

To the Graduate Council:

I am submitting herewith a dissertation written by Yunnhon Lo entitled "Bayesian parameter estimation for compartmental models in biology and physics." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Nuclear Engineering.



Dr. Peter G. Groer, Major Professor

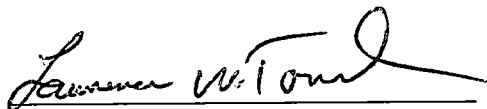
We have read this dissertation
and recommend its acceptance:



Dr. Mark Kot



Dr. Laurence F. Miller



Dr. Lawrence W. Townsend

Accepted for the Council:



Associate Vice Chancellor and

Dean of The Graduate School

BAYESIAN PARAMETER ESTIMATION FOR COMPARTMENTAL
MODELS IN BIOLOGY AND PHYSICS

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee Knoxville

Yunnhon Lo

May 2000

DEDICATION

This dissertation is dedicated in loving memory to my mother.

ACKNOWLEDGEMENTS

I would like to extend my sincere gratitude to Dr. Peter G. Groer, my major professor, for his guidance, advice and patience throughout this research. My thanks go to Dr. Mark Kot, Dr. Larry Miller and Dr. Larry Townsend for helping with my studies and for serving on my graduate committee. I would also like to thank Dr. Gary Smith of the University of Tennessee Medical Center in Knoxville for the clinical FDG PET data.

I am forever grateful to my family and friends for their endless patience, support and encouragement. Finally, I would like to acknowledge the financial support for this research provided by the University of Tennessee's Department of Nuclear Engineering in the form of a research assistantship, which was supported in part by a grant from Duke Power Company.

ABSTRACT

We demonstrated that the use of Bayes' Theorem, with the Box and Draper likelihood, to estimate the parameters of compartmental models is an improvement over current "ad hoc" parameter estimation methods. This method has several novel features that are useful in parameter estimation. First, the remaining parameter uncertainty is described by the posterior density, which cannot be obtained with classical regression methods. Second, highest posterior density contours can be used to illustrate uncertainty of parameter pairs, and their shape changes can be used to describe the influence of reduced data sets and/or different models on the estimation uncertainty. Third, information from other experiments and sources can be incorporated using appropriate prior distribution.

Two areas of application for this technique are biology and physics. Three biokinetic models were studied: the exchange of calcium at bone surfaces in beagles, human cerebral glucose metabolism, and the exchange of serum albumin in human. In physics, we estimated the half-lives of ^{226}Ra , ^{222}Rn and ^{218}Po from simulated decay data. In addition, different reduced data sets were also examined for each model to show their influence on parameter uncertainty.

We applied the Bayesian method to two and three-compartment models. The presence of bimodality and "divergent" behavior in the posterior densities is new and unexpected. They are due to the likelihood and can be changed using prior information and/or the amount of data used. For example, the use of Normal priors stopped the

“divergence” in the bone calcium study. However, it also introduced bimodality for all three parameters.

Interestingly, the omission of the extravascular space data in the serum albumin analysis did not diminish the estimation accuracy. Instead, estimation precision was increased for three of the four parameters, as indicated by smaller contours. When open contours are present, the estimation variances are large and can be infinite. Finally, we showed that radioactive decay can be described using compartmental models and that half-lives can be estimated using Box and Draper’s method. As always, the most precise estimates were obtained using data for individual compartments.

TABLE OF CONTENTS

<i>CHAPTER</i>	<i>PAGE</i>
1. INTRODUCTION	1
1.1 Compartmental Model	2
1.2 Non-Bayesian Parameter Estimation Method	3
1.3 Models Examined	3
2. BAYESIAN APPROACH	4
2.1 Bayes' Theorem	4
2.2 Box and Draper Likelihood Equation	5
2.3 Highest Posterior Density Contour	7
3. EXCHANGE OF CALCIUM AT BONE SURFACES IN BEAGELS	11
3.1 Mathematical Model	11
3.2 ⁴⁵ Ca Biokinetic Data	13
3.3 Uniform Priors – All Ten Data Points	13
3.3.1 Both bone surfaces and plasma data are used	17
3.3.2 Only the bone surfaces data are used	24
3.3.3 Only the plasma data are used	30
3.3.4 Review of the results for uniform priors with all ten data	37
3.4 Uniform Priors – Last Four Data Points Omitted	41
3.4.1 First six bone surfaces and plasma data are used	41
3.4.2 First six bone surfaces data used	48
3.4.3 First six plasma data used	55
3.4.4 Review of the results for uniform priors with first six data	61

3.5 Normal Priors – All Ten Data Points	65
4. LOCAL HUMAN CEREBRAL METABOLISM OF GLUCOSE	77
4.1 Mathematical Model	77
4.2 Clinical Data	79
4.3 Analysis of Clinical Data	81
4.4 Analysis of Simulated Data	93
5. EXCHANGE OF HUMAN SERUM ALBUMIN	109
5.1 Mathematical Model	109
5.2 Iodoalbumin Biokinetic Data	110
5.3 Bayesian Analysis	113
5.3.1 All data are used	113
5.3.2 Only the ascitic fluid data are used	124
5.3.3 Only the plasma data are used	134
5.3.4 Both the ascitic fluid and the plasma data are used	144
5.3.5 Review of the results for the iodoalbumin analyses	154
6. ESTIMATION OF THE HALF-LIVES OF ^{226}Ra, ^{222}Rn AND ^{218}Po	161
6.1 Mathematical Model	161
6.2 Simulated Decay Data	162
6.3 Analysis of Simulated Data	167
6.3.1 Decay of ^{226}Ra to ^{222}Rn	168
6.3.2 Decay of ^{222}Rn to ^{218}Po	175
7. CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE WORK	180
REFERENCES	183
APPENDICES	186

A	Normalized Posterior Surface Density Plots	187
B	Sample Computer Codes Written in C and Mathematica [®]	211
C	Partial ²²⁶ Ra, ²²² Rn and ²¹⁸ Po Data List and Results	227
VITA		234

LIST OF FIGURES

<i>FIGURE</i>	<i>PAGE</i>
2.1 A HPD contour c created by a plane z parallel to parameter θ axes at $f(\theta) = z$.	8
2.2 Illustration showing the iterative HPD volume calculation with two possible scenarios: prism inside and outside the contour c or HPD region R .	9
3.1 A two-compartment three-parameter model describing the exchange of calcium at bone surfaces in beagles.	11
3.2 Plot of normalized ^{45}Ca bone surfaces and plasma specific activities as a function of time in beagles.	14
3.3 Normalized marginal posterior density for the calcium exchange rate λ_{12} in beagles with uniform priors for the smallest and largest integration limits.	15
3.4 Normalized marginal posterior density for the calcium exchange rate λ_{21} in beagles with uniform priors for the smallest and largest integration limits.	16
3.5 Normalized marginal posterior density the calcium exchange rate μ in beagles with uniform priors for the smallest and largest integration limits.	16
3.6 Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with all ^{45}Ca data and uniform priors.	18
3.7 Solution of the differential equations for the parameter estimates calculated with all ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	19
3.8 Solution of the differential equations for the parameter estimates calculated with all ^{45}Ca data and uniform priors fitted to the beagles plasma ^{45}Ca data.	19
3.9 Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with all ^{45}Ca data and uniform priors.	21
3.10 Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with all ^{45}Ca data and uniform priors.	22
3.11 Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with all ^{45}Ca data and uniform priors.	23

3.12	Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.	25
3.13	Solution of the differential equations for the parameter estimates calculated with the bone surfaces ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	26
3.14	Solution of the differential equations for the parameter estimates calculated with the bone surfaces ^{45}Ca data and uniform priors fitted to the beagles plasma ^{45}Ca data using.	26
3.15	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.	27
3.16	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.	28
3.17	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.	29
3.18	Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the plasma ^{45}Ca data and uniform priors.	31
3.19	Solution of the differential equations for the parameter estimates calculated with the plasma ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data using.	32
3.20	Solution of the differential equations for the parameter estimates calculated with the plasma ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	33
3.21	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the plasma ^{45}Ca data and uniform priors.	34
3.22	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the plasma ^{45}Ca data and uniform priors.	35
3.23	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the plasma ^{45}Ca data and uniform priors.	36
3.24	Normalized marginal posterior density for the calcium exchange rate λ_{12} in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.	38

3.25	Normalized marginal posterior density for the calcium exchange rate λ_{21} in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.	38
3.26	Normalized marginal posterior density for the calcium exchange rate μ in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.	39
3.27	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.	39
3.28	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.	40
3.29	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.	40
3.30	Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the first six ^{45}Ca data and uniform priors.	42
3.31	Solution of the differential equations for the parameter estimates calculated with the first six ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	44
3.32	Solution of the differential equations for the parameter estimates calculated with the first six ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	44
3.33	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the first six ^{45}Ca data and uniform priors.	45
3.34	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the first six ^{45}Ca data and uniform priors.	46
3.35	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the first six ^{45}Ca data and uniform priors.	47
3.36	Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.	49

3.37	Solution of the differential equations for the parameter estimates calculated with the first six bone surfaces ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	50
3.38	Solution of the differential equations for the parameter estimates calculated with the first six bone surfaces ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	51
3.39	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.	52
3.40	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.	53
3.41	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.	54
3.42	Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.	56
3.43	Solution of the differential equations for the parameter estimates calculated with the first six plasma ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	57
3.44	Solution of the differential equations for the parameter estimates calculated with the first six plasma ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.	57
3.45	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.	58
3.46	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.	59
3.47	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.	60
3.48	Normalized marginal posterior density for the calcium exchange rate λ_{12} in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.	62

3.49	Normalized marginal posterior density for the calcium exchange rate λ_{21} in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.	63
3.50	Normalized marginal posterior density for the calcium exchange rate μ in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.	63
3.51	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.	64
3.52	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.	64
3.53	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.	65
3.54	Plot of the normalized ^{45}Ca bone surfaces and plasma specific activities as a function of time in rabbits.	66
3.55	Normalized marginal posterior densities for the calcium exchange rates in rabbits calculated with all ^{45}Ca data and uniform priors.	68
3.56	Normal prior density of λ_{12} , λ_{21} and μ calculated with rabbits ^{45}Ca data.	69
3.57	Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with all ^{45}Ca data and Normal priors.	71
3.58	Solution of the differential equations for the parameter estimates calculated with all ^{45}Ca data and Normal priors fitted to the beagles bone surfaces ^{45}Ca data.	72
3.59	Solution of the differential equations for the parameter estimates calculated with all ^{45}Ca data and Normal priors fitted to the beagles plasma ^{45}Ca data.	72
3.60	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with all ^{45}Ca data and Normal priors.	74
3.61	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with all ^{45}Ca data and Normal priors.	75
3.62	Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with all ^{45}Ca data and Normal priors.	76

