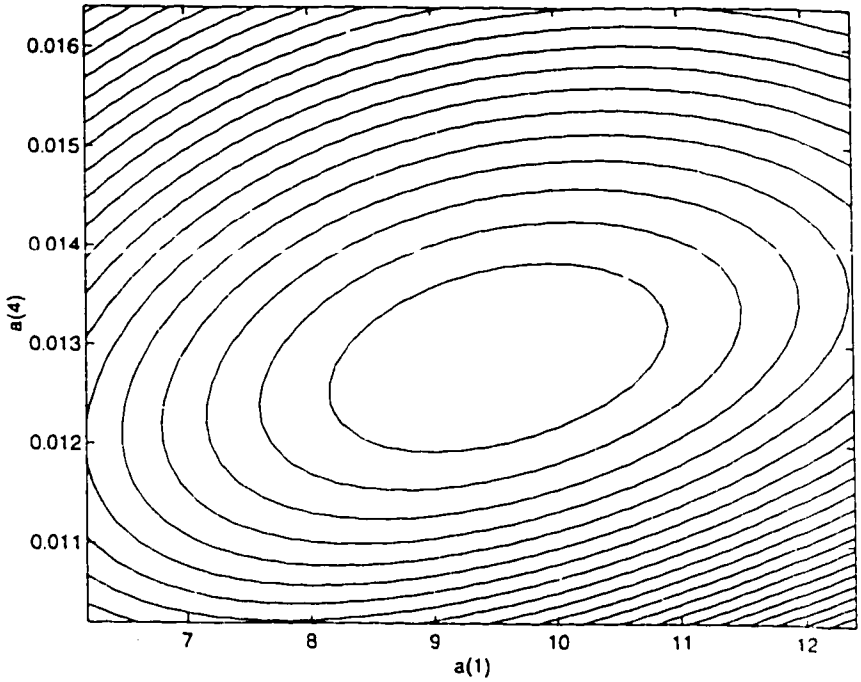


Figure 4.13 Contour Plot of a(1) and a(5) with other parameters fixed for subject 2

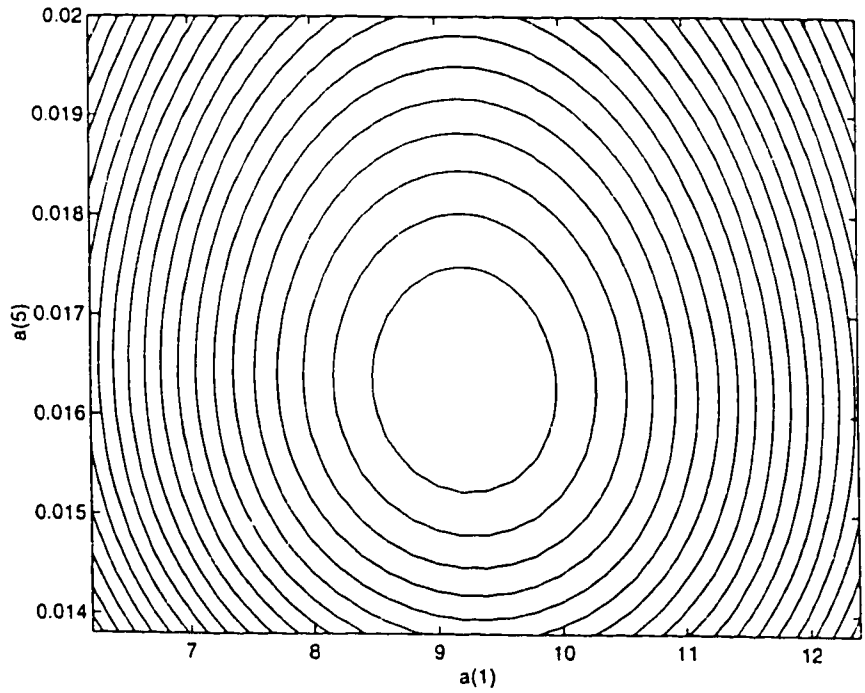


Figure 4.14 Contour Plot of a(1) and a(6) with other parameters fixed for subject 2

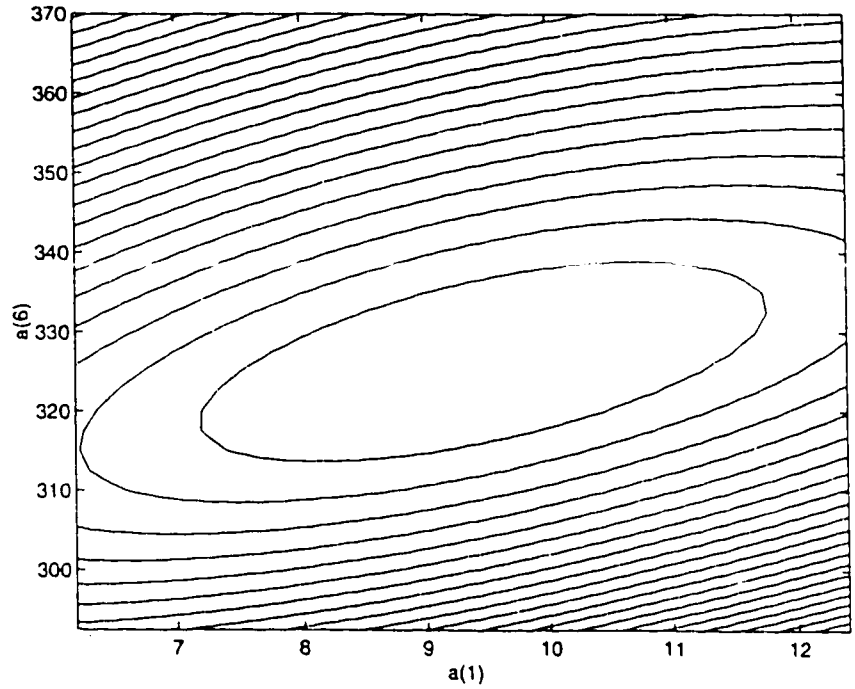


Figure 4.15 Contour Plot of a(2) and a(3) with other parameters fixed for subject 2

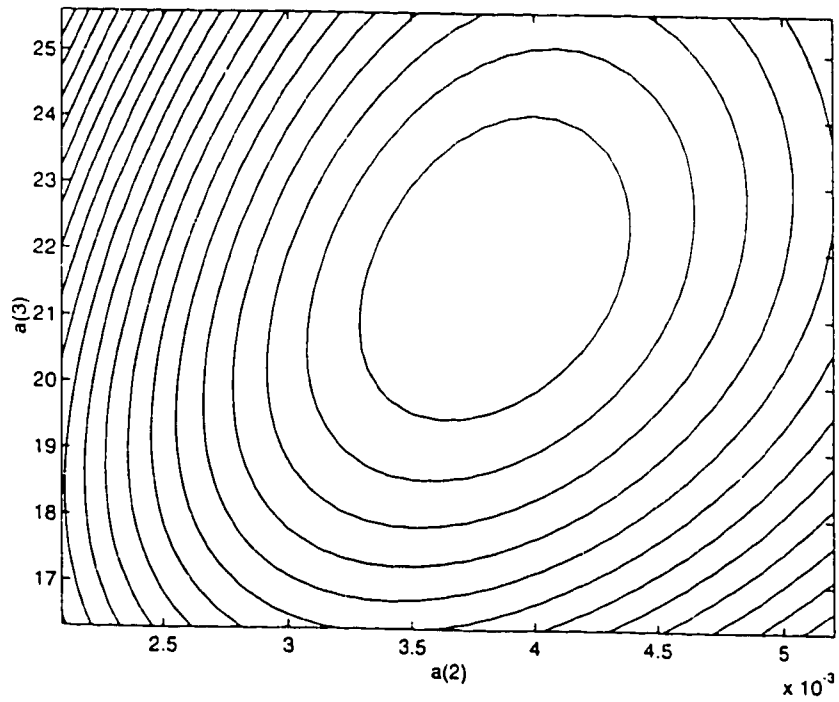


Figure 4.16 Contour Plot of a(2) and a(4) with other parameters fixed for subject 2

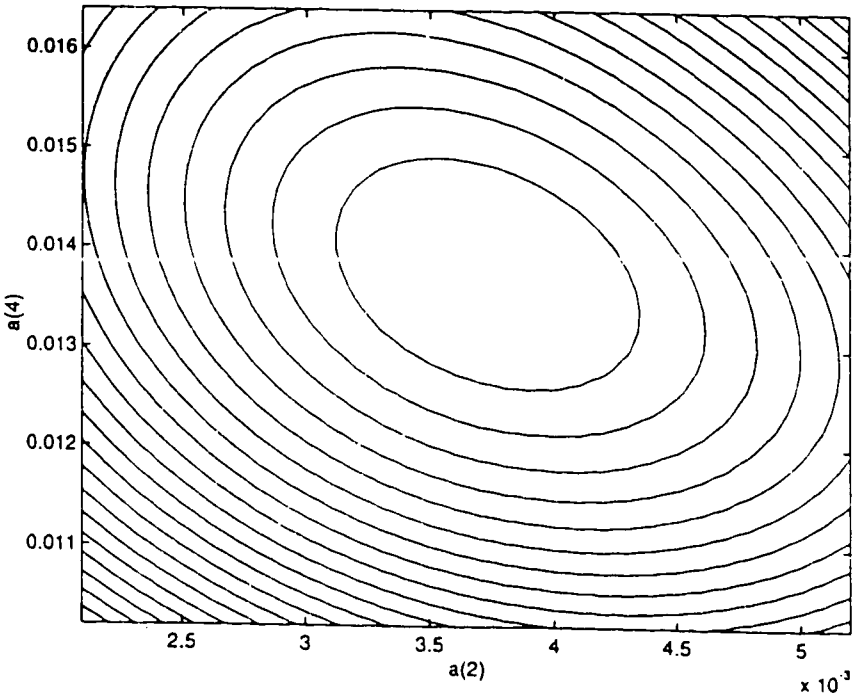


Figure 4.17 Contour Plot of a(2) and a(5) with other parameters fixed for subject 2

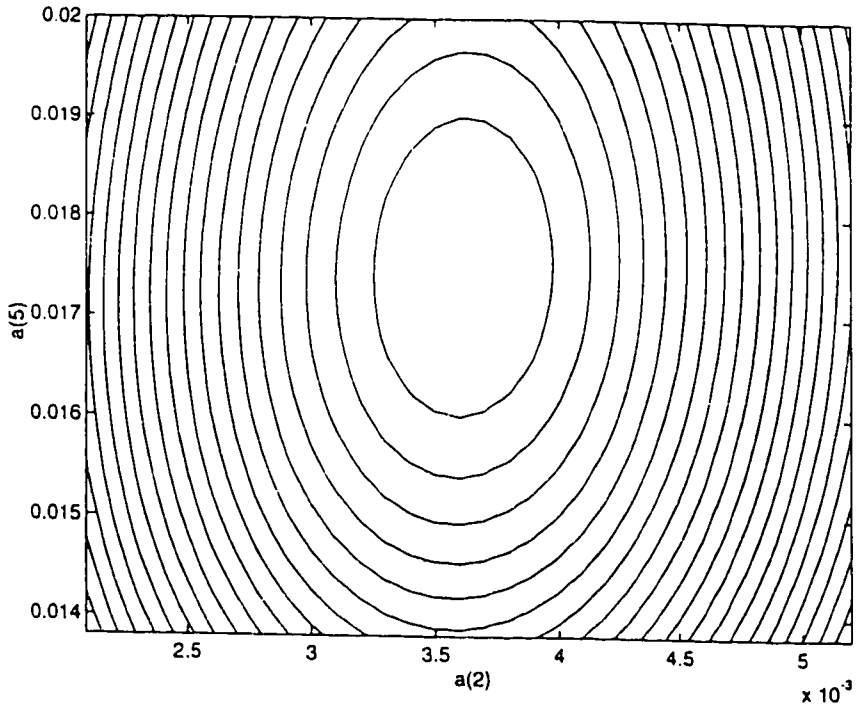


Figure 4.18 Contour Plot of a(2) and a(6) with other parameters fixed for subject 2

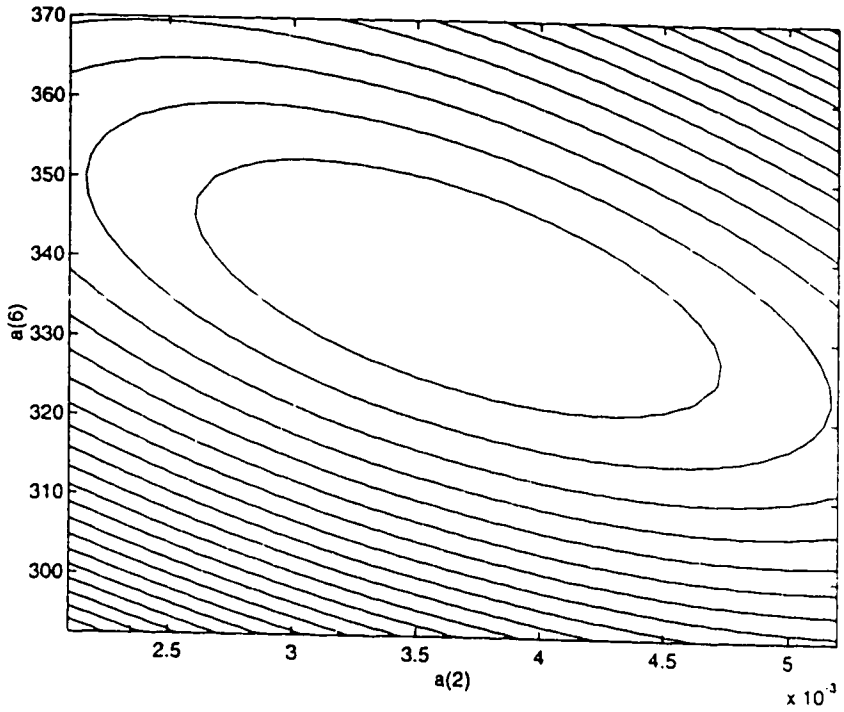


Figure 4.19 3-D Plot of a(3) and a(4) with other parameters fixed for subject 2

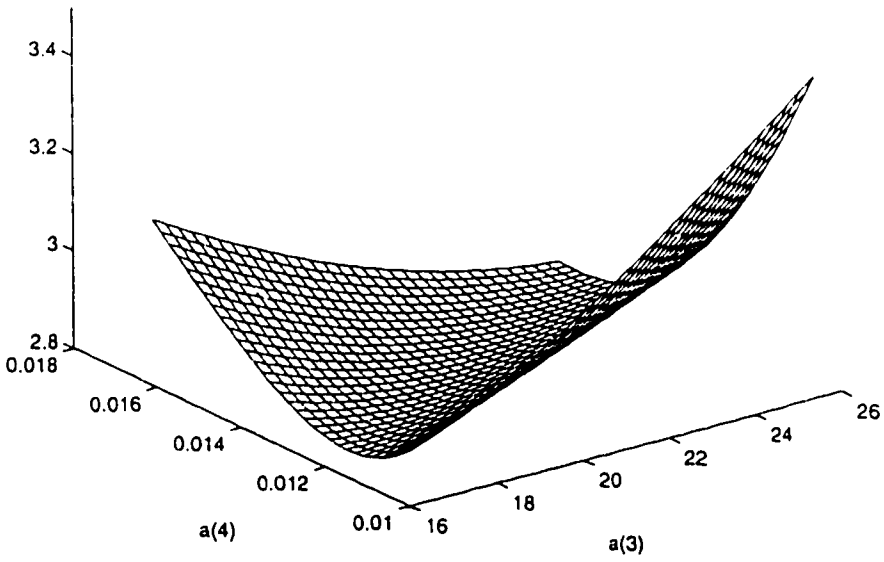


Figure 4.20 Contour Plot of a(3) and a(5) with other parameters fixed for subject 2

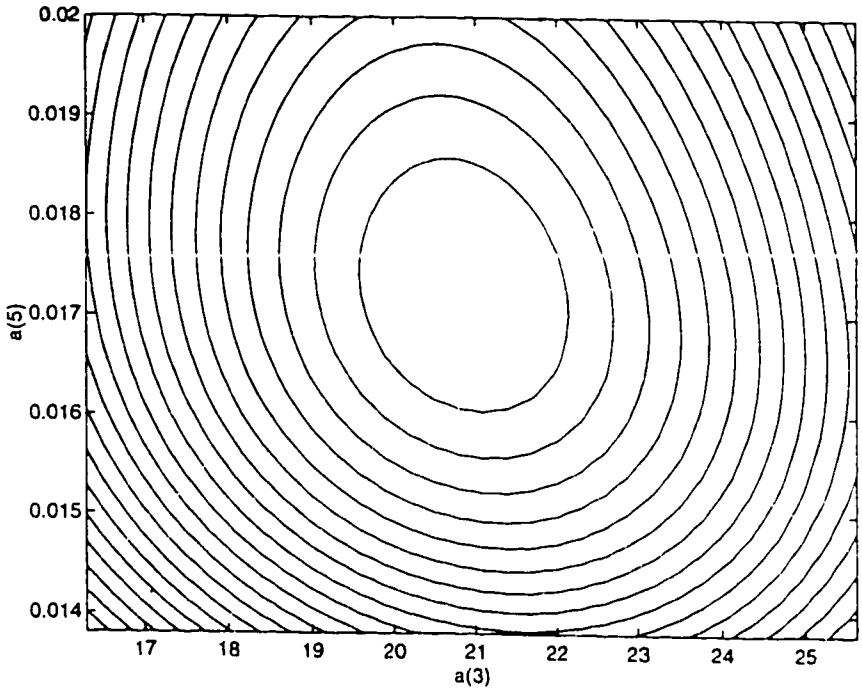


Figure 4.21 Contour Plot of a(3) and a(6) with other parameters fixed for subject 2

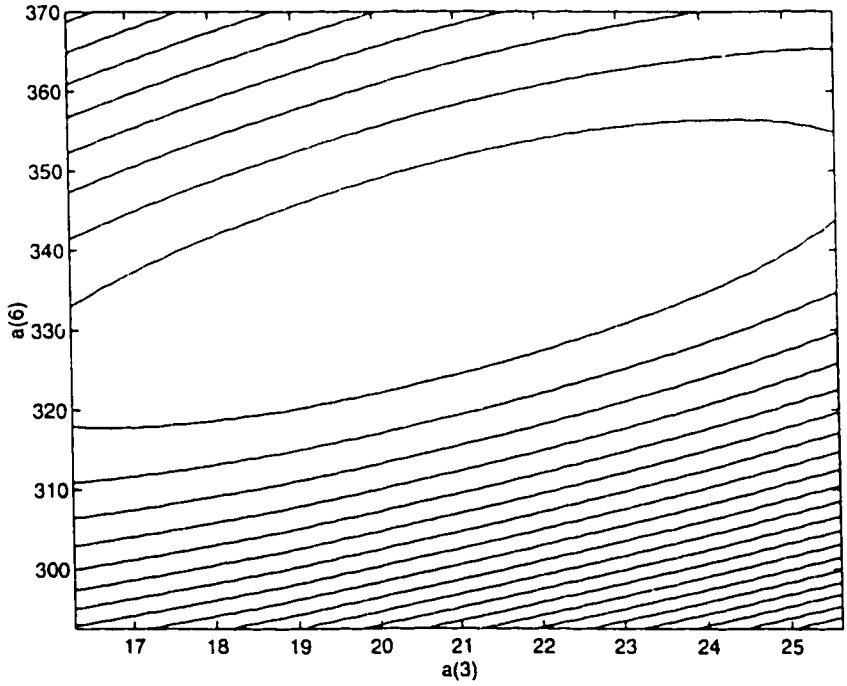


Figure 4.22 Contour Plot of a(4) and a(5) with other parameters fixed for subject 2

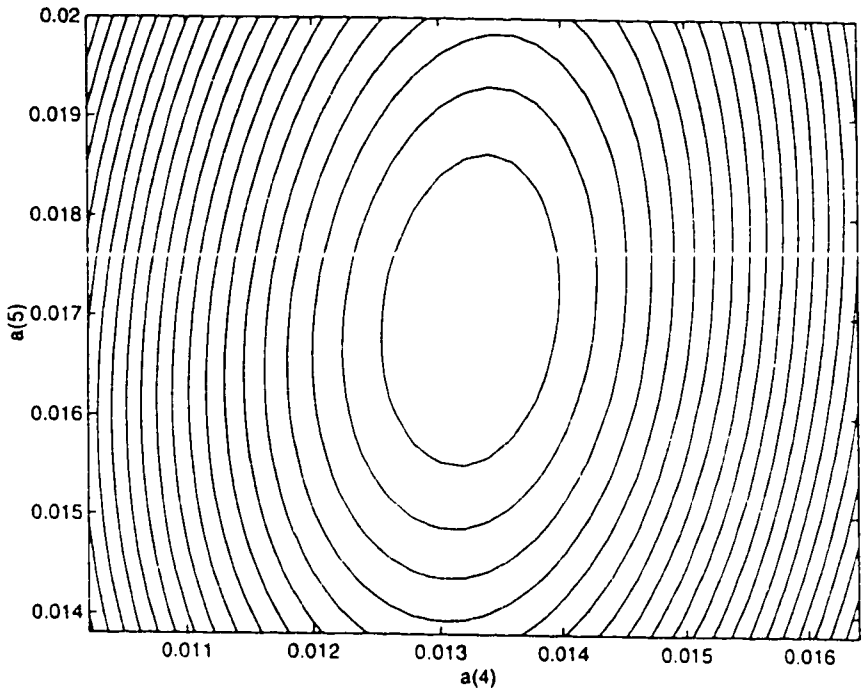


Figure 4.23 Contour Plot of a(4) and a(6) with other parameters fixed for subject 2

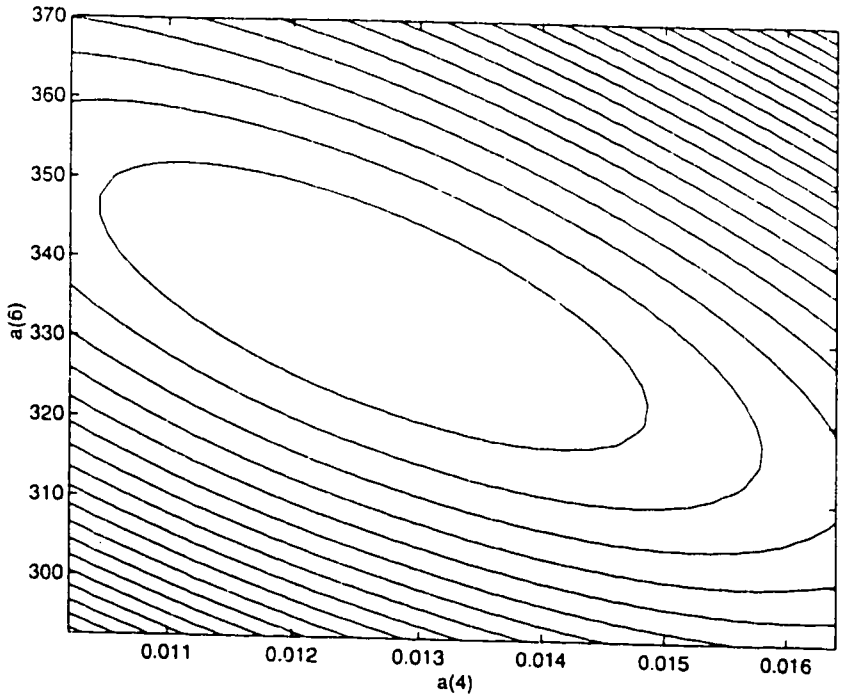


Figure 4.24 Contour Plot of a(5) and a(6) with other parameters fixed for subject 2

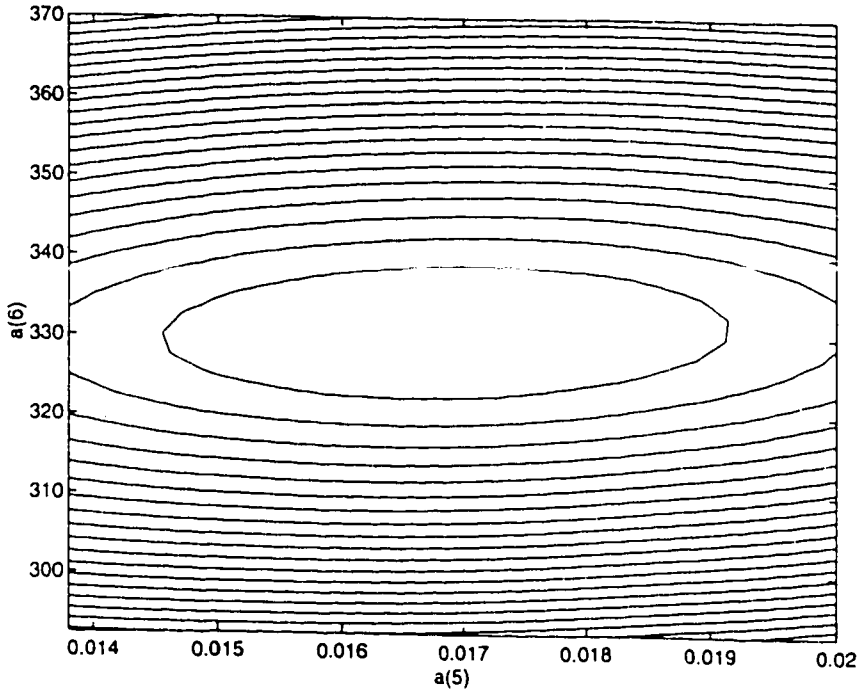


Figure 4.25 3-D Plot of a(1) and a(2) with other parameters fixed for subject 11

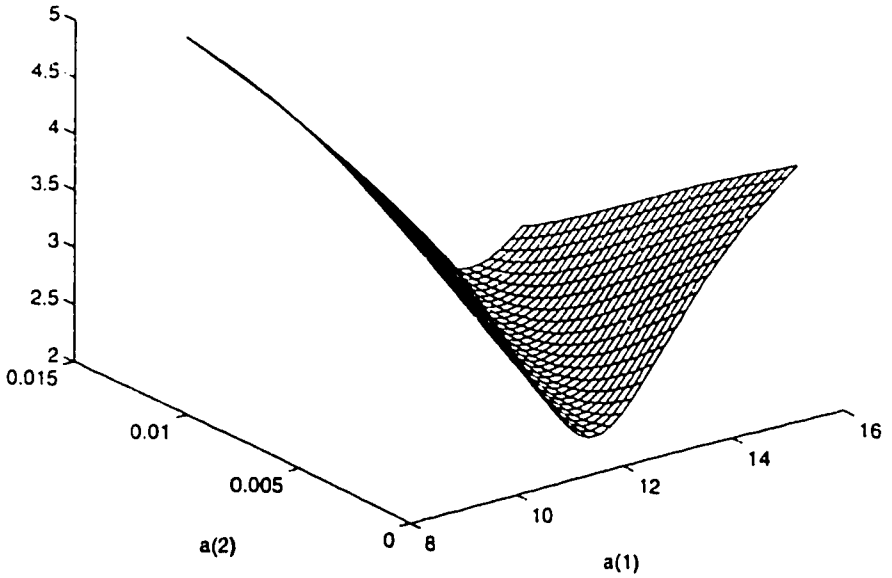


Figure 4.26 Contour Plot of a(1) and a(3) with other parameters fixed for subject 11