4.1	A three-compartment catenary system describing the local human cerebral metabolism of ^{18}F -fluorodeoxyglucose (FDG).	78
4.2	Three-compartment catenary system describing the local human cerebral metabolism of ^{18}F -fluorodeoxyglucose with spillover factor and compartmental lumping.	81
4.3	Normalized marginal posterior densities for human cerebral gray matter glucose metabolism rates calculated with clinical FDG PET data and uniform priors.	83
4.4	Solution of the differential equations for the parameter estimates calculated with clinical FDG PET data and uniform priors fitted to the human cerebral plasma FDG data.	85
4.5	Solution of the differential equations for the parameter estimates calculated with clinical FDG PET data and uniform priors fitted to the human cerebral gray matter tissue FDG and FDG-6-P data.	85
4.6	Solution of the differential equations fitted to the human cerebral plasma FDG data using the published average rate constants with no spillover factor.	86
4.7	Solution of the differential equations fitted to the human cerebral gray matter tissue FDG and FDG-6-P data using the published average rate constants with no spillover factor.	86
4.8	Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_2 calculated with clinical FDG PET data and uniform priors.	87
4.9	Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_3 calculated with clinical FDG PET data and uniform priors.	88
4.10	Ninety and ninety-five percent HPD contours for human cerebral gray matter glucose metabolism rates K_1 and K_4 calculated with clinical FDG PET data and uniform priors.	89
4.11	Ninety and ninety-five percent HPD contours for human cerebral gray matter glucose metabolism rates K_2 and K_3 calculated with clinical FDG PET data and uniform priors.	90
4.12	Ninety and ninety-five percent HPD contours for human cerebral gray matter glucose metabolism rates K_2 and K_4 calculated with clinical FDG PET data and uniform priors.	91

4.13	Ninety and ninety-five percent HPD contours for human cerebral gray matter glucose metabolism rates K_3 and K_4 calculated with clinical FDG PET data and uniform priors.	92
4.14	Normalized marginal posterior density for the human cerebral gray matter glucose metabolism rate K_1 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	96
4.15	Normalized marginal posterior density for the human cerebral gray matter glucose metabolism rate K_2 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	96
4.16	Normalized marginal posterior density for the human cerebral gray matter glucose metabolism rate K_3 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	97
4.17	Normalized marginal posterior density for the human cerebral gray matter glucose metabolism rate K_4 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	97
4.18	Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 5% noise and uniform priors fitted to the simulated human cerebral plasma FDG data.	98
4.19	Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 5% noise and uniform priors fitted to the simulated human cerebral gray matter tissue FDG and FDG-6-P data.	99
4.20	Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 10% noise and uniform priors fitted to the simulated human cerebral plasma FDG data.	99
4.21	Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 10% noise and uniform priors fitted to the simulated human cerebral gray matter tissue FDG and FDG-6-P data.	100
4.22	Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 25% noise and uniform priors fitted to the simulated human cerebral plasma FDG data.	100
4.23	Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 25% noise and uniform priors fitted to the simulated human cerebral gray matter tissue FDG and FDG-6-P data.	101

4.24	Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_2 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	102
4.25	Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_3 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	103
4.26	Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_4 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	104
4.27	Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_2 and K_3 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	105
4.28	Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_2 and K_4 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	106
4.29	Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_3 and K_4 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	107
5.1	Three-compartment catenary system describing the exchange of ^{131}I labeled human serum albumin administered intraperitoneally.	110
5.2	Relative specific activities of ^{131}I albumin in ascitic fluid, plasma and extravascular fluid and urinary excretion of radioactivity as a function of time following intraperitoneal injection of ^{131}I albumin.	111
5.3	Normalized marginal posterior densities for the human serum albumin exchange rates calculated with all iodoalbumin data and uniform priors.	115
5.4	Solution of the differential equations for the parameter estimates calculated from all iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human ascitic fluid iodoalbumin data.	116
5.5	Solution of the differential equations for the parameter estimates calculated from all iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human plasma iodoalbumin data.	116
5.6	Solution of the differential equations for the parameter estimates calculated from all iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human extravascular spaces iodoalbumin data	117

5.7	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with all iodoalbumin data and uniform priors.	118
5.8	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with all iodoalbumin data and uniform priors.	119
5.9	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with all iodoalbumin data and uniform priors.	120
5.10	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with all iodoalbumin data and uniform priors.	121
5.11	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with all iodoalbumin data and uniform priors.	122
5.12	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with all iodoalbumin data and uniform priors.	123
5.13	Normalized marginal posterior density for the human serum albumin exchange rates calculated with the ascitic fluid iodoalbumin data and uniform priors.	125
5.14	Solution of the differential equations for the parameter estimates calculated from the ascitic fluid iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human ascitic fluid iodoalbumin data.	126
5.15	Solution of the differential equations for the parameter estimates calculated from the ascitic fluid iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human plasma iodoalbumin data.	126
5.16	Solution of the differential equations for the parameter estimates calculated from the ascitic fluid iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human extravascular space iodoalbumin data.	127
5.17	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with the ascitic fluid iodoalbumin data and uniform priors.	128

5.18	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with the ascitic fluid iodoalbumin data and uniform priors.	129
5.19	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with the ascitic fluid iodoalbumin data and uniform priors.	130
5.20	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with the ascitic fluid iodoalbumin data and uniform priors.	131
5.21	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with the ascitic fluid iodoalbumin data and uniform priors.	132
5.22	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with the ascitic fluid iodoalbumin data and uniform priors.	133
5.23	Normalized marginal posterior density for the human serum albumin exchange rates calculated with the plasma iodoalbumin data and uniform priors.	134
5.24	Solution of the differential equations for the parameter estimates calculated from the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human ascitic fluid iodoalbumin data.	136
5.25	Solution of the differential equations for the parameter estimates calculated from the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human plasma iodoalbumin data.	136
5.26	Solution of the differential equations for the parameter estimates calculated from the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human extravascular space iodoalbumin data.	137
5.27	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with the plasma iodoalbumin data and uniform priors.	138
5.28	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with the plasma iodoalbumin data and uniform priors.	139

5.29	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with the plasma iodoalbumin data and uniform priors.	140
5.30	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with the plasma iodoalbumin data and uniform priors.	141
5.31	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with the plasma iodoalbumin data and uniform priors.	142
5.32	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with the plasma iodoalbumin data and uniform priors.	143
5.33	Normalized marginal posterior density for the human serum albumin exchange rates calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	145
5.34	Solution of the differential equations for the parameter estimates calculated from both the ascitic fluid and the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human ascitic fluid iodoalbumin data.	146
5.35	Solution of the differential equations for the estimates calculated from both the ascitic fluid and the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human plasma iodoalbumin data.	146
5.36	Solution of the differential equations for the parameter estimates calculated from both the ascitic fluid and the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human extravascular iodoalbumin data.	147
5.37	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	148
5.38	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	149
5.39	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	150

5.40	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	151
5.41	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	152
5.42	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	153
5.43	Normalized marginal posterior density for the human serum albumin exchange rate K_1 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	155
5.44	Normalized marginal posterior density for the human serum albumin exchange rate K_2 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	155
5.45	Normalized marginal posterior density for the human serum albumin exchange rate K_3 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	156
5.46	Normalized marginal posterior density for the human serum albumin exchange rate K_4 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	156
5.47	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	157
5.48	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	158
5.49	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	158

5.50	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	159
5.51	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	159
5.52	Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	160
6.1	Parent – daughter decay scheme, where λ_i are the decay constants.	162
6.2	Parent – daughter decay schemes for (a) $^{226}\text{Ra} - ^{222}\text{Rn}$ and (b) $^{222}\text{Rn} - ^{218}\text{Po}$.	163
6.3	Histogram of the posterior mean for the ^{226}Ra half-lives in years for 500 simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.	171
6.4	Histogram of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.	171
6.5	Histogram of the posterior mean for the ^{226}Ra half-lives in years for 500 simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.	173
6.6	Histogram of the posterior mean of the ^{222}Rn half-lives in days for 500 simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.	173
6.7	Histogram of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.	176
6.8	Histogram of the posterior mean for the ^{218}Po half-lives in minutes for 500 simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.	176
6.9	Histogram of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.	178
6.10	Histogram of the posterior mean for the ^{218}Po half-lives in minutes for 500 simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.	178

LIST OF TABLES

<i>TABLE</i>	<i>PAGE</i>
3.1 Normalized ^{45}Ca bone surfaces and plasma specific activities in beagles.	14
3.2 Posterior means, modes and standard deviations for the calcium exchange rates in beagles calculated with all ^{45}Ca data and uniform priors.	18
3.3 Comparison of the residence time of calcium ions in beagles.	18
3.4 Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with all ^{45}Ca data and uniform priors.	20
3.5 Posterior means, modes and standard deviations for the calcium exchange rates in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.	25
3.6 Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.	30
3.7 Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with the plasma ^{45}Ca data and uniform priors.	31
3.8 Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the plasma ^{45}Ca data and uniform priors.	33
3.9 Bayesian parameter estimates for the calcium exchange rates in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.	37
3.10 Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with the first six ^{45}Ca data and uniform priors.	43
3.11 Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the first six ^{45}Ca data and uniform priors.	48
3.12 Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.	49

3.13	Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.	51
3.14	Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.	56
3.15	Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.	61
3.16	Bayesian parameter estimates for the calcium exchange rates in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.	62
3.17	Normalized ^{45}Ca bone surfaces and plasma specific activities in rabbits.	66
3.18	Posterior means and standard deviations for the calcium exchange rates in rabbits calculated with all ^{45}Ca data and uniform priors.	68
3.19	Beagle Normal prior means and standard deviations.	68
3.20	Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with all ^{45}Ca data and Normal priors.	71
3.21	Comparison of residence time of calcium ions in beagles calculated with Normal priors.	71
3.22	Ninety and ninety-five percent HPD contours z values for various combinations of the calcium exchange rates in beagles calculated with all ^{45}Ca data and Normal priors.	73
4.1	Clinical FDG PET data in plasma and in cerebral gray matter tissue in human.	80
4.2	Published average FDG metabolism rates in human cerebral gray matter, and the extrapolated integration limits for Bayesian analysis.	82
4.3	Posterior modes, means and standard deviations for the human cerebral gray matter glucose metabolism rates calculated with clinical FDG PET data and uniform priors.	84
4.4	Ninety and ninety-five percent HPD contour z values for various combinations of the human cerebral gray matter glucose metabolism rates calculated with clinical FDG PET data and uniform priors.	93
4.5	Local human cerebral gray matter FDG PET data sets simulated using the published average rate constants with 5, 10 and 25% noise.	95

4.6	Posterior modes, means and standard deviations for the human cerebral gray matter glucose metabolism rates calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.	98
4.7	Ninety and ninety-five percent HPD contour z values for various combinations of the human cerebral gray matter glucose metabolism rates calculated with uniform priors and simulated FDG PET data sets 5, 10 and 25% noise.	108
5.1	Activities of ^{131}I labeled human serum albumin in the ascitic fluid, the plasma and the extravascular spaces administered intraperitoneally.	112
5.2	Posterior modes, means and standard deviations for the human serum albumin exchange rates calculated with all iodoalbumin data and uniform priors.	115
5.3	Ninety and ninety-five percent HPD contour z values for various combinations of the human serum albumin exchange rates calculated with all iodoalbumin data and uniform priors.	117
5.4	Posterior modes, means and standard deviations for the human serum albumin exchange rates calculated with the ascitic fluid iodoalbumin data and uniform priors.	125
5.5	Ninety and ninety-five percent HPD contour z values for various combinations of the human serum albumin exchange rates calculated with the ascitic fluid iodoalbumin data and uniform priors.	127
5.6	Posterior modes, means and standard deviations for the human serum albumin exchange rates calculated with the plasma iodoalbumin data and uniform priors.	135
5.7	Ninety and ninety-five percent HPD contour z values for various combinations of the human serum albumin exchange rates calculated with the plasma iodoalbumin data and uniform priors.	137
5.8	Posterior modes, means and standard deviations for the human serum albumin exchange rates calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	1 ⁴⁵
5.9	Ninety and ninety-five percent HPD contour z values for various combinations of the human serum albumin exchange rates calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.	154
5.10	Bayesian parameter estimates for the human serum albumin exchange rates calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.	157

6.1	Simulated radioactive decay data based on an initial parent activity of 10pCi and Normal random error.	166
6.2	Frequency of the posterior mean for the ^{226}Ra half-lives in years for 500 simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.	169
6.3	Frequency of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.	169
6.4	Frequency of the posterior mean for the ^{226}Ra half-lives in years for 500 simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.	172
6.5	Frequency of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.	172
6.6	Frequency of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.	175
6.7	Frequency of the posterior mean for the ^{218}Po half-lives in minutes for 500 simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.	175
6.8	Frequency of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.	177
6.9	Frequency of the posterior mean for the ^{218}Po half-lives in minutes for 500 simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.	177

CHAPTER 1

INTRODUCTION

Parameter estimation for compartmental models is an inverse problem that uses statistical methods to find the values of the transfer coefficients from observed data. Inferences about the model parameters are possible through the use of differential equations to model compartmental interactions and Bayes' Theorem. There are several advantages of using Bayesian method to estimate model parameters; the ease of incorporating prior knowledge about the parameters, and the use of posterior densities to characterize the remaining uncertainty about the parameters. Although typically used for biological systems, the method described here can be adapted for various applications in engineering and in physical sciences. To demonstrate these techniques and advantages, three sets of biokinetic and a set of simulated radioactive decay data are examined in this dissertation.

This dissertation is organized into seven different chapters and three appendices. The first half of chapter 1 presents the motivation behind the research and an outline of the dissertation. The remainder of the chapter discusses the definition of a compartmental model, current estimation method, and types of models examined. Chapter 2 introduces some of the theoretical concepts used in the research, such as Bayes' Theorem, Box-Draper likelihood, and highest posterior density (HPD) contour. Chapter 3, 4 and 5 discuss the results of biokinetic analyses of the exchange of ^{45}Ca at bone surfaces in beagles, the local cerebral metabolic rate of ^{18}F labeled glucose in human, and the

exchange of iodoalbumin in human, respectively. Chapter 6 discusses a use of the Bayesian method in physics through the estimation of the half-lives of ^{226}Ra , ^{222}Rn , and ^{218}Po from simulated decay data. Chapter 7 contains summary, conclusions and future work. Finally, additional figures, simulation data and selected computer codes used in the analysis are listed in Appendix A, B and C, respectively.

1.1 Compartmental Models

A compartmental system is made up of finite, homogenous, and well-mixed compartments. Each compartment interacts with its neighboring compartments and the environment by exchanging material or mass. The theory and application of compartmental analysis can be summarized in three general steps (Jacquez, 1985). The first step is to develop a compartmental model for the system of interest. This requires considerable background in the field in order to justify the use of a particular compartmental model. Second, formulate a set of differential equations describing the desired compartmental system. Third and perhaps the most difficult step is the inverse problem, estimation of the model parameters from observed data.

Some of the above descriptions for compartmental models do not apply to radioactive decay. However, since radioactive decay can be described by similar differential equations, compartmental models can be used to describe radioactive decay. Thus, radioactive half-life can be estimated using the Box and Draper likelihood.

1.2 *Non-Bayesian Parameter Estimation Method*

The most common parameter estimation method is regression or curve fitting. The theory behind it is simple, fit the solution of the differential equations to the observed data by adjusting the regression variables until a desired criterion such as least-squares error is met. Although regression produces point estimates, one drawback is the impossibility to describe the remaining uncertainty. This is why Bayes' Theorem is useful. It facilitates the derivation of the probability densities characterizing the remaining uncertainty about parameters given the observed data.

1.3 *Models Examined*

To demonstrate the advantages of the Bayesian parameter estimation technique, two application areas were examined: biology and physics. For biological systems, three biokinetic models were studied. The first biokinetic model is the exchange of ^{45}Ca at bone surfaces in beagles, and can be described by a two-compartment three-parameter system. The remaining two biokinetic models describe the local human cerebral fluorodeoxyglucose metabolism and the exchange of iodoalbumin administered intraperitoneally in human, both described by a three-compartment four-parameter catenary system. As for the second application area, physics, only one model was studied. We estimated the half-lives of ^{226}Ra , ^{222}Rn , and ^{218}Po using a two-compartment two-parameter model. Since no actual decay data was available, simulated decay data were used.

CHAPTER 2

BAYESIAN APPROACH

The core of the Bayesian parameter estimation approach used here is a result derived using Bayes' Theorem by Box and Draper (Box and Draper, 1965). Since the analysis often involves joint inferences about several parameters, the traditional visual aid, the marginal density plot, is inadequate. Instead, a two-dimensional plot called highest posterior density (HPD) contour plot is used to illustrate the uncertainty about pairs of parameters. This chapter introduces Bayes' Theorem, the general theory behind the Box and Draper likelihood, and the concept of the HPD contour.

2.1 *Bayes Theorem*

In classical statistical inference, the quality of the estimators and test statistics is judged based on their performance with repeated samples. However, it can be argued that the performance in repeated sampling is not an appropriate basis for drawing inferences from observational data (Crowder *et al.*, 1995). In the Bayesian point of view, probability statements about the unknown parameters are made conditionally on the observed data:

$$p(\theta | D) \propto p(\theta) \cdot L(\theta | D). \quad (2.1)$$

The posterior density $p(\theta | D)$ quantifies the remaining uncertainty about the parameter θ given the likelihood of the data $L(\theta | D)$, and the prior belief $p(\theta)$.

The likelihood plays an important role in Bayes' Theorem. It is the function through which the data modify the prior knowledge of θ , and represents the information about θ coming from the data (Box and Tiao, 1973). The other factor in Bayes' Theorem is the prior density. It represents the often subjective information about the unknown parameters before updating with the observed data. In other words, Bayes' Theorem is a mechanism by which one's prior beliefs are revised in the light of the sample information (Crowder *et al.*, 1995). Furthermore, the posterior means and variances can be easily calculated from the joint posterior density using the following definitions:

$$\begin{aligned} \text{Posterior Mean of } \theta &= E(\theta) = \int \theta \cdot p(\theta | \text{data}) \\ E(\theta^2) &= \int \theta^2 \cdot p(\theta | \text{data}) \end{aligned} \quad (2.2)$$

$$\text{Posterior Variance of } \theta = E(\theta^2) - E(\theta)^2$$

2.2 Box and Draper Likelihood Equation

The parameter estimation technique used here is a special form of a more generalized procedure developed by Box and Draper (Box and Draper, 1965). It starts by assuming that for k compartments with m common parameters ($\theta_1, \theta_2, \dots, \theta_m$), n sets of observations are available and that the u_{th} set of observation consists of compartmental responses y_{uk} at time x_u . If the observation errors are normally distributed and are related to the response y_{uk} through:

$$y_{uk} = f(x_u, \theta) + \epsilon_{uk}, \quad (2.3)$$

then the likelihood for the data $\bar{y}$ given (Σ, θ) based on a multivariate Normal error density is:

$$p(\bar{y}|\Sigma, \theta) = (2\pi)^{-\frac{1}{2}nk} |\sigma^{ij}|^{\frac{n}{2}} \exp\left(-\frac{1}{2} \sum_{i=1}^k \sum_{j=1}^k \sigma^{ij} S(\theta)\right), \quad i, j = 1, 2, \dots, m. \quad (2.4)$$

σ^{ij} is the variance-covariance matrix of y , and $S(\theta)$ is a $m \times m$ symmetric matrix defined as:

$$S_{ij}(\theta) = S_{ij}(\theta_i, \theta_j) = \sum_{u=1}^n [y_{ui} - f_i(x_u, \theta_i)] \cdot [y_{uj} - f_j(x_u, \theta_j)], \quad i, j = 1, 2, \dots, m. \quad (2.5)$$

$f(x_u, \theta)$ is the expectation function and represents, in compartmental analysis, the solutions of the differential equations describing the system. Assuming uniform prior distribution for θ and using a Jeffrey's prior

$$p(\sigma^{ij}) = |\sigma^{ij}|^{-\frac{1}{2}(k+1)}, \quad (2.6)$$

and Wishart distribution, the likelihood for the model parameters θ is simplified to (Box and Draper, 1965):

$$L(\theta) \propto |S(\theta)|^{-n/2}, \quad -\infty < \theta < \infty, \quad n \geq m. \quad (2.7)$$

Because of the way it was derived, the Box and Draper likelihood, Eqn. (2.7), has the following characteristics (Box and Draper, 1965):

- Input variables x_u are either common or not common to more than one output.
- Parameters θ are either common or not common to more than one output.
- Expectation functions are either linear or nonlinear in the parameters.