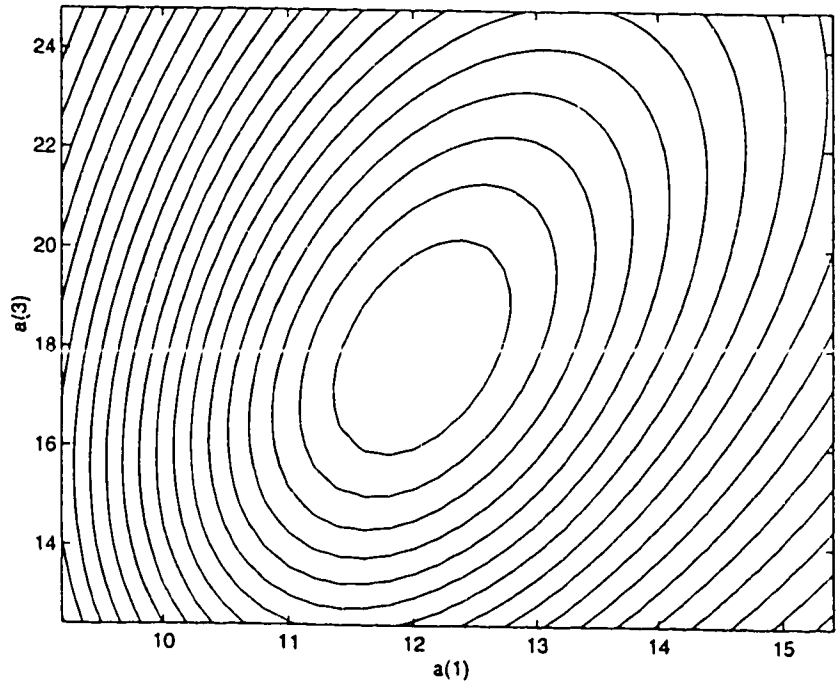


Figure 4.27 Contour Plot of a(1) and a(4) with other parameters fixed for subject 11

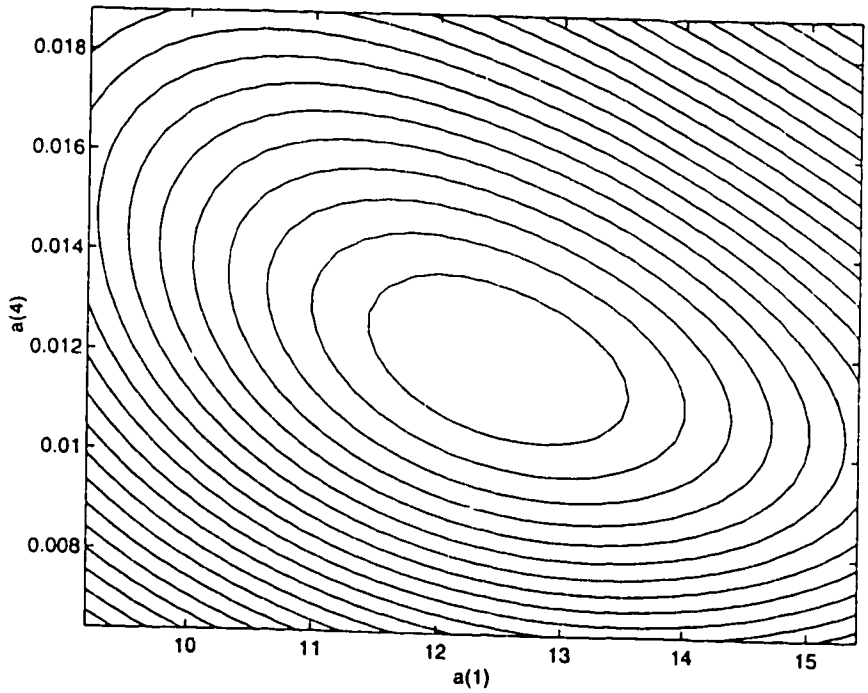


Figure 4.28 Contour Plot of a(1) and a(5) with other parameters fixed for subject 11

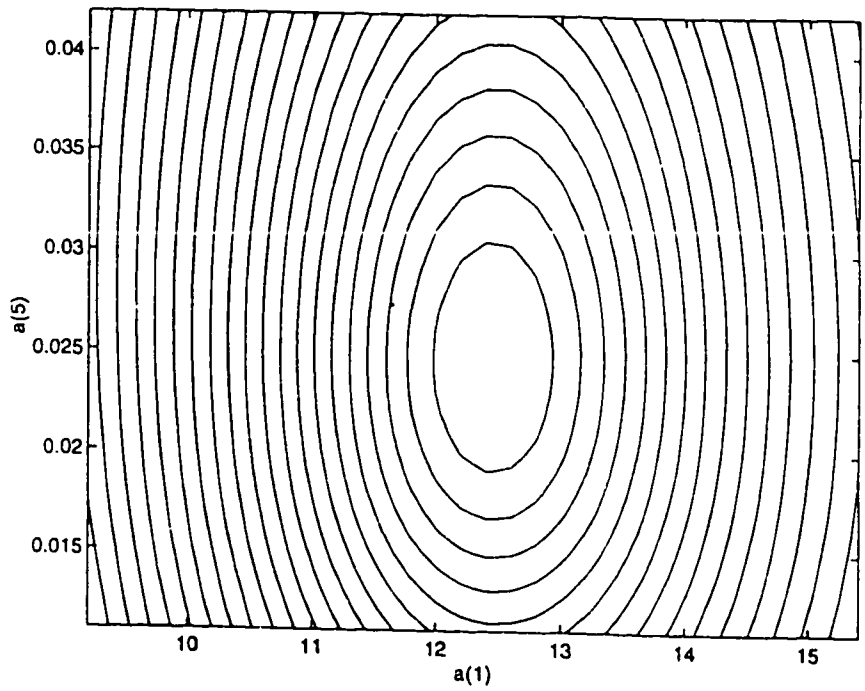


Figure 4.29 Contour Plot of a(1) and a(6) with other parameters fixed for subject 11

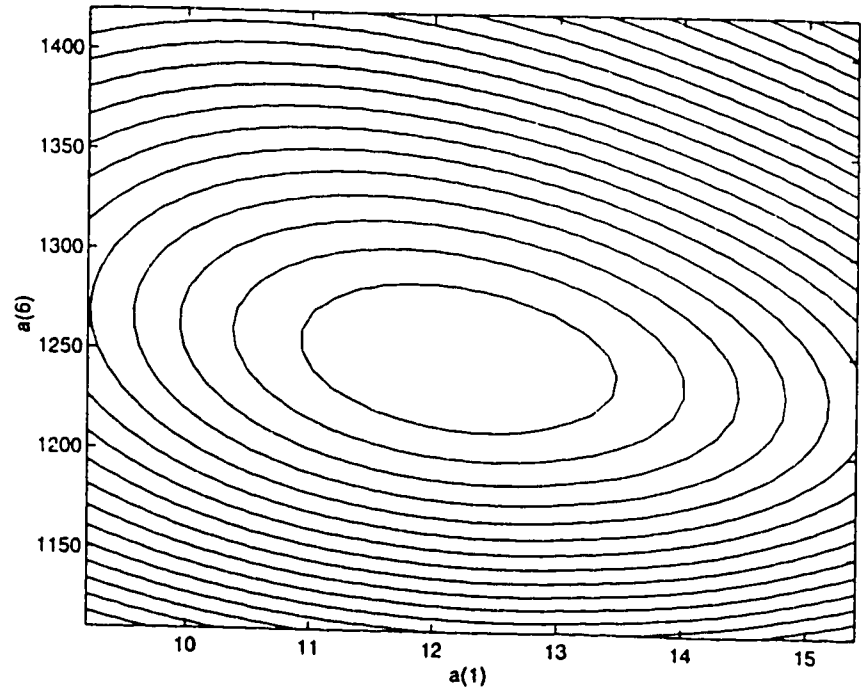


Figure 4.30 Contour Plot of a(2) and a(3) with other parameters fixed for subject 11

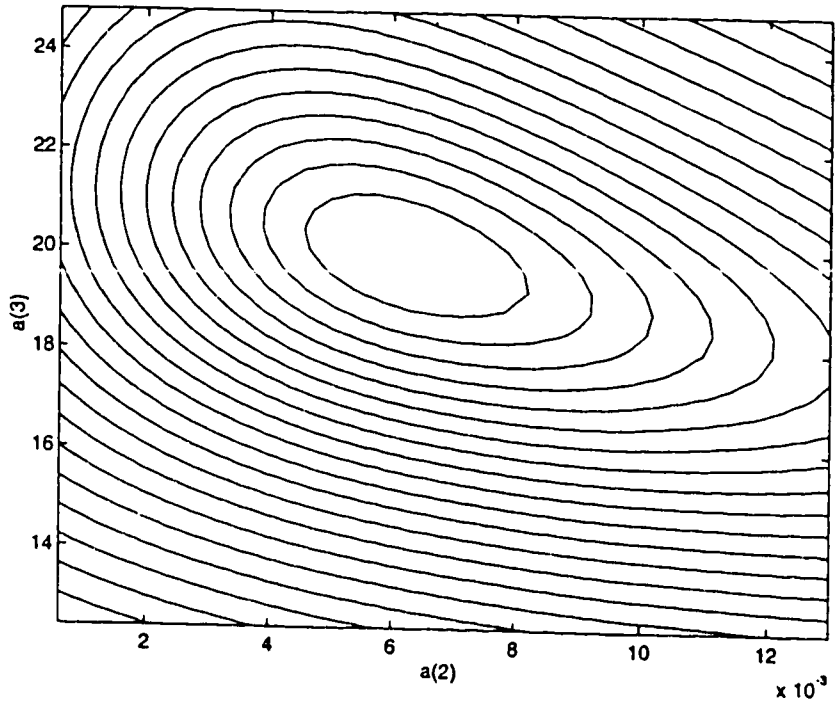


Figure 4.31 Contour Plot of a(2) and a(4) with other parameters fixed for subject 11

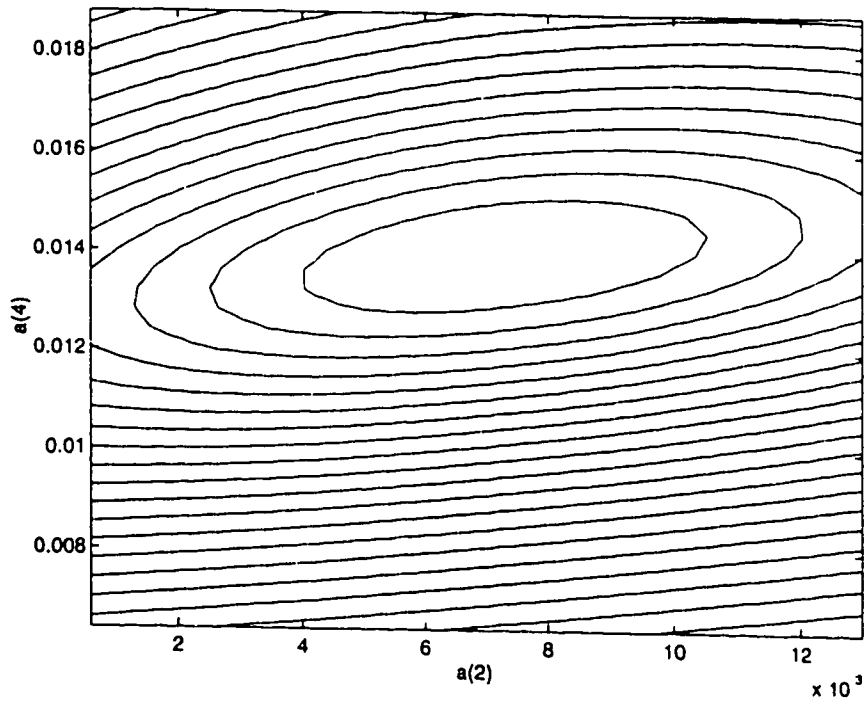


Figure 4.32 Contour Plot of a(2) and a(5) with other parameters fixed for subject 11

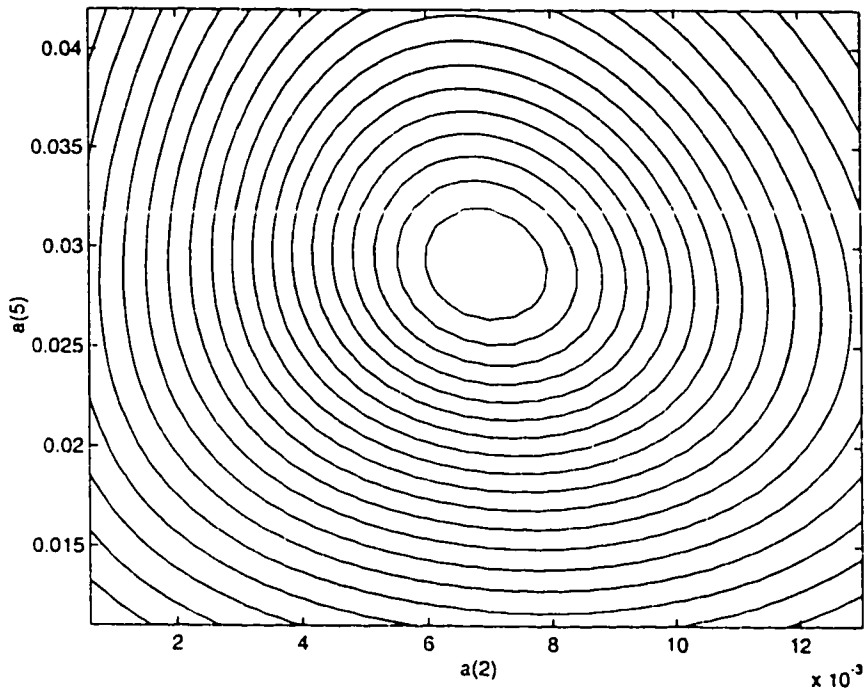


Figure 4.33 Contour Plot of a(2) and a(6) with other parameters fixed for subject 11