2.3 *Highest Posterior Density Contour*

One advantage of using Bayes' Theorem is the ability to use posterior densities to characterize the remaining uncertainty about the parameters given the observed data. It is common to use marginal posterior densities to describe such uncertainty, but joint probability statements about certain parameter combinations cannot be easily grasped from marginal density plots. One way of summarizing the information about joint inferences is through highest posterior density (HPD) contours or regions.

An HPD contour or region is a two dimensional analogue of the Bayesian confidence interval. The region is defined such that the probability density of every point inside it is at least as large as that of any point outside it. Mathematically, a $100(1 - \alpha)$ percent HPD region $\mathbf{R}$ can be defined as:

$$\frac{\int_{\mathbf{R}} p(\theta|\mathbf{y}) d\theta}{\int_{\Theta} p(\theta|\mathbf{y}) d\theta} = (1 - \alpha), \quad (2.7)$$

where Θ is the parameter space. Graphically, the HPD region $\mathbf{R}$ and the corresponding HPD contour c are created by a plane parallel to the parameter θ axes intersecting the posterior density at $f(\theta) = z$, see Fig. 2.1. If the posterior density is normalized, then the volume of the HPD region $\mathbf{R}$, defined by contour c at height z , is equal to $(1 - \alpha)$. Therefore, contour c represents $100(1 - \alpha)$ percent HPD.

An HPD contour or region should be carefully distinguished from a classical confidence region. A Bayesian HPD region has a direct probability interpretation of the

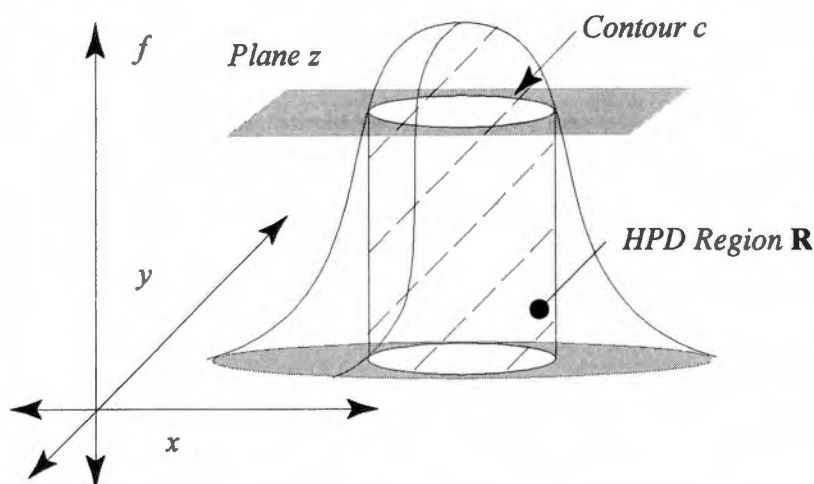


Figure 2.1. A HPD contour c created by a plane z parallel to parameter θ axes at $f(\theta) = z$.

uncertainty about the unknown parameters. Where as hypothetical repetitions are needed to provide an interpretation for the classical, non-Bayesian confidence region. Hence, a true value lies within the 95% HPD region with a 95% probability, and it will lie 95% of the time in the 95% different classical confidence regions calculated from repeated samples. There are infinite numbers of ways such HPD contours can be chosen. In this dissertation, 90 and 95 percent HPD contours will be used.

An HPD contour or region should be carefully distinguished from a classical confidence region. A Bayesian HPD region has a direct probability interpretation of the uncertainty about the unknown parameters. Where as hypothetical repetitions are needed to provide an interpretation for the classical, non-Bayesian confidence region. Hence, a true value lies within the 95% HPD region with a 95% probability, and it will lie 95% of the time in the 95% different classical confidence regions calculated from repeated samples. There are infinite numbers of ways such HPD contours can be chosen. In this dissertation, 90 and 95 percent HPD contours will be used.

The easiest way of calculating the volume of $\mathbf{R}$ is through iterative brute force methods using a normalized probability density. Using Fig. 2.2 as a guide, the first step is to partition the x and y axes into small grids. Second, select a z value between zero and f_{max} . This value will be used by graphical programs to draw the contours. Next, the posterior density is evaluated at the center of each grid to see if its “prism” is inside the contour c . If it is, then the volume of the prism at (x_i, y_j) is calculated and added to memory. Otherwise, the prism is outside region $\mathbf{R}$, and it is discarded.

Since an HPD contour plot is two-dimensional, numerical integration over the non-plotted parameter(s) is performed whenever the multidimensional posterior density is evaluated at each grid center. When all of the grids are evaluated, the percentage for the HPD described by the contour c is equal to the sum of the calculated “prism” volumes in memory. Finally, the steps are repeated for different z values until a desired HPD volume is found. A pseudocode describing this method is listed at the end of this chapter.

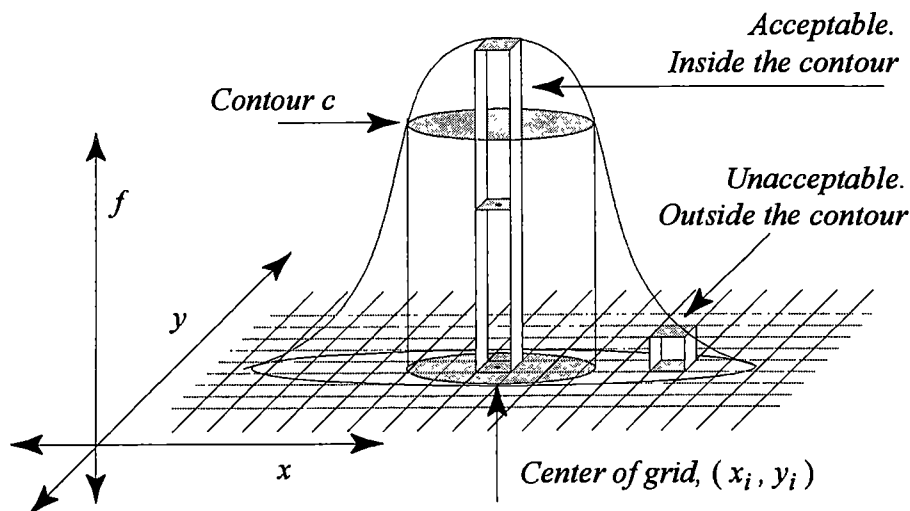


Figure 2.2. Illustration showing the iterative HPD volume calculation with two possible scenarios: prism inside and outside the contour c or HPD region $\mathbf{R}$.

```

/* Pseudocode for calculating HPD volume using normalized
   density f() and iterative method */

Input z_value, number_of_x_grids, number_of_y_grids
Input range_x_min, range_x_max, range_y_min, range_y_max
dx = (range_x_max - range_x_min)/number_of_grids_in_x
dy = (range_y_max - range_y_min)/number_of_grids_in_y
ddx = dx/2
ddy = dy/2
Grid_area = dx*dy

/* Initialize HPD volume and start grid selection loop */
Volume = 0.0
For I = xmin to xmax step dx
  {
    x = I + ddx
    For j = ymin to ymax step dy
      {
        y = j + ddy
        If number of density's parameters > 2
          Function = Integrate f() over other parameters
        Else
          Function = Evaluate[f(x,y)]
        Endif
        /* Test to see if current point is inside contour c */
        If Function >= z_value
          Volume = Grid_area * Function + Volume
        Else Endif
      }
    }
  }
Volume = 100*HPDVolume
Output "Approximate", Volume, "Percent HPD at z =", z_value
End of Program

```

CHAPTER 3

EXCHANGE OF CALCIUM AT BONE SURFACES IN BEAGLES

The exchange of calcium at bone surfaces in beagles can be described by a two-compartment three-parameter model. Illustrated in Fig. 3.1, λ_{12} , λ_{21} and μ are the parameters representing the exchange of calcium to and from the bone surfaces and blood plasma compartments. Discussions about the mathematical model and the differential equations used to describe the compartmental system are presented in section 3.1. Followed by a brief statement about the biokinetic data in section 3.2. The Bayesian estimation results using uniform and Normal priors for two types of observations, all observations versus incomplete observations, are presented in sections 3.3 through 3.5.

3.1 *Mathematical Model*

Assuming the compartments are homogenous and have constant exchange rates, the differential equations describing the exchange of calcium at bone surfaces in beagles are given in Eqn. (3.1). The equations are two simultaneous first order linear differential

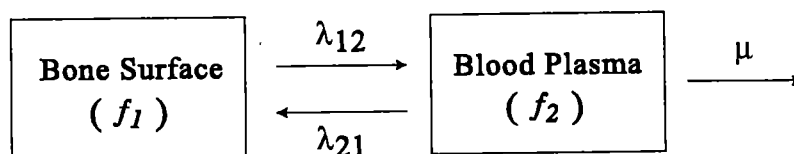


Figure 3.1. A two-compartment three-parameter model describing the exchange of calcium at bone surfaces in beagles.

$$\begin{aligned}\frac{df_1}{dt} &= \lambda_{21}f_2 - \lambda_{12}f_1 \\ \frac{df_2}{dt} &= \lambda_{12}f_1 - (\lambda_{21} + \mu)f_2\end{aligned}\tag{3.1}$$

equations with each individual term representing a basic process occurring in the system. Assuming initial calcium concentration of f_2^0 for plasma and zero for bone surfaces, the above differential equations can be solved using the method of eigenvalues (Jacques, 1985):

$$\begin{aligned}f_1(\lambda_{12}, \lambda_{21}, \mu, t) &= \frac{\lambda_{21}f_2^0}{m_1 - m_2} (e^{-m_2 t} - e^{-m_1 t}) \\ f_2(\lambda_{12}, \lambda_{21}, \mu, t) &= \frac{f_2^0}{m_1 - m_2} [(\lambda_{12} - m_2) e^{-m_2 t} - (\lambda_{12} - m_1) e^{-m_1 t}]\end{aligned}\tag{3.2}$$

where

$$\begin{aligned}m_1 &= \frac{1}{2} \left(\lambda_{12} + \lambda_{21} + \mu + \sqrt{(\lambda_{12} + \lambda_{21} + \mu)^2 - 4\lambda_{12}\mu} \right) \\ m_2 &= \frac{1}{2} \left(\lambda_{12} + \lambda_{21} + \mu - \sqrt{(\lambda_{12} + \lambda_{21} + \mu)^2 - 4\lambda_{12}\mu} \right)\end{aligned}$$

$-m_1$ and $-m_2$ are the eigenvalues of the system matrix for Eqn. (3.1), and they are independent of the initial conditions

$$\begin{pmatrix} -\lambda_{12} - m & \lambda_{21} \\ \lambda_{12} & -\lambda_{21} - \mu - m \end{pmatrix}.\tag{3.3}$$

3.2 ⁴⁵Ca Biokinetic Data

The biokinetic data used came from an earlier autoradiographic study on the exchange of ⁴⁵Ca at bone surfaces in beagles (Rowland, 1966). Plotted in Fig. 3.2 and listed in Table 3.1, the data consist of ten normalized measurements of ⁴⁵Ca specific activity at bone surfaces and in plasma with an initial plasma specific activity of 27.1 $\mu\text{Ci/mg}$ ⁴⁵Ca (Groer and Marshall, 1973). The bone surfaces activity at one hour (see Table 3.1) is an average of four normalized midpoint surface activities (Rowland, 1966).