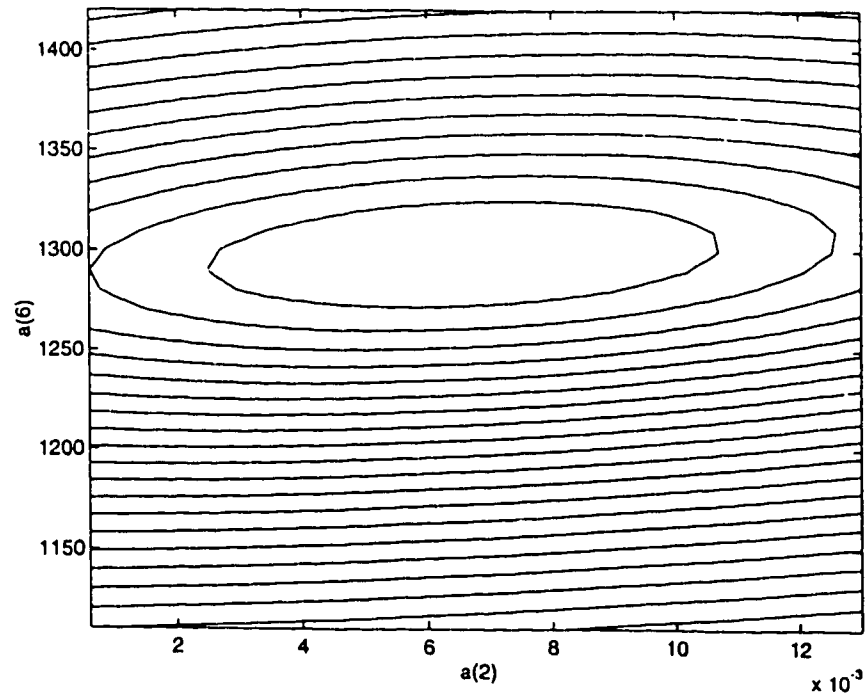


Figure 4.34 3-D Plot of a(3) and a(4) with other parameters fixed for subject 11

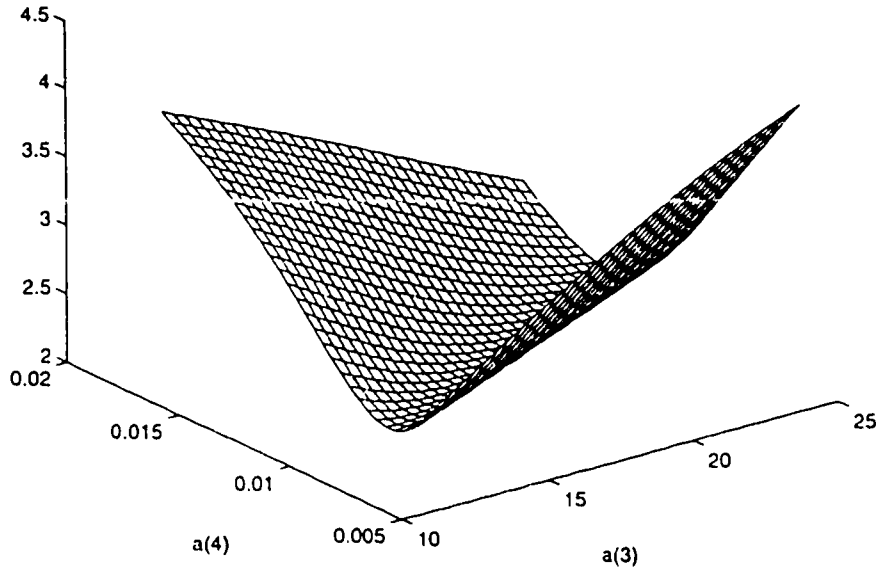


Figure 4.35 Contour Plot of a(3) and a(5) with other parameters fixed for subject 11

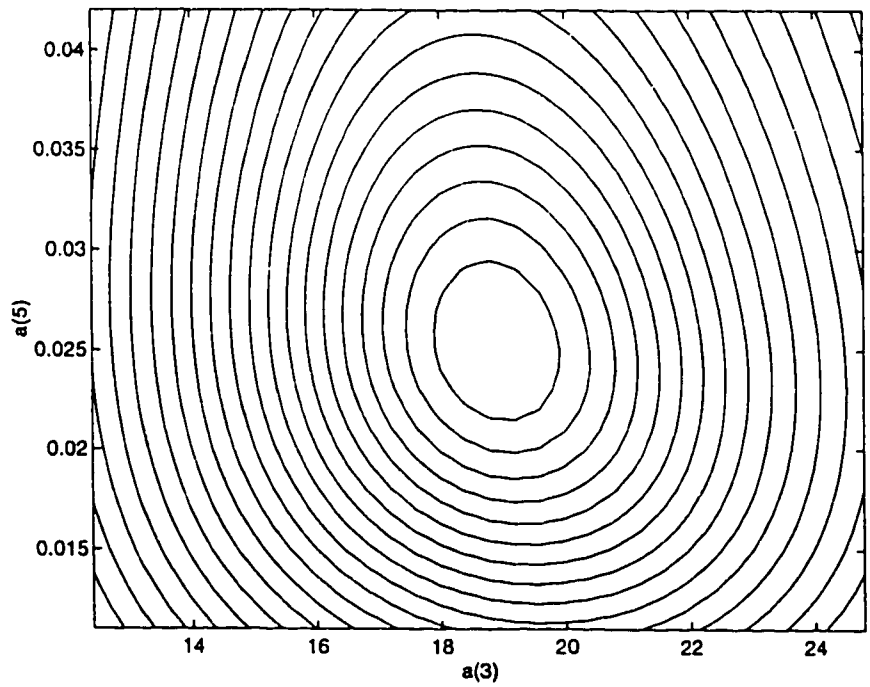


Figure 4.36 Contour Plot of a(3) and a(6) with other parameters fixed for subject 11

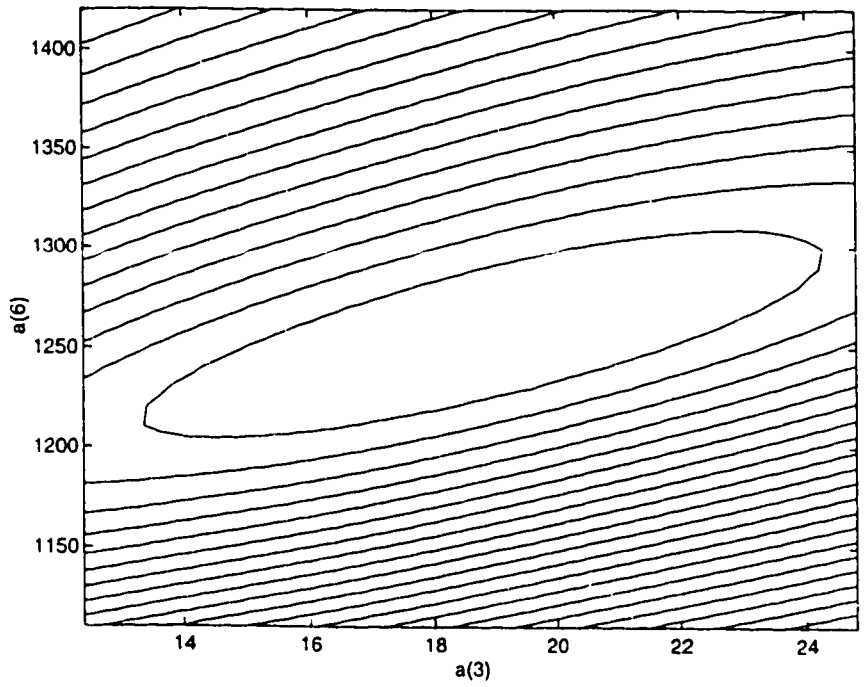


Figure 4.37 Contour Plot of a(4) and a(5) with other parameters fixed for subject 11

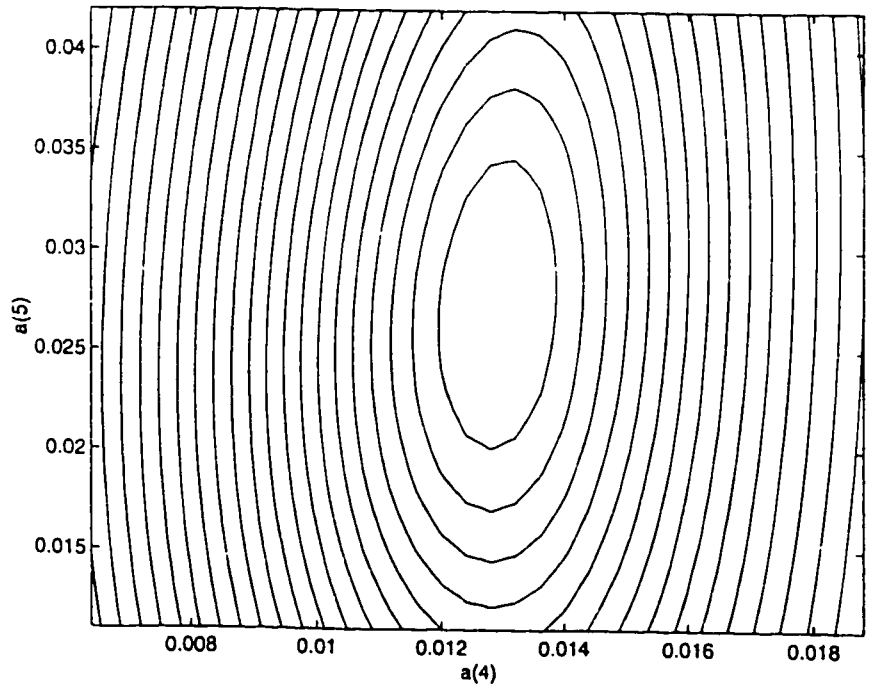


Figure 4.38 Contour Plot of a(4) and a(6) with other parameters fixed for subject 11

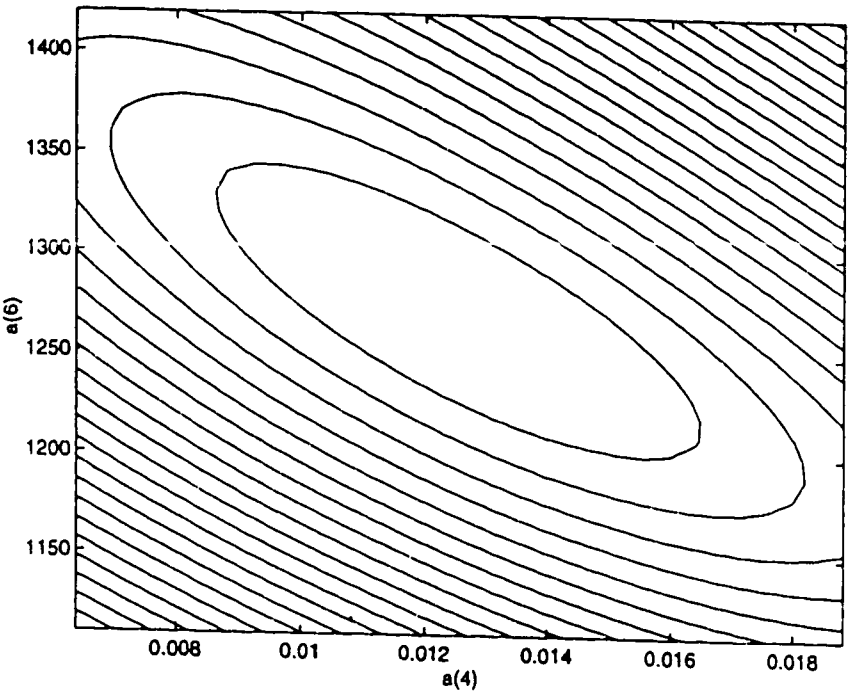


Figure 4.39 Contour Plot of a(5) and a(6) with other parameters fixed for subject 11

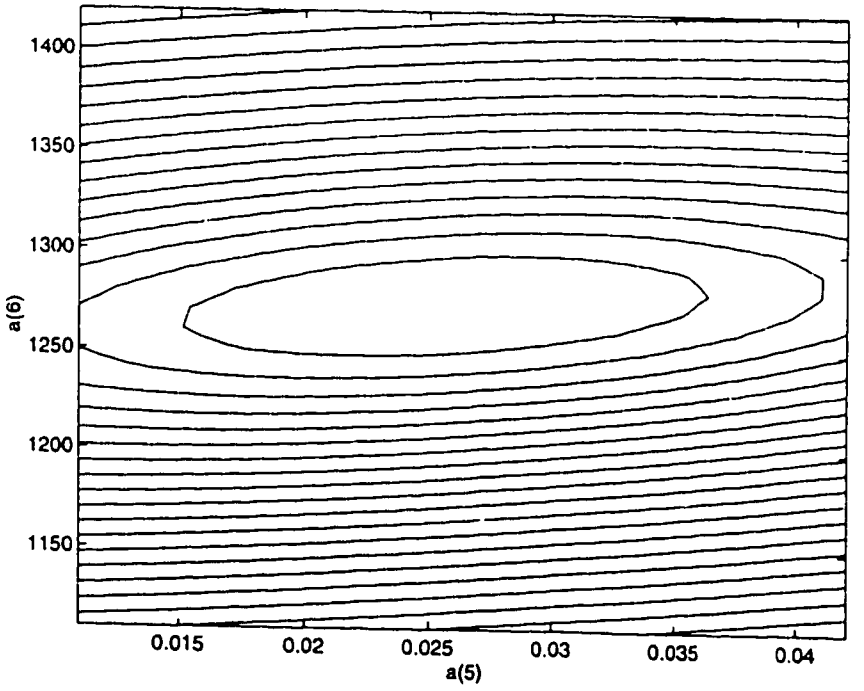


Figure 4.40 Probability Plot of a(1) and a(3) with other parameters fixed for subject 2

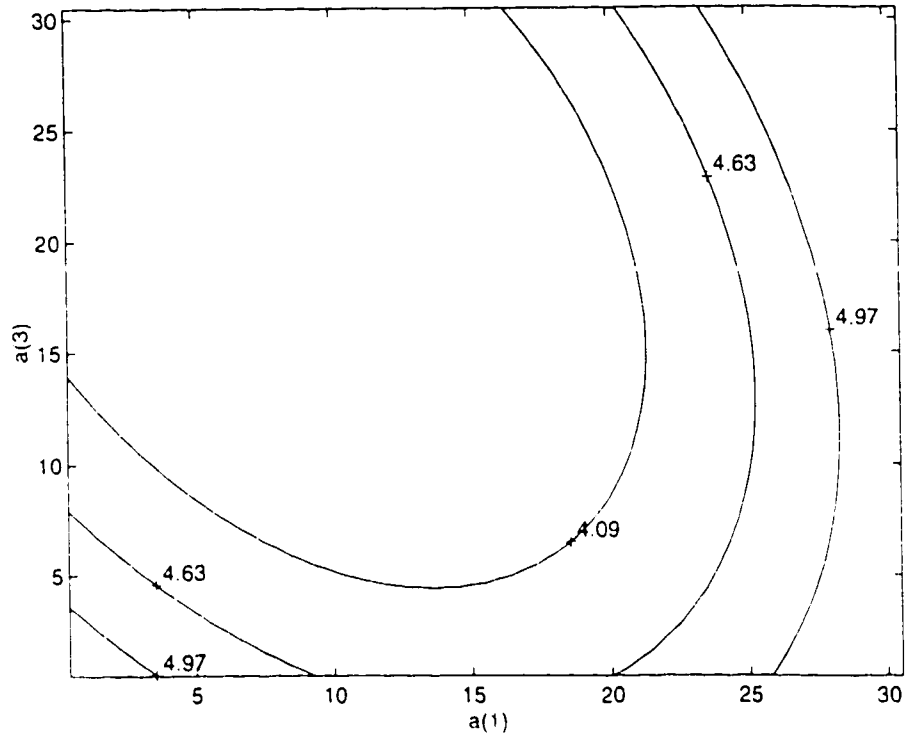


Figure 4.41 Probability Plot of a(2) and a(4) with other parameters fixed for subject 2

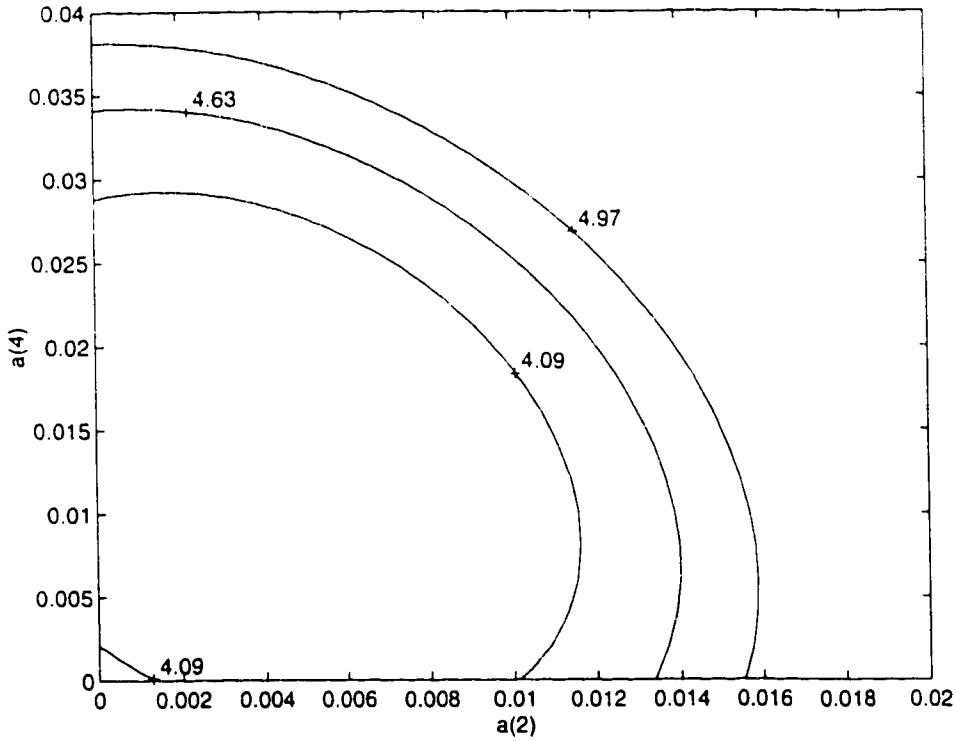


Figure 4.42 Probability Plot of a(1) and a(3) with other parameters fixed for subject 11

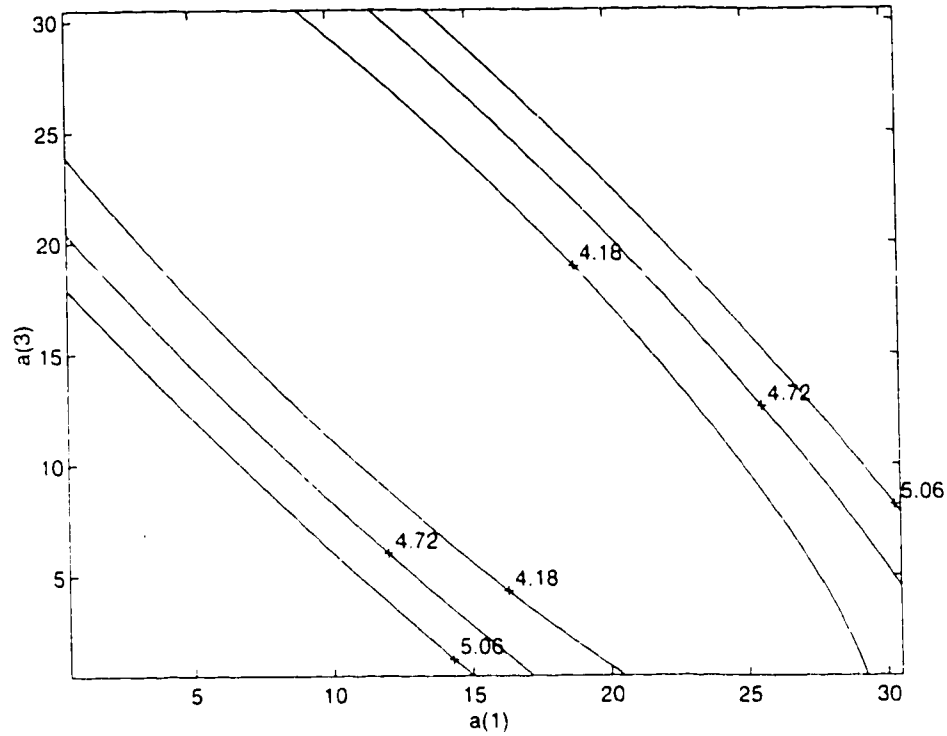
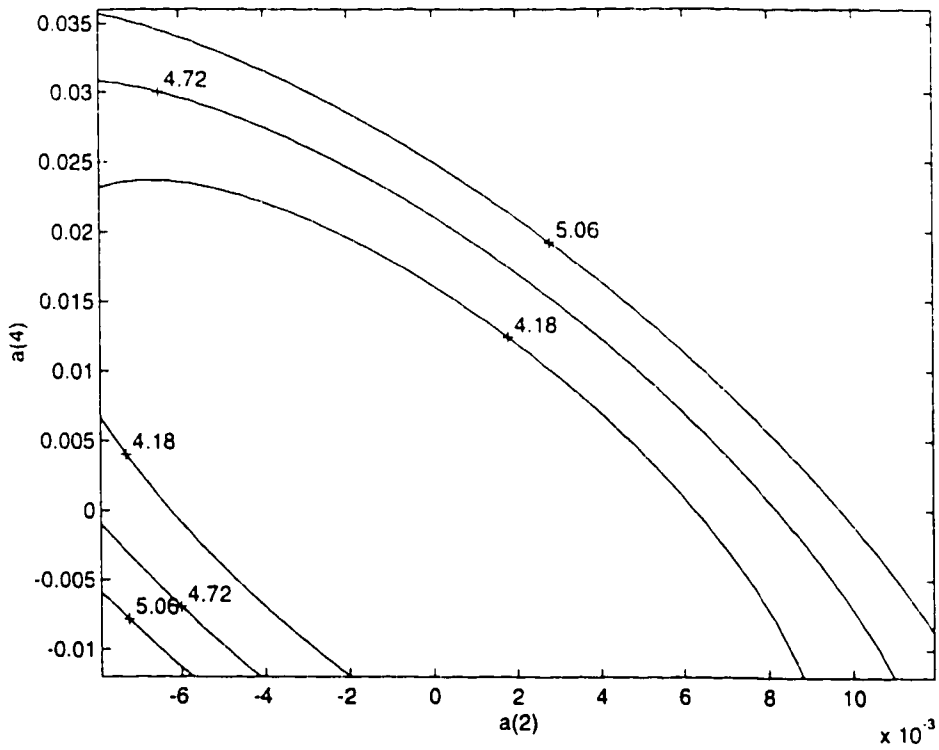