3.3 Uniform Priors – All Ten Data Points

The first part of the analysis uses uniform priors. Therefore, the joint posterior density of the parameters λ_{12} , λ_{21} and μ is proportional to the Box and Draper likelihood, Eqn. (2.6). For a two-compartment three-parameter model and ten data points, the joint posterior density of the parameters λ_{12} , λ_{21} and μ can be written as:

$$p(\lambda_{12}, \lambda_{21}, \mu \mid \text{data}) \propto \left[S_{11}(\theta) S_{22}(\theta) - S_{12}(\theta)^2 \right]^{-5}, \quad (3.4)$$

where

$$S_{11}(\theta) = \sum_{u=1}^{10} \left[y_{u1} - f_1(\lambda_{12}, \lambda_{21}, \mu, t_u) \right]^2$$

$$S_{22}(\theta) = \sum_{u=1}^{10} \left[y_{u2} - f_2(\lambda_{12}, \lambda_{21}, \mu, t_u) \right]^2$$

$$S_{12}(\theta) = S_{21}(\theta) = \sum_{u=1}^{10} \left[y_{u1} - f_1(\lambda_{12}, \lambda_{21}, \mu, t_u) \right] \cdot \left[y_{u2} - f_2(\lambda_{12}, \lambda_{21}, \mu, t_u) \right]$$

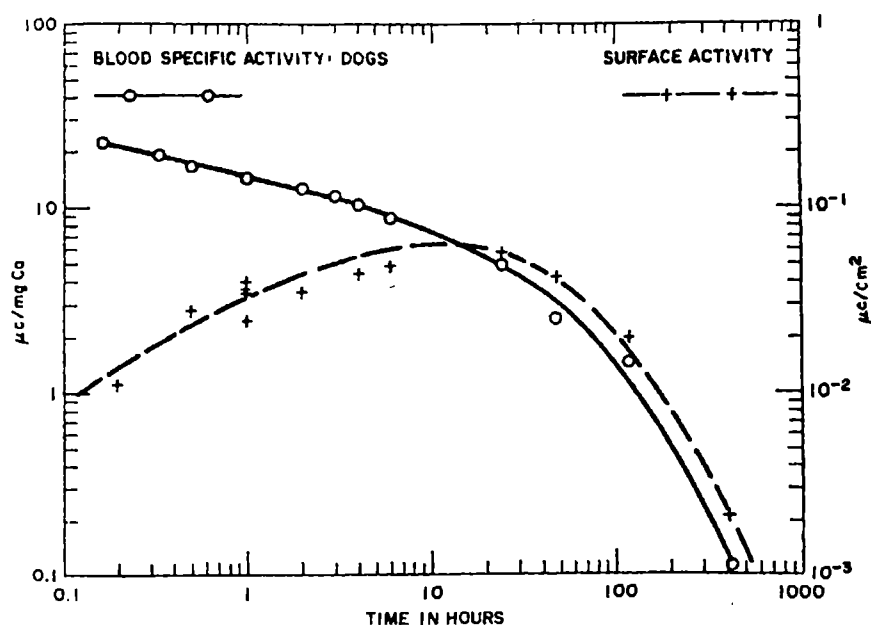


Figure 3.2. Plot of normalized ^{45}Ca bone surfaces and plasma specific activities as a function of time in beagles. Source: Rowland, R. E. Exchangeable Bone Calcium. Clinical Orthopedics and Related Research. 49: 233-248; 1966.

Table 3.1. Normalized ^{45}Ca bone surfaces and plasma specific activities in beagles.

Time (hours)	Compartment Activity ($\mu\text{Ci/mg } ^{45}\text{Ca}$)	
	Bone Surface	Plasma
0	0	27.1
0.2	1.1	22
0.52	2.81	17
1	3.39 ^a	15
2	3.53	14
4	4.37	9.5
6	4.89	8
24	5.79	5
48	4.16	2.3
120	1.97	1.3
408	0.21	0.1

^a Average of four normalized midpoint bone surfaces activities.

Due to the complexity of the posterior density, integration of the density over the parameters has to be done numerically. To select a set of integration limits, series of 3D surface and marginal posterior density plots were generated using various integration limits. Plots of the marginal posterior density for parameters λ_{12} , λ_{21} and μ using the smallest and largest integration limits are shown in Figs. 3.3 through 3.5.

The marginal density plots showed two interesting facts: bimodality for parameter μ and monotonic increase or “divergent” behavior for parameter λ_{12} . Both features are reproducible using various numerical integration algorithms and software packages. Since the posterior densities were derived using uniform priors, the likelihood function is the cause of these phenomena. From Fig. 3.2, the relevant time scale extends to about 500 hours or $\lambda = 1/500 = 0.002$ 1/h. If the integration limits $0 \leq \lambda_{12} \leq 0.2$ and $0 \leq \lambda_{21}, \mu \leq 1$ are chosen, bimodality and the divergent behaviors are reduced.

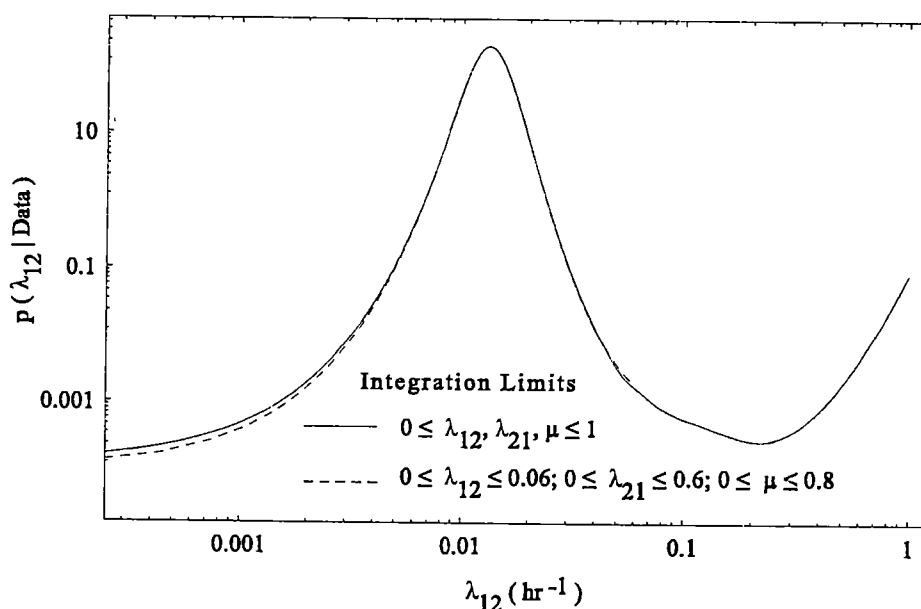


Figure 3.3. Normalized marginal posterior density for the calcium exchange rate λ_{12} in beagles with uniform priors for the smallest and largest integration limits.

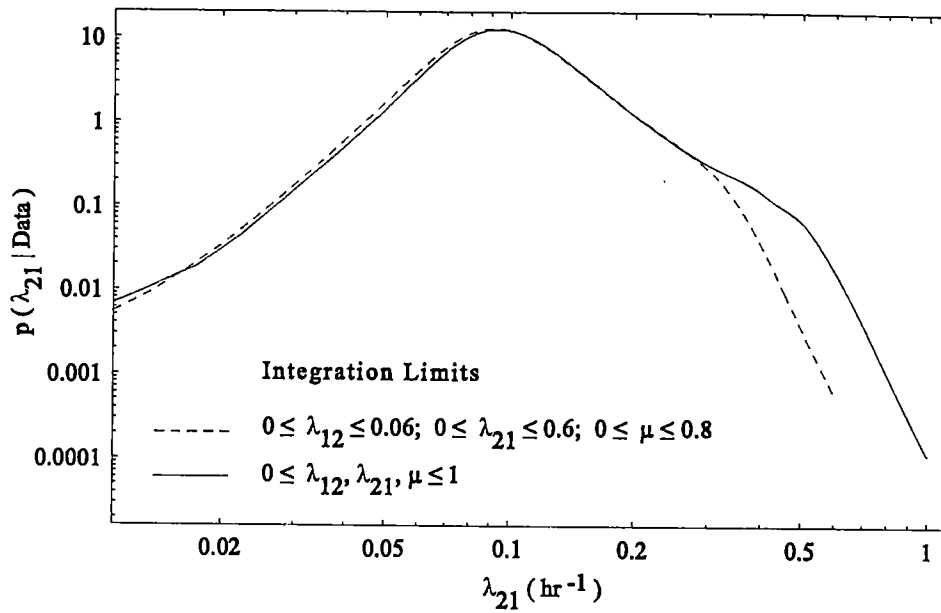


Figure 3.4. Normalized marginal posterior density for the calcium exchange rate λ_{21} in beagles with uniform priors for the smallest and largest integration limits.