Figure 4.43 Probability Plot of a(2) and a(4) with other parameters fixed for subject 11



```
/*************************************************************************/
/*      This program was written in C as a grid search for examining the starting      */
/*   values of parameters in Nonlinear Least Squares with weights for Person 3.       */
/*      There are many steps to search the parameters at different ranges in order     */
/*   to find proper starting values, which closely satisfy the minimum sum of         */
/*   square of the functions. Both rough and fine steps of search were applied.       */
/*      The results of the grid search for person 3 are as follows:                    */
/*   a[1]=2 a[2]=0.0002 a[3]=22.4 a[4]=0.0119 a[5]=0.018 a[6]=270.7                   */
/*   Cd_lb=a[1]  Cd_bl=a[2]  Cd_kb=a[3]  Cd_bk=a[4]  Cd_ku=a[5]  R=a[6]  */
/*************************************************************************/


#include <stdio.h>
#include <stdlib.h>
#include <math.h>
#include <conio.h>

#define na   7 /*   a[0] was not used              */
#define nt   10 /*  The number of observations  */
#define nu   4 /*   The number of responses     */

double e1, e2, e3;
double pi=3.14159265358979;
int t[nt]={0, 2, 7, 15, 27, 54, 64, 76, 100, -9};
double u[nu][nt]=
  {28.88, 27.04, 31.72, 28.08, 16.64, 19.76,  8.84,  18.2,  10.4, 29.64,
   11900,    0,    0,    0,    0,    0,    0, 13600,    0,    0,
   24000,    0,    0,    0,    0,    0,    0, 24000,    0,    0,
  431.43,537.98,372.86,474.06,420.80,372.86,266.33,223.72,229.04,330.25};
float w[nu]={4, 4000, 6000, 72};
double am,an,af,ak,al1,al2,al3,ap,g,h1,h2,h3,r1,r2,r3,s1,s2,s3,t1,t2,t3;
double v1,v2,v3,v4,v5,v6,v7,v8,v9, am1, am2, am3,g1,g2,g3,g4,g5,g6,o;
double f[nu][nt], ah[nu][nt];
int i,j, j0, j1, j2, j3, j4, j5, tm;
```

```
double a[na]={0, 0, 0, 0, 0, 0, 0};
double  y1=28.88, y2=11900, y3=24000;
void savefiles(void);

main() {

  a[1]=.1; a[2]=.0001; a[3]=20.2; a[4]=0.0114; a[5]=0.015; a[6]=195.4;

   for (j5=0; j5 < 5; j5++) {
        a[1]=a[1]+.1;
        a[2]=0.0001;
     for (j4=0; j4 < 10; j4++) {
        a[2]=a[2]+0.0001;
        a[3]=20.2;
     for (j3=0; j3 < 5; j3++) {
        a[3]=a[3]+.1;
        a[4]=0.0114;
     for (j2=0; j2 < 10; j2++) {
        a[4]=a[4]+0.0001;
        a[5]=0.015;
     for (j1=0; j1 < 10; j1++) {
        a[5]=a[5]+0.001;
        a[6]=195.4;
     for (j0=0; j0 < 10; j0++) {
        a[6]=a[6]+.1;

        am=a[1]+a[2]+a[3]+a[4]+a[5];
        an=a[1]*a[4]+a[1]*a[5]+a[2]*a[4]+a[2]*a[5]+a[3]*a[2]+a[3]*a[5];
        ap=a[3]*a[2]*a[5];
        af=-am*am/3.+an;
        g=ap-am*an/3.+2./27.*am*am*am;
        ak=acos(-g/2.*sqrt(-(3./af)*(3./af)*(3./af)));
        h1=2.*sqrt(-af/3.)*cos((ak+2.*pi)/3.);
        h2=2.*sqrt(-af/3.)*cos((ak+4.*pi)/3.);
        h3=2.*sqrt(-af/3.)*cos((ak+6.*pi)/3.);
        al1=h1-am/3.;
        al2=h2-am/3.;
        al3=h3-am/3.;
```

```
        r1 = a[1]/(a[2]+al1);
        r2 = a[1]/(a[2]+al2);
        r3 = a[1]/(a[2]+al3);
        s1 = a[3]/(a[4]+a[5]+al1);
        s2 = a[3]/(a[4]+a[5]+al2);
        s3 = a[3]/(a[4]+a[5]+al3);
        t1 = sqrt(1.+r1*r1+s1*s1);
        t2 = sqrt(1.+r2*r2+s2*s2);
        t3 = sqrt(1.+r3*r3+s3*s3);

        v1 = 1./t1;   v2 = 1./t2;   v3 = 1./t3;
        v4 = r1/t1;   v5 = r2/t2;   v6 = r3/t3;
        v7 = s1/t1;   v8 = s2/t2;   v9 = s3/t3;

        for(i=0; i < nt; i++) {

         am1 = al1*t[i];  am2 = al2*t[i];      am3 = al3*t[i];
         e1 = expl(am1);  if( t[i] < 0)  e1=1.;
         e2 = expl(am2);  e3 = expl(am3);

    g1=y1*v1*e1*v5*v9-y1*v1*e1*v6*v8-y1*v2*e2*v4*v9+y1*v2*e2*v6*v7+
        y1*v3*e3*v4*v8-y1*v3*e3*v5*v7-y2*v1*e1*v2*v9+y2*v1*e1*v3*v8+
        y2*v2*e2*v1*v9-y2*v2*e2*v3*v7-y2*v3*e3*v1*v8+y2*v3*e3*v2*v7+
        y3*v1*e1*v2*v6-y3*v1*e1*v3*v5-y3*v2*e2*v1*v6+
        y3*v2*e2*v3*v4+y3*v3*e3*v1*v5-y3*v3*e3*v2*v4;

    g4=a[2]*a[3]*v3*e3*v2*v4+a[1]*v3*e3*v1*v8*a[5]-a[1]*v3*e3*v2*
        v7*a[4]-a[1]*v3*e3*v2*v7*a[5]-a[2]*a[3]*v1*e1*v2*v6+
        a[2]*a[3]*v1*e1*v3*v5+a[2]*a[3]*v2*e2*v1*v6-a[2]*a[3]*v2*
        e2*v3*v4-a[2]*a[3]*v3*e3*v1*v5-a[1]*v1*e1*v3*v8*a[4]-
        a[1]*v1*e1*v3*v8*a[5];

/* f[0][i] is an expectation function of Cd_b at t[i]  */

    f[0][i]=g1/(v1*v5*v9-v1*v6*v8-v4*v2*v9+v4*v3*v8+v7*v2*v6-
        v7*v3*v5)+(g4+a[1]*v1*e1*v2*v9*a[4]+a[1]*v1*e1*v2*v9*a[5]-
        a[1]*v2*e2*v1*v9*a[4]-a[1]*v2*e2*v1*v9*a[5]+a[1]*v2*e2*v3*
        v7*a[4]+a[1]*v2*e2*v3*v7*a[5]+a[1]*v3*e3*v1*v8*a[4]-
        a[2]*v3*e3*v4*v8*a[5]+a[2]*v3*e3*v5*v7*a[4]+a[2]*v3*e3*v5*v7*
        a[5]-a[2]*v3*e3*v4*v8*a[4]+a[2]*v2*e2*v4*v9*a[4]+a[2]*v2*e2*
```

```
v4*v9*a[5]-a[2]*v2*e2*v6*v7*a[4]-a[2]*v2*e2*v6*v7*a[5]-
a[2]*v1*e1*v5*v9*a[4]-a[2]*v1*e1*v5*v9*a[5]+a[2]*v1*e1*v6*v8*
a[4]+a[2]*v1*e1*v6*v8*a[5]-a[2]*v4*v2*v9*a[5]+a[2]*v4*v3*v8*
a[4]+a[2]*v4*v3*v8*a[5]+a[2]*v7*v2*v6*a[4]+a[2]*v7*v2*v6*a[5]-
a[2]*v7*v3*v5*a[4]-a[2]*v7*v3*v5*a[5]+a[2]*v1*v5*v9*a[4]+
a[2]*v1*v5*v9*a[5]-a[2]*v1*v6*v8*a[4]-a[2]*v1*v6*v8*a[5]-
a[2]*v4*v2*v9*a[4])/(v1*v5*v9-v1*v6*v8-v4*v2*v9+v4*v3*v8+
v7*v2*v6-v7*v3*v5)/a[2]/a[3]/a[5]*a[6];

g2=-y1*v4*e1*v5*v9+y1*v4*e1*v6*v8+y1*v5*e2*v4*v9-y1*v5*e2*v6*
v7-y1*v6*e3*v4*v8+y1*v6*e3*v5*v7+y2*e1*v4*v2*v9-y2*e1*v4*v3*
v8-y2*v5*e2*v1*v9+y2*v5*e2*v3*v7+y2*v6*e3*v1*v8-y2*v6*e3*v2*
v7-y3*v4*e1*v2*v6+y3*v4*e1*v3*v5+y3*v5*e2*v1*v6-y3*v5*e2*v3*
v4-y3*v6*e3*v1*v5+y3*v6*e3*v2*v4;

g5=a[2]*v4*e1*v5*v9*a[4]+a[2]*v4*e1*v5*v9*a[5]-a[2]*v4*e1*v6*
v8*a[4]-a[2]*v4*e1*v6*v8*a[5]-a[2]*v5*e2*v4*v9*a[4]-
a[2]*v5*e2*v4*v9*a[5]+a[2]*v5*e2*v6*v7*a[4]+a[2]*v5*e2*v6*
v7*a[5]+a[2]*v6*e3*v4*v8*a[4]+a[2]*v6*e3*v4*v8*a[5]-
a[2]*v6*e3*v5*v7*a[4];

/* f[1][i] is an expectation function of Cd_1 at t[i]  */

f[1][i]=-g2/(v1*v5*v9-v1*v6*v8-v4*v2*v9+v4*v3*v8+v7*v2*v6-
v7*v3*v5)-(g5-a[2]*v6*e3*v5*v7*a[5]-a[1]*e1*v4*v2*v9*a[4]-
a[1]*e1*v4*v2*v9*a[5]+a[1]*e1*v4*v3*v8*a[4]+a[1]*e1*v4*v3*
v8*a[5]+a[1]*v5*e2*v1*v9*a[4]+a[1]*v5*e2*v1*v9*a[5]-
a[1]*v5*e2*v3*v7*a[4]-a[1]*v5*e2*v3*v7*a[5]-a[1]*v6*e3*v1*
v8*a[4]-a[1]*v6*e3*v1*v8*a[5]+a[1]*v6*e3*v2*v7*a[4]+a[1]*
v6*e3*v2*v7*a[5]+a[2]*a[3]*v4*e1*v2*v6-a[2]*a[3]*v4*e1*v3*
v5-a[2]*a[3]*v5*e2*v1*v6+a[2]*a[3]*v5*e2*v3*v4+a[2]*a[3]*
v6*e3*v1*v5-a[2]*a[3]*v6*e3*v2*v4+a[1]*v7*v3*v5*a[4]+a[1]*
v7*v3*v5*a[5]-a[1]*v1*v5*v9*a[4]-a[1]*v1*v5*v9*a[5]+a[1]*
v1*v6*v8*a[4]+a[1]*v1*v6*v8*a[5]+a[1]*v4*v2*v9*a[4]+a[1]*
v4*v2*v9*a[5]-a[1]*v4*v3*v8*a[4]-a[1]*v4*v3*v8*a[5]-a[1]*
v7*v2*v6*a[4]-a[1]*v7*v2*v6*a[5])/(v1*v5*v9-v1*v6*v8-v4*
v2*v9+v4*v3*v8+v7*v2*v6-v7*v3*v5)/a[2]/a[3]/a[5]*a[6];

g3=y1*v7*e1*v5*v9-y1*v7*e1*v6*v8-y1*v8*e2*v4*v9+y1*v8*e2*v6*v7+
y1*v9*e3*v4*v8-y1*v9*e3*v5*v7-y2*v7*e1*v2*v9+y2*v7*e1*v3*v8+
```

```
        y2*v8*e2*v1*v9-y2*v8*e2*v3*v7-y2*v9*e3*v1*v8+y2*v9*e3*v2*v7+
        y3*e1*v7*v2*v6-y3*e1*v7*v3*v5-y3*v8*e2*v1*v6+y3*v8*e2*v3*v4+
        y3*v9*e3*v1*v5-y3*v9*e3*v2*v4;

      g6=-a[2]*a[3]*v9*e3*v2*v4+a[2]*a[3]*v1*v6*v8+a[2]*a[3]*v4*v2*v9-
        a[2]*a[3]*v4*v3*v8-a[2]*a[3]*v7*v2*v6-a[2]*a[3]*v1*v5*v9+
        a[2]*a[3]*v7*v3*v5+a[2]*v8*e2*v6*v7*a[4]+a[2]*v8*e2*v6*v7*
        a[5]-a[2]*v8*e2*v4*v9*a[4];

/* f[2][i] is an expectation function of Cd_k at t[i]  */

      f[2][i]=g3/(v1*v5*v9-v1*v6*v8-v4*v2*v9+v4*v3*v8+v7*v2*v6-
        v7*v3*v5)-(g6-a[2]*v8*e2*v4*v9*a[5]-a[2]*v7*e1*v6*v8*a[4]-
        a[2]*v7*e1*v6*v8*a[5]+a[2]*v7*e1*v5*v9*a[4]+a[2]*v7*e1*v5*
        v9*a[5]-a[2]*v9*e3*v5*v7*a[5]-a[2]*v9*e3*v5*v7*a[4]+a[2]*
        v9*e3*v4*v8*a[4]+a[2]*v9*e3*v4*v8*a[5]+a[1]*v9*e3*v2*v7*
        a[4]+a[1]*v9*e3*v2*v7*a[5]-a[1]*v9*e3*v1*v8*a[5]-a[1]*v9*
        e3*v1*v8*a[4]-a[1]*v8*e2*v3*v7*a[5]+a[1]*v8*e2*v1*v9*a[5]-
        a[1]*v8*e2*v3*v7*a[4]+a[1]*v7*e1*v3*v8*a[5]+a[1]*v8*e2*v1*
        v9*a[4]+a[1]*v7*e1*v3*v8*a[4]-a[1]*v7*e1*v2*v9*a[4]-a[1]*
        v7*e1*v2*v9*a[5]-a[2]*a[3]*v8*e2*v1*v6+a[2]*a[3]*v8*e2*v3*
        v4+a[2]*a[3]*v9*e3*v1*v5-a[2]*a[3]*e1*v7*v3*v5+a[2]*a[3]*
        e1*v7*v2*v6)/(v1*v5*v9-v1*v6*v8-v4*v2*v9+v4*v3*v8+v7*
        v2*v6-v7*v3*v5)/a[2]/a[3]/a[5]*a[6];

/* f[3][i] is an expectation function of Cd_u at t[i]  */

      f[3][i]=a[5]*f[2][i];
  }

  o=0;  /* set initial iteration zero  */

  for(i=0; i<nu; i++) {
   for(j=0; j<nt; j++) {
      if(u[i][j]<0.0001)
        f[i][j] = u[i][j];
      ah[i][j] = (f[i][j]-u[i][j])*(f[i][j]-u[i][j])/w[i]/w[i];
      o = o+ah[i][j];
   }
  }
```

```
   if(o<27.28) {
     printf("%5.2f %6.4f %5.2f %6.4f %6.4f %5.2f
                              %7.4f\n",a[1],a[2],a[3],a[4],a[5],a[6],o);
    savefiles();
  }
 }
 }
 }
 }
 }
 }
return(0);
}

void savefiles(void)
{
 FILE *outdata;
 if((outdata=fopen("pson03.dat","a")) != NULL)
 {  fprintf(outdata,"%5.2f %6.4f %5.2f %6.4f %6.4f %5.2f %7.4f\n",
                      a[1],a[2],a[3],a[4],a[5],a[6],o);
    fclose(outdata);
 }
 return;
}
```

```
% This program was written in MATLAB for generating contour plots to verify the
% convergence of the results from the non-linear equations

function o=expect(a)
%  This is for PERSON ALL
%  c_bl=a(1), c_lb=a(2), c_bk=a(3), c_kb=a(4), c_ku=a(5), R=a(6), Ck=a(7);

%      [-((a(1)+a(3))   a(2)          a(4)  ]
%  A=[       a(1)      -a(2)           0    ]
%      [       a(3)        0   -(a(4)+a(5))]

%      [a(6)]
%  B=[  0  ]
%      [  0  ]

%  F(4,:)=a(5).*F(3,:)     F(4,:)=a(7).*F(3,:)

% V is a 3x3 eigen vector matrix;

% VI is inverse of V;

% E is an eigen value matrix;

% Y0 is an initial value vector for observations;

% S is vector of solutions of a system of differential equations;


y1=38; y2=37400; y3=42000;
% y1, y2 and y3 are initial values

nt=12;
% nt is numbers of observations

a(1)=8.725;    a(2)=0.00388;   a(3)= 21.725;
a(4)=0.012945;  a(5)=0.01686;   a(6)=325.026;

for k1=1:32
 a(5)=0.0136+0.0002*k1;
for k2=1:32
 a(6)=290+2.5*k2;

 w = [8; 4000; 6000; 128];
```

```
t = [0; 2; 7; 15; 27; 40; 54; 64; 76; 100; -4; -9];
u = [y1 45.24  37.44 14.04 22.88 25.48 32.76 24.44 29.12 26.0 41.6 39.9;
   y2   0    0    0    0    0    0    0  44200   0  0    0;
   y3   0    0    0    0    0    0    0  24000   0  0    0;
   696.56 686.66 548.26 601.49 484.39 212.92 479.06 511 314.05 479.06
   819.73 851.67];

A=[-(a(1)+a(3)),a(2),a(4);a(1),-a(2),0;a(3),0,-(a(4)+a(5))];
B=[a(6);0;0];

m=a(1)+a(2)+a(3)+a(4)+a(5);
n=a(1).*a(4)+a(1).*a(5)+a(2).*a(4)+a(2).*a(5)+a(3).*a(2)+a(3).*a(5);
p=a(3).*a(2).*a(5);   f=-m^2./3+n;
g=p-m.*n./3+2./27.*m^3;
k=acos(-g./2.*sqrt(-(3./f)^3));
h1=2.*sqrt(-f./3).*cos((k+2.*pi)./3);
h2=2.*sqrt(-f./3).*cos((k+4.*pi)./3);
h3=2.*sqrt(-f./3).*cos((k+6.*pi)./3);
l1=h1-m./3; l2=h2-m./3; l3=h3-m./3;
delta=(g./2)^2+(f./3)^3;
r1=a(1)./(a(2)+l1); s1=a(3)./(a(4)+a(5)+l1); t1=sqrt(1+r1^2+s1^2);
r2=a(1)./(a(2)+l2); s2=a(3)./(a(4)+a(5)+l2); t2=sqrt(1+r2^2+s2^2);
r3=a(1)./(a(2)+l3); s3=a(3)./(a(4)+a(5)+l3); t3=sqrt(1+r3^2+s3^2);
V=[1./t1,1./t2,1./t3;r1./t1,r2./t2,r3./t3;s1./t1,s2./t2,s3./t3];
VI=inv(V);

for j=1:nt
 if t(j) > 0
  e1=exp(l1.*t(j));
 else
  e1=1;
 end
 e2=exp(l2.*t(j)); e3=exp(l3.*t(j));
 E=[e1,0,0;0,e2,0;0,0,e3];
 Y0=[y1;y2;y3]; I=eye(3); AI=inv(A);
 S=V*E*VI*Y0+(V*E*VI-I)*AI*B;
 F(1,j)=S(1);
 F(2,j)=S(2);
 F(3,j)=S(3);
 F(4,j)=a(5).*S(3);
```

```
end

o=0;

for i=1:4
 for j=1:nt
  if u(i,j) < 0.00001
   u(i,j)=F(i,j);
  end
  o=o+((F(i,j)-u(i,j))/w(i))^2;
 end
end

 d2(k2)=a(6);
 p1(k1,k2)=log(o);
end
 d1(k1)=a(5);
end
 p1
%mesh(d1,d2,p1)
contour(d1,d2,p1,20)
xlabel('a(5)'),ylabel('a(6)'),title ('P2 Plot')
```

```
% The program was written in MATLAB for generating the fitted data for person 3
% The values of parameters are form the results of  nonlinear optimization

function o=expt03(a)

a(1)=.0075; a(2)=.00001; a(3)=29.9925; a(4)=.0257; a(5)=.0185; a(6)=164.5246;

y1=28.88; y2=11900; y3=24000;  /* Initial values */

nt=229;  /*Total fitted points */

for i=1:nt
 t(i)=0.5.*(i-1)-9;
end
m=a(1)+a(2)+a(3)+a(4)+a(5);
n=a(1).*a(4)+a(1).*a(5)+a(2).*a(4)+a(2).*a(5)+a(3).*a(2)+a(3).*a(5);
p=a(3).*a(2).*a(5);    f=-m^2./3+n;
g=p-m.*n./3+2./27.*m^3;
k=acos(-g./2.*sqrt(-(3./f)^3));
h1=2.*sqrt(-f./3).*cos((k+2.*pi)./3);
h2=2.*sqrt(-f./3).*cos((k+4.*pi)./3);
h3=2.*sqrt(-f./3).*cos((k+6.*pi)./3);
l1=h1-m./3;  l2=h2-m./3;  l3=h3-m./3;

r1=a(1)./(a(2)+l1);  s1=a(3)./(a(4)+a(5)+l1);  t1=sqrt(1+r1^2+s1^2);
r2=a(1)./(a(2)+l2);  s2=a(3)./(a(4)+a(5)+l2);  t2=sqrt(1+r2^2+s2^2);
r3=a(1)./(a(2)+l3);  s3=a(3)./(a(4)+a(5)+l3);  t3=sqrt(1+r3^2+s3^2);

v1=1./t1;  v2=1./t2;  v3=1./t3;
v4=r1./t1; v5=r2./t2; v6=r3./t3;
v7=s1./t1; v8=s2./t2; v9=s3./t3;

V=[1./t1,1./t2,1./t3;r1./t1,r2./t2,r3./t3;s1./t1,s2./t2,s3./t3];
VI=inv(V);


for i=1:nt
 if t(i) <= 0
   e1=1;
 else
```

```
  e1=exp(l1.*t(i));
end
e2=exp(l2.*t(i)); e3=exp(l3.*t(i));

 E=[e1,0,0;0,e2,0;0,0,e3];
 Y0=[y1;y2;y3]; I=eye(3); AI=inv(A);
 S=V*E*VI*Y0+(V*E*VI-I)*AI*B;
 F(1,j)=S(1);
 F(2,j)=S(2);
 F(3,j)=S(3);
 F(4,j)=a(5).*S(3);

end

f1=fopen('pson03.dat','w');
for i=1:nt
    fprintf(f1,'%5.1f  %10.3f  %10.3f  %10.3f  %10.3f\n',t(i), F(1,i), F(2,i), F(3,i), F(4,i));
end
  fclose(f1);
```

```
title 'Nonlinear Optimization for Person 3';

/*************************************************************************/
/*       This program was written in SAS/IML for obtaining optimization results      */
/*       from either nonlinear least-squares or bayesian determinant minimization    */
/*                  nlpnra is subroutine of Newton-Raphson Method                     */
/*                                                                                    */
/*************************************************************************/

proc iml;

/*************************************************************************/
/*          func module represents objective function for nonlinear optimization      */
/*           nles is an objective function for nonlinear least-squares estimation     */
/*           dbet is an objective function for nonlinear least-squares estimation     */
/*************************************************************************/

/* A is a transfer coefficient matrix
   B is an input vector
  Y0 is a vector for initial values of responses
 obs is a matrix of observations                                                    */


start func(a) global(t, obs, pi, Y0, w);
 m  = a[1]+a[2]+a[3]+a[4]+a[5];
 n  = a[1]*a[4]+a[1]*a[5]+a[2]*a[4]+a[2]*a[5]+a[3]*a[2]+a[3]*a[5];
 p  = a[3]*a[2]*a[5];   f=-(m**2)/3+n;
 g  = p-m*n/3.+2./27.*m**3;
 k  = arcos(-g/2.*sqrt(-(3./f)**3));
 h1 = 2*sqrt(-f/3)*cos((k+2*pi)/3);
 h2 = 2*sqrt(-f/3)*cos((k+4*pi)/3);
 h3 = 2*sqrt(-f/3)*cos((k+6*pi)/3);
 l1 = h1-m/3; l2=h2-m/3; l3=h3-m/3;
 r1 = a[1]/(a[2]+l1); s1=a[3]/(a[4]+a[5]+l1); tt1=sqrt(1+r1**2+s1**2);
 r2 = a[1]/(a[2]+l2); s2=a[3]/(a[4]+a[5]+l2); tt2=sqrt(1+r2**2+s2**2);
 r3 = a[1]/(a[2]+l3); s3=a[3]/(a[4]+a[5]+l3); tt3=sqrt(1+r3**2+s3**2);
 v=( 1/tt1 || 1/tt2 || 1/tt3 ) //
    (r1/tt1 || r2/tt2 || r3/tt3) //
    (s1/tt1 || s2/tt2 || s3/tt3);
```

```
AMTRIX= ( -(a[1]+a[3]) || a[2] ||          a[4]) //
        (          a[1] || -a[2] ||           0) //
        (          a[3] ||     0 || -(a[4]+a[5]));

B = a[6] // 0 // 0;

I=I(3); VI=inv(V); AI=inv(AMTRIX);

nt=10;
free z1 z2 z3 z4 z5;
do j = 1 to nt;
 if t[j] > 0 then e1=exp(l1*t[j]);
 else  e1=1;
 e2=exp(l2*t[j]); e3=exp(l3*t[j]);

 E=(e1 || 0 || 0 ) // (0 || e2 || 0) // (0 || 0 || e3);

 f1=V*E*VI*Y0 + (V*E*VI-I)*AI*B;

 z1 = z1 || f1;
end;

z2 = (a[5]*z1[3,]);
z3 = z1 // z2;
do i = 1 to 4;
 do j = 1 to nt;
  if abs(obs[i,j]) < 1.e-5 then z3[i,j] = 0;
 end;
end;

 z4 = (z3 - obs)/w;
 z5 = z4*z4`;
 nles = trace(z5);

  return(nles);

/* bdet = det(z5);
  return(dbet);                                          */
```

```
finish func;

/* Initial values, time, weights, and observations          */

  Y0 = {28.88, 11900, 24000};
  pi = 3.14159265358979;
   t = {0 2 7 15 27 54 64 76 100 -9};
  w = {  4   4   4   4   4   4   4   4   4   4,
       4000 4000 4000 4000 4000 4000 4000 4000 4000 4000,
       6000 6000 6000 6000 6000 6000 6000 6000 6000 6000,
         72   72   72   72   72   72   72   72   72   72};

 obs = {28.88 27.04 31.72  28.08  16.64 19.76  8.84   18.2 10.4 29.64,
      11900   0   0    0    0   0    0   13600   0   0,
      24000   0   0    0    0   0    0   24000   0   0,
      431.43 537.98 372.86 474.06 420.8 372.86 266.33 223.72 229.04 330.25};

/* obs = {28.88 27.04 31.72  28.08  16.64 19.76  8.84   18.2 10.4 29.64,
      11900   16848.74 17213.94  4913.306 15521.89 8039.733 14954.28 13600
      19039.68 13132.03,
      24000   21573.35 28795.43 22477.62  23131.6  25365.74 22007.19  24000
      26519.72 30688.41,
      431.43 537.98 372.86 474.06 420.8 372.86 266.33 223.72 229.04 330.25};  */

/*  'a' is a vector of starting values for unknown parameters
   optn is a vector of printout options
    con is a matrix for parameter constraints
     tc is a vector of the termination criteria                          */

     a = {17 .043 18.4 .0092 .018 141};
  optn = {0 4};
   con = { 0. 0.  0. 0. 0.  0.  . .,
           30. 1. 30. 1. 1. 2000. . .,
            1. . 1. . .   . -1 30};
    tc = {500 1000 0 1.e-4 0 0 0 0 0 0 0 0 0};

call nlpnra(rc, xres, "func", a) opt=optn blc=con tc=tc;
     aaa=xres; nles=func(aaa);
```

```
 call nlpfdd (crit, grad, hess, "func", aaa);


/*************************************************************************/
/*                    Confidence Inteval or HPD region                   */
/*                                                                       */
/*************************************************************************/

 resms = nles/(24-6);
    esd = sqrt(resms);
  ihess=inv(hess);
 dihess=vecdiag(ihess);
  t=1.734;

aub=j(1, 6, 0);
alb=j(1, 6, 0);

do i = 1 to 6;
   aub[i] = aaa[i]+t*esd*sqrt(2*dihess[i]);
   alb[i] = aaa[i]-t*esd*sqrt(2*dihess[i]);
 end;

print "confidence Inteval";
print aub a alb;

quit;
```