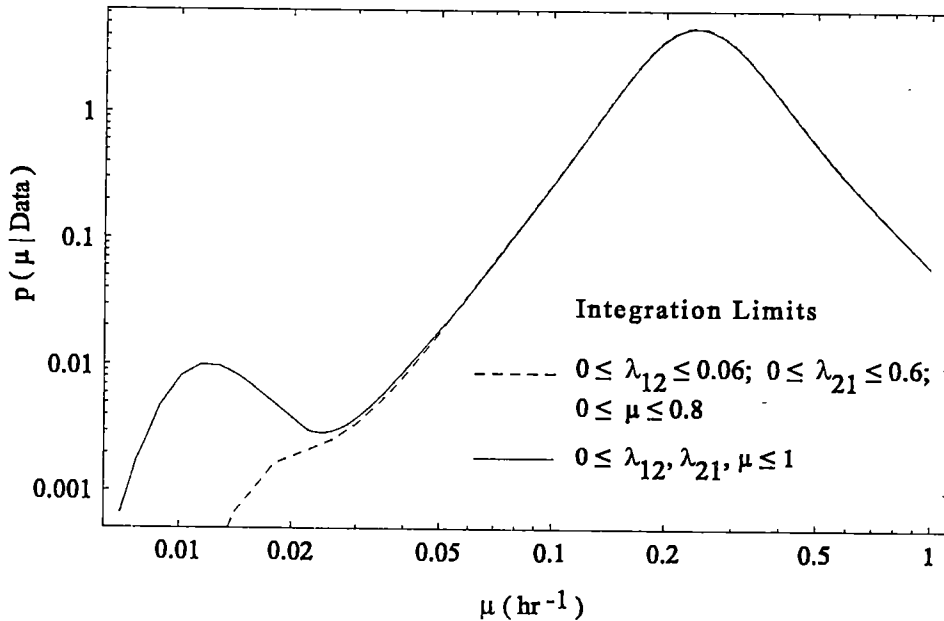


Figure 3.5. Normalized marginal posterior density the calcium exchange rate μ in beagles with uniform priors for the smallest and largest integration limits. Notice the bimodality of the density.

3.3.1 Both bone surfaces and plasma data are used

If both plasma and bone surfaces data are used, the joint posterior density is the same as Eqn. (3.4). A log-log plot of the normalized marginal posterior density for the parameters is shown in Fig. 3.6. The posterior modes, means and standard deviations of the estimated parameters are listed in Table 3.2. From the marginal density plot, the presence of bimodality in parameter μ is clear. Because the second mode is small and only visible in the log-log plots, the bimodality can be easily overlooked. The appearance of bimodality is interesting and is due to the likelihood. The next two sections will show the relationship between the data and the bimodality.

Next, we will compare the estimated residence time of ^{45}Ca at bone surfaces calculated from our model with the published values. In our model, the residence time τ is equal to the inverse of the ^{45}Ca exchange rates at bone surfaces:

$$\tau = (\lambda_{12} + \lambda_{21})^{-1}. \quad (3.5)$$

Rowland judged τ in beagles to be about 400 minutes (Rowland, 1966). The Bayesian estimates calculated using posterior means gave a value of about 440 minutes and about 570 minutes when calculated using posterior modes, see Table 3.3.

We next fitted the solution of the differential equations, Eqn. (3.4), to the data using the estimated parameter values. Plots of the fits using both posterior modes and means for the bone surfaces data are shown in Fig. 3.7, and for the plasma data in Fig. 3.8. Although the values of the parameter estimates are not the same, both fitting methods produced almost identical results.

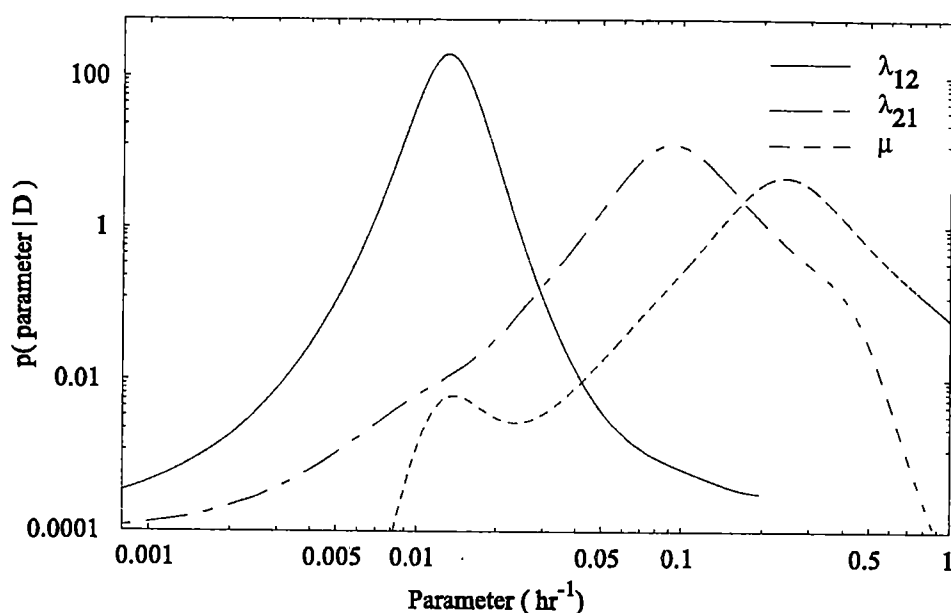


Figure 3.6. Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with all ^{45}Ca data and uniform priors. The means ($\mu\text{Ci/mg } ^{45}\text{Ca hr}$) are $\lambda_{12} = 0.01365 \pm 0.00262$, $\lambda_{21} = 0.1227 \pm 0.0644$ and $\mu = 0.3122 \pm 0.146$.

Table 3.2. Posterior means, modes and standard deviations for the calcium exchange rates in beagles calculated with all ^{45}Ca data and uniform priors.

	λ_{12}	λ_{21}	μ
	(μCi/mg ^{45}Ca hour)		
Posterior Mean	0.01365 ± 0.00262	0.1227 ± 0.0644	0.3122 ± 0.146
Posterior Mode	0.0131	0.0915	0.240

Table 3.3. Comparison of the residence time of calcium ions in beagles.

	Rowland ^a	Bayesian Approach	
		Posterior Means	Posterior Modes
τ (min)	400	440	570

^a Rowland, R. E. Exchangeable Bone Calcium. Clin. Orthop. Res. 49: 233-248; 1966.

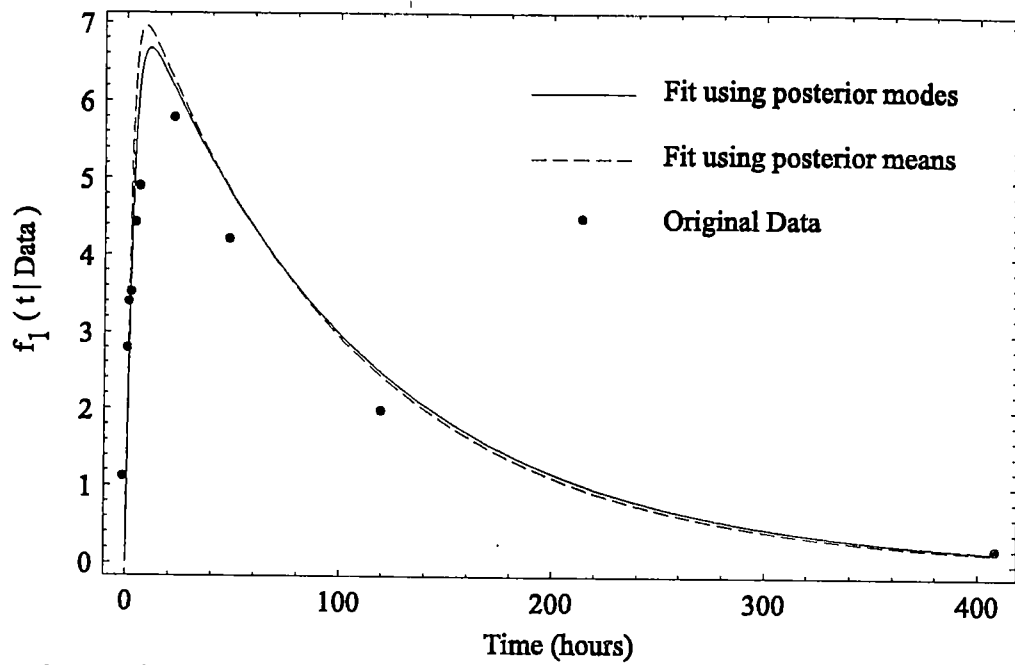


Figure 3.7. Solution of the differential equations for the parameter estimates calculated with all ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

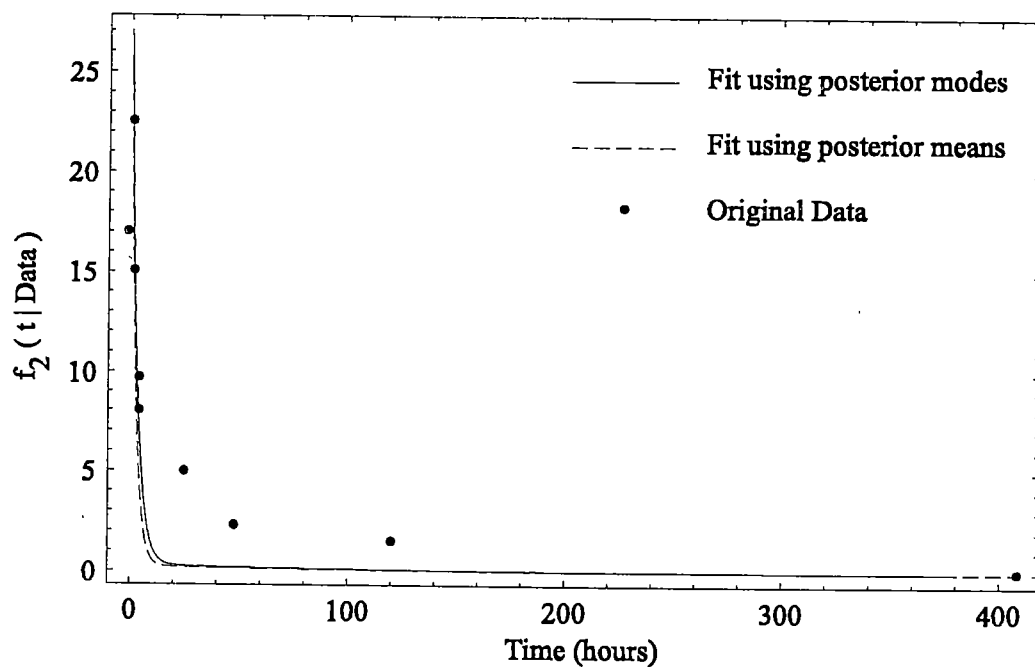


Figure 3.8. Solution of the differential equations for the parameter estimates calculated with all ^{45}Ca data and uniform priors fitted to the beagles plasma ^{45}Ca data.

Finally, we describe the generation of the highest posterior density (HPD) contour plots for the parameters. Since an HPD contour plot is two-dimensional and we have three parameters, three separate HPD contour plots are needed to cover all of the possible combinations of the parameters: $(\lambda_{12}, \lambda_{21})$, (λ_{12}, μ) and (λ_{21}, μ) . Using the HPD volume calculation procedures described in section 2.3, the 90 and 95 percent HPD z values are listed in Table 3.4. The corresponding HPD contours are plotted in Figs. 3.9 through 3.11. The resulting HPD contours are closed, which indicate good estimation results. Precision of any estimation procedure, of course, depends on the available data. The next two sections will discuss what happens to the estimates when single compartmental data are used in the analysis.