APPENDIX

Notations:

$\overline{A}$	symmetric matrix of elements of a_{ij}
A^T	transpose matrix of A
tr(A)	trace of matrix A
|A|	determinant of matrix A
$\left\|\frac{\partial Y}{\partial X}\right\|$	Jacobian of transformation, $\left\|\frac{\partial (y_1, \ldots, y_n)}{\partial (x_1, \ldots, x_n)}\right\|$
$\propto$	proportional to
$\doteq$	approximately equal to
L[X]	a linear operator of X such that L[X]=X'-A(t)X
(LH)	a linear homogenous system
(LN)	a linear non-homogenous system

Theorem 3.1 If A is a matrix with dimension m×n and B is with n×m, then

tr (AB) = tr (BA)[18].

Proof. $\text{tr (AB)} = \sum_{i=1}^{m}\sum_{j=1}^{n} a_{ij} b_{ji} = \sum_{i=1}^{n}\sum_{j=1}^{m} b_{ij} a_{ji} = \text{tr (BA)}.$

Theorem 3.2 An elementary transformation on a matrix B is equivalent to $E_1 \ldots E_n B E_{n+1} \ldots E_m$, where some E's are of type of a diagonal matrix D

with a constant a in the ith position and 1's elsewhere, and the remaining E' are of the type of a matrix E containing 1's in diagonal and a constant a in the *i*th row and the *j*th column and 0's elsewhere. If B is a square and non-singular matrix, then B can be expressed as

$B = E_n^{-1} \ldots E_1^{-1} E_m^{-1} E_{n+1}^{-1} = T_m T_{m-1} \ldots T_1$,

where T's are of type of D or E.

Theorem 3.3 $\left|\frac{\partial X}{\partial Y}\right| = 1/\left|\frac{\partial Y}{\partial X}\right|$, if $\left|\frac{\partial Y}{\partial X}\right| \neq 0$.

Theorem 3.4 If $X = F_1(A)$ and $Y = F_2(B)$ are transformations from variables X and Y to new variables A and B, then Jacobian $\left|\frac{\partial (X, Y)}{\partial (A, B)}\right| = \left|\frac{\partial X}{\partial A}\right| \times \left|\frac{\partial Y}{\partial B}\right|$.

Theorem 3.5 $\left|\frac{\partial Y}{\partial X}\right| = \left|\frac{\partial A}{\partial X}\right| \times \left|\frac{\partial B}{\partial A}\right| \times \left|\frac{\partial Y}{\partial B}\right|$, where A and B are any functions of X and Y such that none of the terms on the right-hand side vanish.

Theorem 3.6a The Jacobian of the linear transformation $Y = aX$ (Y, X: p×q), where a is non-zero constant scalar, is $\left|\frac{\partial Y}{\partial X}\right| = a^{pq}$.

Proof. $y_{ij} = ax_{ij}$, $\partial y_{ij}/\partial x_{ij} = a$ and $\partial y_{ij}/\partial y_{ik} = 0$ $(i \neq k)$. Therefore the scheme of coefficients is diagonal with pq a's in the main diagonal.

Theorem 3.6b The Jacobian of the linear transformation $\overline{Y} = a\overline{X}$ $(\overline{Y}, \overline{X}: p \times p)$, where a is non-zero constant scalar, is $\left|\frac{\partial \overline{Y}}{\partial \overline{X}}\right| = a^{1/2p(p+1)}$.

This result is directly obtained from Theorem 3.6a.

Theorem 3.6c The Jacobian of the linear transformation Y = AX (Y, X: p×1; A: p×p) is

$$\left|\frac{\partial Y}{\partial X}\right| = |A|.$$

Proof. $y_i = \sum_{k=1}^{p} a_{ik} x_k$ and $\partial y_i/\partial x_j = a_{ij}$, therefore $\left|\frac{\partial Y}{\partial X}\right| = |A|$.

Theorem 3.6d The Jacobian of the linear transformation Y = AX (Y,X: p×q; A: p×p) is

$$\left|\frac{\partial Y}{\partial X}\right| = |A|^q.$$

Proof. This follows Theorems 3.6d and 3.4, since the transformation of each column of Y is independent of the others and there are q such columns of Y, the J of each column transformation being |A|.

Theorem 3.6e The Jacobian of the linear transformation Y = XA (Y, X; p×q; A: q×q) is

$$\left|\frac{\partial Y}{\partial X}\right| = |A|^p.$$

Proof. Write $Y' = A' X'$ and the result follows directly from Theorem 3.6d.

Theorem 3.6f The Jacobian of the transformation $Y = AXB$ (Y, X: $p\times q$; A: $p\times p$; B: $q\times q$) is $\left|\frac{\partial Y}{\partial X}\right| = |A|^q \times |B|^p$.

Proof. Let $Z = AX$ and $Y = ZB$. Then, $\left|\frac{\partial Z}{\partial X}\right| = |A|^q$ and $\left|\frac{\partial Y}{\partial Z}\right| = |A|^p$. Using Theorem 3.4, the result follows.