Table 3.4. Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with all ^{45}Ca data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
λ_{12} and λ_{21}	83	34
λ_{12} and μ	35	15
λ_{21} and μ	4.53	1.34

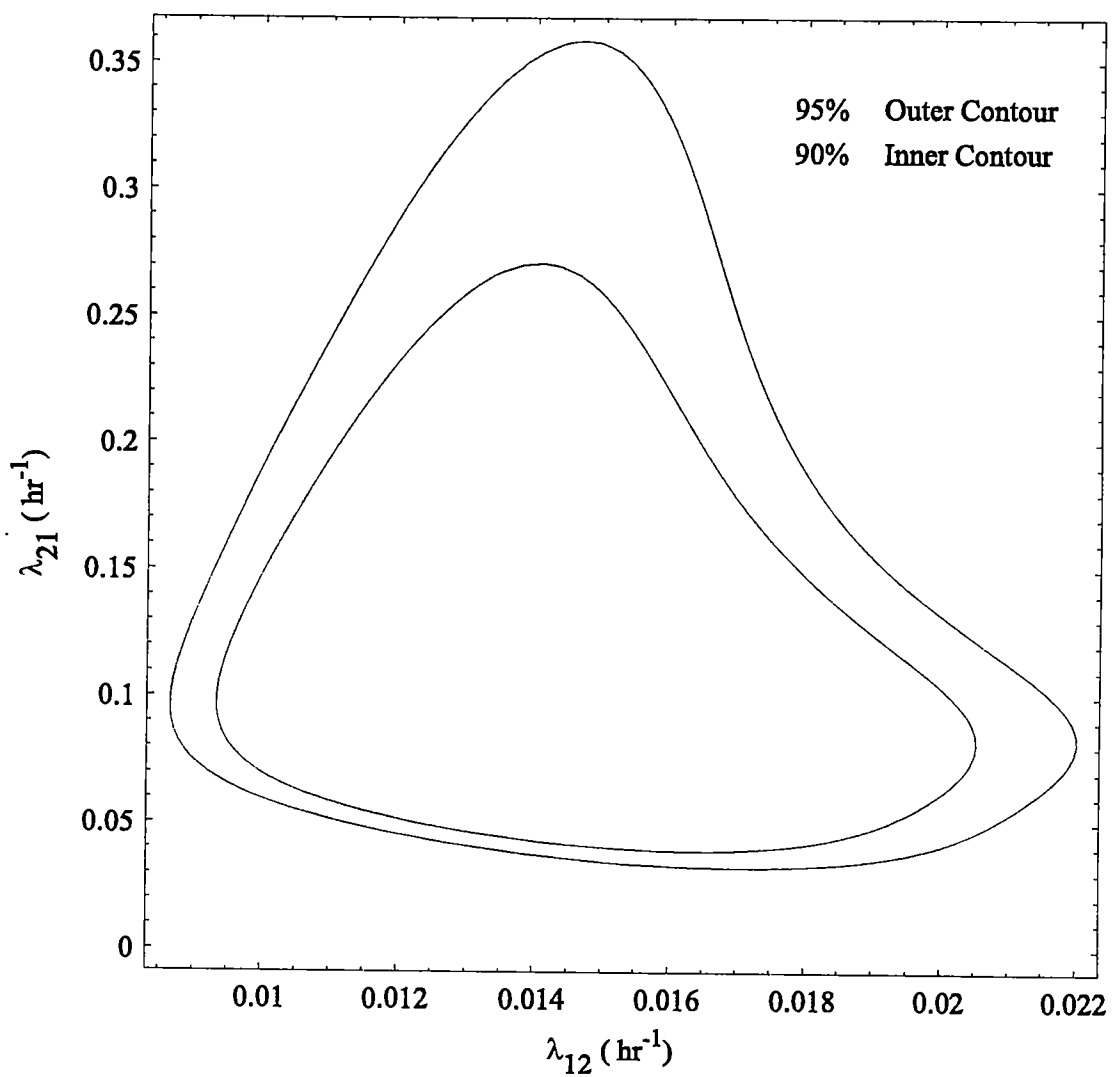


Figure 3.9 Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with all ^{45}Ca data and uniform priors.

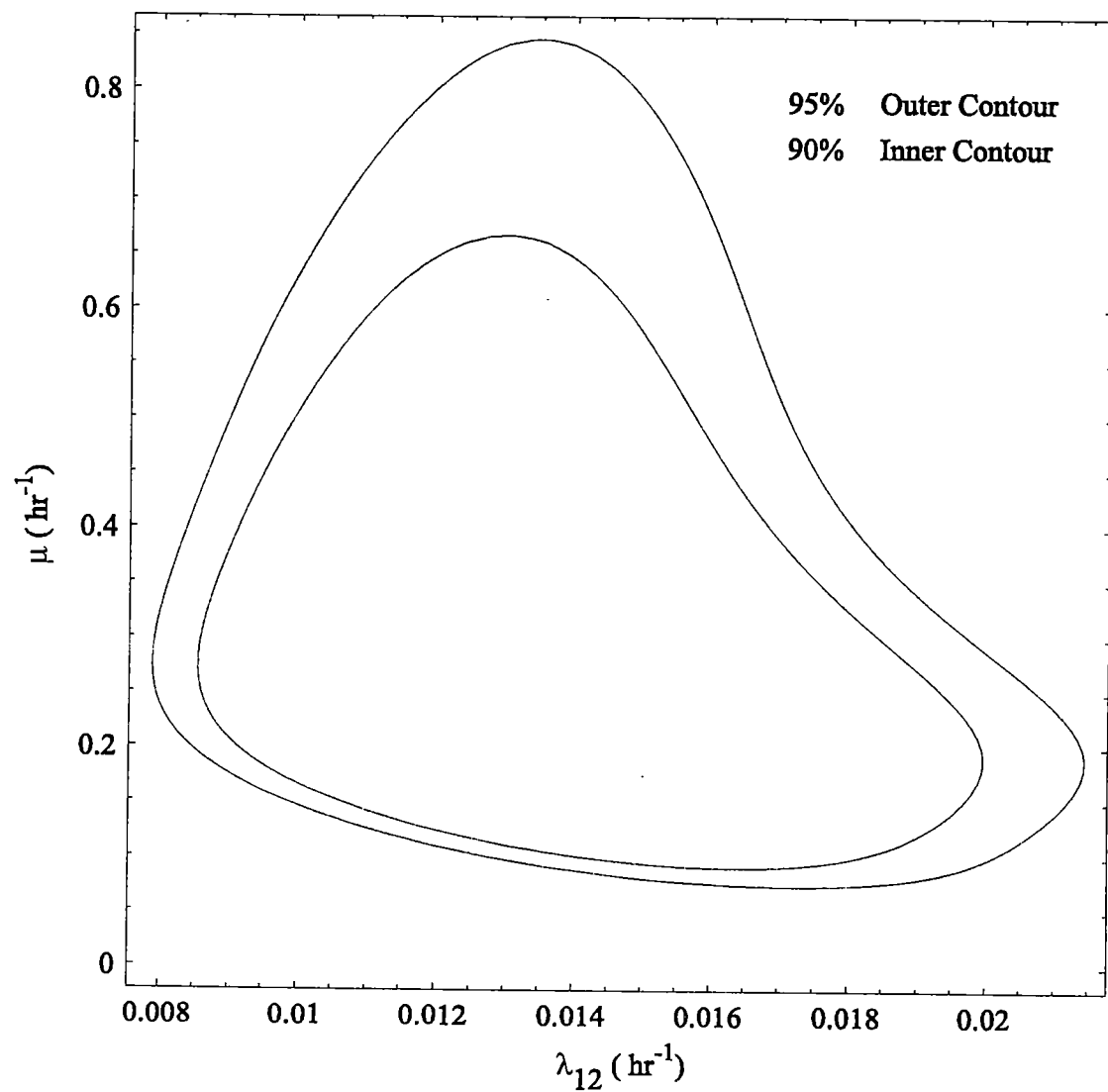


Figure 3.10. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with all ^{45}Ca data and uniform priors.