Theorem 3.6g The Jacobian of the transformation $\overline{Y} = B\overline{X}B'$ ($\overline{Y}$, B, $\overline{X}$: $p\times p$) is

$$\left|\frac{\partial \overline{Y}}{\partial \overline{X}}\right| = |B|^{p+1} \quad (3\text{-}9).$$

Proof. Assume B is a non-singular matrix. Using Theorem 3.2, write $B = T_m T_{m-1} \ldots T_2 T_1$. Then $\overline{Y} = T_m T_{m-1} \ldots T_2 T_1 \overline{X} T_1' T_2' \ldots T_{m-1}' T_m'$. Let $\overline{Y}_i = T_i \overline{Y}_{i-1} T_i'$ $(i = 1, \ldots, m)$, $\overline{Y}_0 = \overline{X}$, and $\overline{Y}_m = \overline{Y}$. Then, by Theorem 3.4, $\left|\frac{\partial \overline{Y}}{\partial \overline{X}}\right| = \left|\frac{\partial \overline{Y}_1}{\partial \overline{X}}\right| \times \left|\frac{\partial \overline{Y}_2}{\partial \overline{Y}_1}\right| \times \ldots \times \left|\frac{\partial \overline{Y}_m}{\partial \overline{Y}_{m-1}}\right|$.

Let A be any of the T's with form of D mentioned in Theorem 3.2. It is obvious that $|A| = a$. The transformation $\overline{Y}_i = A\overline{Y}_{i-1}A'$ implies $y_{ii} = a^2x_{ii}$; $y_{ij} = ax_{ij}$ $(i \neq j)$; $y_{jk} = x_{jk}$ $(j,k \neq i)$, and hence $\left|\frac{\partial \overline{Y}_i}{\partial \overline{Y}_{i-1}}\right| = a^{p+1} = |A|^{p+1}$.

Let P be any of the T's with form of E mentioned in Theorem 3.2. It is obvious that $|P| = 1$. The transformation $\overline{Y}_i = P\overline{Y}_{i-1}P'$ implies $y_{ii} = x_{ii} + 2ax_{ij} + a^2x_{jj}$; $y_{ki} = y_{ik} = x_{ik} + ax_{jk}(k \neq i)$, $y_{jk} = x_{jk}$ $(j, k \neq i)$, and hence $\left|\frac{\partial \overline{Y}_i}{\partial \overline{Y}_{i-1}}\right| = 1 = |P|^{p+1}$. Since $\left|\frac{\partial \overline{Y}_i}{\partial \overline{Y}_{i-1}}\right| = |T_i|^{p+1}$ $(i = 1, \ldots m)$, therefore it follows that $\left|\frac{\partial \overline{Y}}{\partial \overline{X}}\right| = |T_m|^{p+1} \times \ldots \times |T_1|^{p+1} = |B|^{p+1}$.

Theorem 4.1 If $\Phi(t)$ is a fundamental matrix of (LH) and if S is a any non-singular constant matrix with dimension n×n, then $\Phi(t)S$ is also a fundamental matrix of (LH).

Proof. Since $\Phi(t)$ is a fundamental matrix, $\Phi(t)^T = A(t)\,\Phi(t)$,

then $(\Phi(t)S)^T = \Phi(t)^T S + \Phi(t)S^T = (A(t)\,\Phi(t))S$, and $\det(\Phi(t)S) = \det\Phi(t)\det(S) \neq 0$,

hence $\Phi(t)S$ is also a fundamental matrix.

Theorem 4.2 If $\Phi(t)$ is a fundamental matrix of (*LH*), for any fundamental matrix of θ (*LH*), $\exists$ a constant nonsingular matrix P with dimension n×n, such that $\theta(t) = \Phi(t)P$.

Proof. Let $\theta=(\theta_1, \theta_2, \ldots\theta_n)$, then θ_i is a solution;

hence, $\theta_i = \Phi(t)P_i$, $i=1,\ldots, n$, $P=(P_1, P_2, \ldots P_n)$.

$\therefore \theta = \Phi(t)P$.

Theorem 4.3 Let r(t) be any solution of L[x]=g; then a general solution of L[x] = g is $\theta(t) = \Phi(t)\, S + r(t)$, where $\Phi(t)$ is any fundamental matrix of L[x]=0 and S is an arbitrary constant vector.

Proof. Let $\theta(t)$ be a solution of (*LN*).

Since r is any solution of (*LN*),

$L[\theta-r]=L[\theta]-L[r]=g-g=0$.

$\therefore$ $(\theta-r)(t)$ is a solution of (*LH*).

Since $\Phi(t)$ is any fundamental matrix, from Theorem 4.2,

$(\theta-r)(t)= \Phi(t)S$, for some a constant vector S.

Therefore,

$\theta(t)= \Phi(t)S+r(t)$.

Theorem 4.4 The vector function $r(t)=\Phi(t)\int_{t_0}^{t}\Phi^{-1}(S)g(S)dS$ is a solution of L[X]=g(t),

where Φ(t) is any fundamental matrix of (*LH*).

Proof. Since Φ(t) is a fundamental matrix, then Φ'(t)=A(t) Φ(t).

$$r(t)=\Phi(t)\int_{t_0}^{t}\Phi^{-1}(S)g(S)dS+\Phi(t)\frac{\partial}{\partial t}[\int_{t_0}^{t}\Phi^{-1}(S)g(S)dS]$$

$$=A(t)[\Phi(t)\int_{t_0}^{t}\Phi^{-1}(S)g(S)dS]+\Phi(t)\Phi^{-1}(t)g(t)$$

$$=A(t)[\Phi(t)\int_{t_0}^{t}\Phi^{-1}(S)g(S)dS]+g(t);$$

hence, the vector function of $r(t)=\Phi(t)\int_{t_0}^{t}\Phi^{-1}(S)g(S)dS$ is a solution of L[X]=g(t).

BIBLIOGRAPHY

1. Al-haddad, I. K., Chettle, D. R., Fletcher J. G. and Fremlin, J. H., A Transportable System for Measurement of Kidney Cadmium *in vivo*, International Journal of Applied Radiation & Isotopes, **32** 109-112, 1981.

2. Anderson, D. H., Lecture Notes in Bio-mathematics, Compartmental Modeling and Tracer Kinetics, Springer-Verlag, New York, 1983.

3. Armstrong, R., R. A., Chettle, D. R., Braithwaite, R.A., Scott, M. C., and Franklin, D. M., Critical Cadmium Levels and Toxicokinetics, Workshop on *In ViVo* Body Composition Studies, 1991.

4. Armstrong, R., Chettle, D. R., Scott, M. C., Blindt, M. and Mason, H. J., Longitudinal Studies of Exposure to Cadmium, British Journal of Industrial Medicine, **49**, 556-559, 1990.

5. Bates, D. M., and Watts, D. G., Nonlinear Regression and Its Applications, John Wiley & Sons, New York, 1988.

6. Biggin, H. C., Chen, N. S., Ettinger, K. V., Fremlin, J. H., Morgan, W. D., Nowotny, R. and Chamberlain, M. J., Nature New Biology, **236**, 187. 1972.

7. Biggin, H. C., Chen, N. S., Ettinger, K. V., Fremlin, J. H., Morgan, W. D., Nowotny, R., Chamberlain, M. J. and Harvey, T. C., Journal of Radioanalyt. Chemistry, **19**, 207, 1974.

8. Box, G.E.P., and Tiao, G.C., Bayesian Inference in Statistical Analysis, John Wiley and Sons, New York, 1973.

9. Braithwaite, R. A., Armstrong, R., Franklin, D. M., Chettle and D. R., Scott, M. C., Cadmium Toxicokinetics Following Long Term Occupational Exposure, In Trace Elements in Health and Disease, Royal Society of Chemistry, Cambridge, 95-103, 1991.

10. Chettle, D. R., Franklin, D. M., Guthrie, C. J. G., Scott, M. C. and Somervaille, L. J., *In Vivo* and *In Vitro* Measurements of Lead and Cadmium, Bio. Trace Elem. Resource, **13** 191-208, 1987.

11. Deemer, W. L. and Olkin, I., The Jacobians of Certain Matrix Transformations Useful in Multivariate Analysis, Biometrika **38**, 345, 1951.

12. Delves, H. T. and Woodward, J., Determination of low levels of Cadmium in the Blood by Electrothermal Atomisation and Atomic Absorption Spectrophotometry, Spectro., **2**, 65, 1981.

13. Duce, R. A., Aritmoto, R., Ray, B. J., Cluni, C. K. and Harder, P. J., Journal of Geophysics Resource, **88**, 5321-5342, 1983.

14. Elinder, C. G., Cadmium and Health, A Toxicological and Epidemiological Appraisal, CRC Press, Boca Raton, 1985.

15. Ellis, K. J., Morgan, W. D., Yasumura, S., Vartsky, D., Zanzi, I. and Cohn, S. H., *In vivo* Measurement of Cadmium in an Occupationally-Exposed Population, 1977.

16. Evans, D. B., Henderson, R. G., Lecture Notes on Nephrology, Blackwell Scientific Publications, 1985.

17. Fisher, R. A., On the Mathematical Foundations of Theoretical Statistics, Philosophical Transactions of the Royal Society, A **222**, 309, 1922.

18. Franklin, A. G., Introduction to Matrices with Applications in Statistics, Wadsworth Publishing Company, Inc., Belmont, California, 1967.

19. Frazer, R. G., Duncan, W. J., and Collar, A. R., Elementary Matrices and Some Applications to Dynamics and Differential Equations, Cambridge University Press, 1965.

20. Franklin, D. M., Armstrong, R., Chettle, D. R. and Scott, M. C., An Improved in vivo Neutron Activation System for Measuring Kidney Cadmium, Physics in Medicine and Biology, Vol. 35, **10** 1397-1408, 1990.

21. Friberg, L., Kjellström, T., Nordberg, G. F. and Vouk, V. B., Handbook on the Toxicology of Metals Volume II, Elsevier Science Publishers B.V., 1986.

22. Friberg, L., Proteinuria and Kidney Injury among Workmen Exposed to Cadmium and Nickel Dust, Journal of Industrial Hygiene and Toxicology, **30**, 32, 1948.

23. Guthrie, C. J. G., The Statistical Analysis of Survey Measurements Made from Workers Exposed to Cadmium (Master's Thesis), University of Birmingham, Birmingham, England, 1987.

24. Guthrie, C.J.G., Chettle, D. R., Franklin, D. M., Scott, M. C., Mason, H. J., Wright, A. L., Gompertz, D. R., Davison, A. G., Fayers, P. M. and Newman-Taylor,

A. J., The Use of Multiple Parameters to Characterize Cadmium Induced Renal dysfunction Resulting from Occupational Exposure, Environmental Research, **65**, 22-41, 1994.

25. Hamburger &, Richet G, Grunfeld J P and Walsh A, Organ Physiology-Structure and Function of the Kidney, W.B. Saunders Company, 1971.

26. Health & Safety Executive, Occupational Medicine & Hygiene Laboratories, Laboratory Methods For Biological Monitoring, 2nd edition, 1985.

27. Jacquez, J. A., Compartmental Analysis in Biology and Medicine, Elsevier, New York, 1972.

28. Jeffreys, H., Theory of Probability, Third edition, Clarendon Press, Oxford, 1961.

29. Kjellström, T., Nordberg, G. F., A kinetic Model of Cadmium Metabolism in the Human Being, Environmental Research, **16**, 248-269, 1978.

30. Mason, H. J., Davison, A. G., Wright, A. L., Fayers, P. M., Venables, K. M., Smith, N. J., Guthrie, C. J. G., Chettle, D. R., Franklin, D. M., Scott, M. C., Holden, H., Gompertz, D.and Newman-Taylor, A. J., Relations between Liver Cadmium, Cumulative Exposure and Renal Function in Cadmium Alloy Workers, British Journal of Industrial Medicine **45**, 793-802, 1988.

31. McAughey, J. J. and Smith, N. J., The Direct Determination of Cadmium in Urine by Electrothermal Atomic Absorption Spectrometry with the L'vov Platform, Anal. Chim. Acta., **156**, 129-137, 1984.

32. R. K. Miller and A. N. Michel, Ordinary Differential Equations, Academic Press, Inc. London, 1982

33. Mishina, A . P. and Proskuryakov, I. V., Higher Algebra, Pergamon Press Ltd., 1965

34. Mogensen, C. E. and SØlling, K., Scand. J., Clin., Lab., Invest., **37**, 477-486, 1977

35. Neter, J., Wasserman, W., and Kutner, M.H., Applied Linear Statistical Models, Richard D. Irwin, Inc., 1990.

36. Nordberg, G. F., Environment Physics Biochemistry, **2**, 7-36, 1972

37. Press, S.J., Bayesian Statistics: Principles, Models, and Applications, John Wiley & Sons, New York, 1989.

38. Roels, H. A., Lauwerys, R. R., Buchet, J. P., Bernard A., Chettle D. R., Harvey, T. C., And Al-Haddad I. K., In Vivo Measurement of Liver and Kidney Cadmium in Workers Exposed to This Metal: Its Significance with Respect to Cadmium in Blood and Urine, Environmental Research **26**, 217-240, 1981.

39. Scott, M. C. and Chettle, D. R., *In vivo* Elemental Analysis in Occupational Medicine, Scand. Journal of Work, Environment Health, **12**, 81-96, 1986.

40. Siegel, C. L., Ueber die Analytische Theorie der Quadratischen Formen, Ann. Math. **36**, 527, 1989.

41. Stigler, S.M. The History of Statistics, The Belknap Press of Harvard University Press, Cambridge, Massachusetts, 1986.

42. Stigler, S. M., Thomas Bayes and Bayesian Inference, Journal of the Royal Statistical Soc. (A), **145**(2), 250-258, 1982.

43. Thomas, B. J., Harvey, T. C., Chettle, D. R., McLellan, J. S. and Fremlin, J. H., A Transportable System for the Measurement of Liver Cadmium *in vivo*, Physics in Medicine and Biology, **24** 432-437, 1979.

44. Wishart, J., The Generalized product Moment Distribution in Samples from a Normal Multivariate Population, Biometrika, **20**, 32, 1928.

45. Zeller, A., An Introduction to Bayesian Inference in Econometrics, Joln Wiley & Sons, New York, 1971.