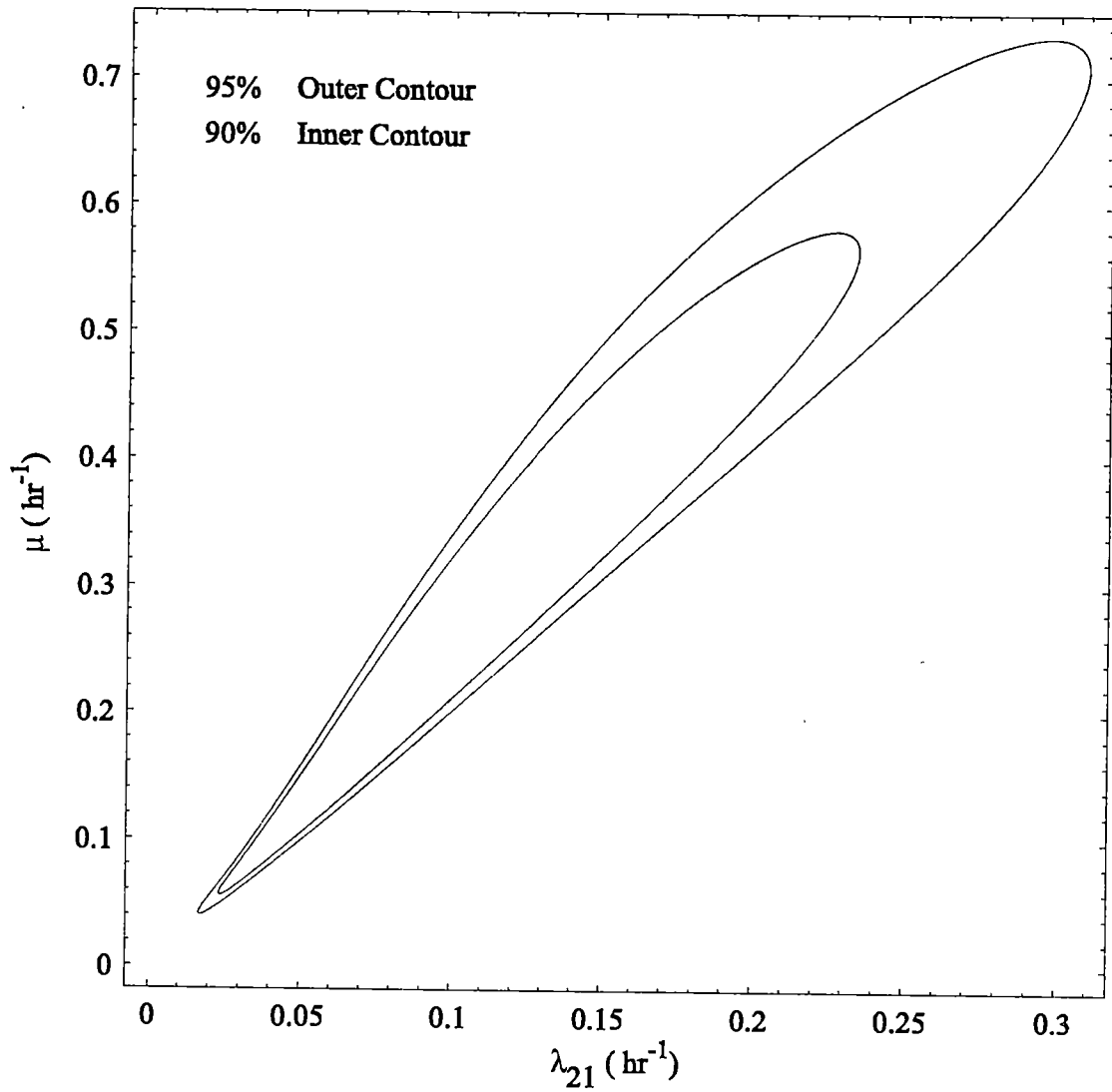


Figure 3.11. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with all ^{45}Ca data and uniform priors.

3.3.2 Only the bone surfaces data are used

This portion of the analysis deals with the consequences of reducing the number of data used in the Bayesian parameter estimation technique. If only the bone surfaces data are used, the joint posterior density with uniform priors is simplified to:

$$p(\lambda_{12}, \lambda_{21}, \mu \mid data) \propto S_{11}(\theta)^{-5}, \quad (3.6)$$

where $S_{11}(\theta)$ was defined earlier by Eqn. (3.4). Using the same integration limits as before, log-log plots of the normalized posterior densities for the parameters are shown in Fig. 3.12 with the Bayesian estimates listed in Table 3.5. Comparing to the analysis using all available data, the use of bone surfaces only data made the bimodality for μ more pronounced and perhaps started a new one for λ_{21} .

Next, the solution of the differential equations was fitted to the data using the estimated parameter values based on bone surfaces data. The fits using both posterior means and modes for the bone surfaces data are shown in Fig. 3.13, and for the plasma data in Fig. 3.14. As expected, the fits are worse than the fits using all available data.

Finally, the effects of reduced data on HPD contour plots are examined. A comparison of the plots of the 90 and 95 percent HPD contours for the bone surfaces data versus both compartmental data are shown in Figs. 3.15 through 3.17, with the corresponding contour z values listed in Table 3.6. The resulting contours are larger and some are open. This is due to the "widening" of the joint posterior density. The open contour indicates that the estimation variance is large and can be infinite.

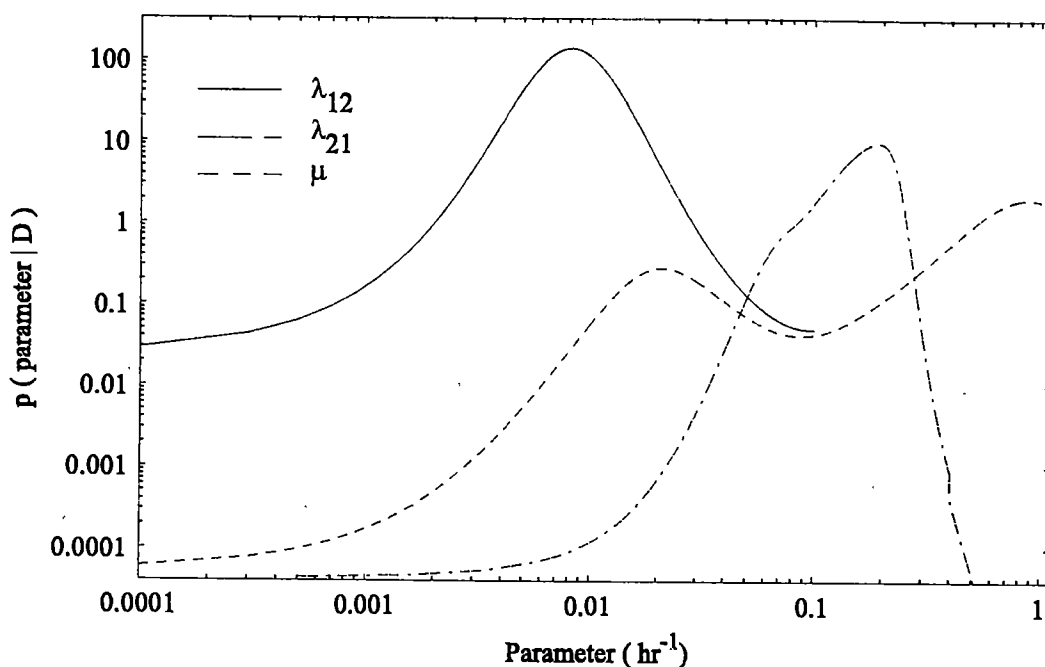


Figure 3.12. Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors. The means ($\mu\text{Ci/mg } ^{45}\text{Ca hour}$) are $\lambda_{12} = 0.01132 \pm 0.014$, $\lambda_{21} = 0.177 \pm 0.049$ and $\mu = 0.7127 \pm 0.199$.

Table 3.5. Posterior means, modes and standard deviations for the calcium exchange rates in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.

	λ_{12}	λ_{21}	μ
	$(\mu\text{Ci/mg } ^{45}\text{Ca hour})$		
Posterior Mean	0.01132 ± 0.014	0.1769 ± 0.0409	0.7127 ± 0.199
Posterior Mode	0.0081	0.192	0.853

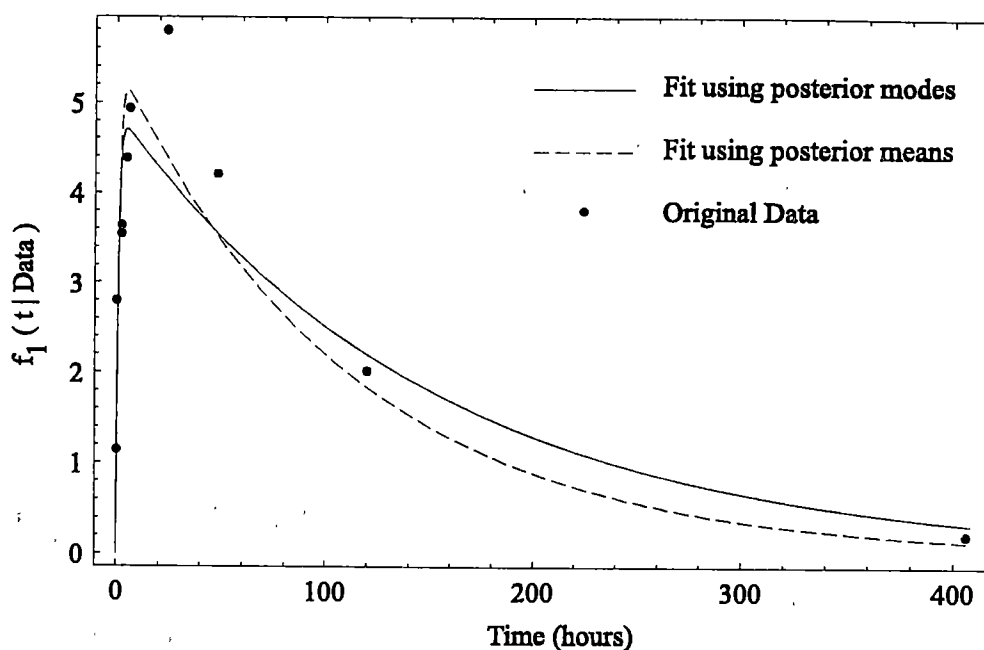


Figure 3.13. Solution of the differential equations for the parameter estimates calculated with the bone surfaces ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

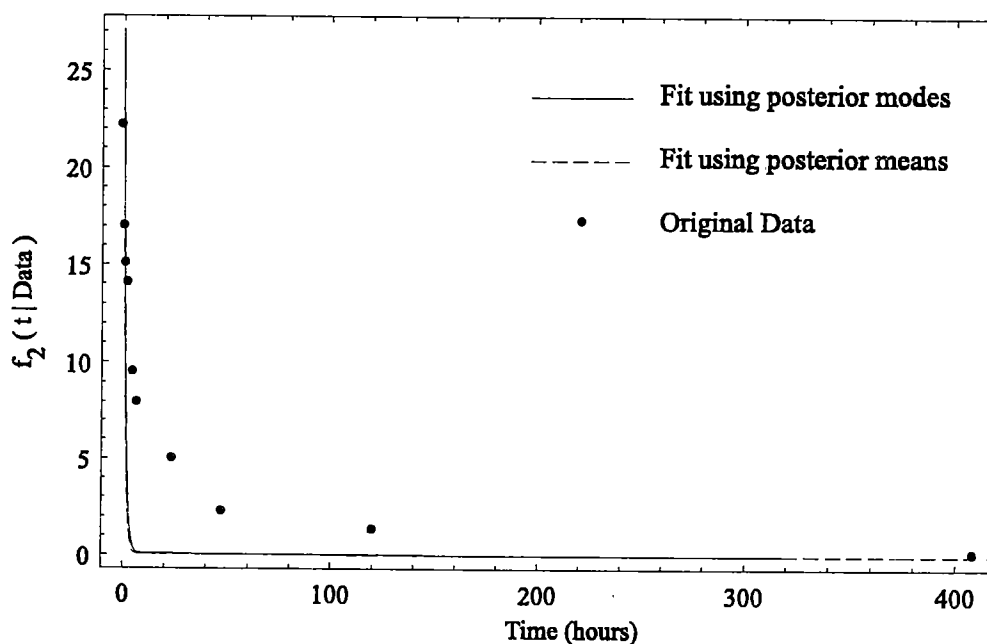


Figure 3.14. Solution of the differential equations for the parameter estimates calculated with the bone surfaces ^{45}Ca data and uniform priors fitted to the beagles plasma ^{45}Ca data using.

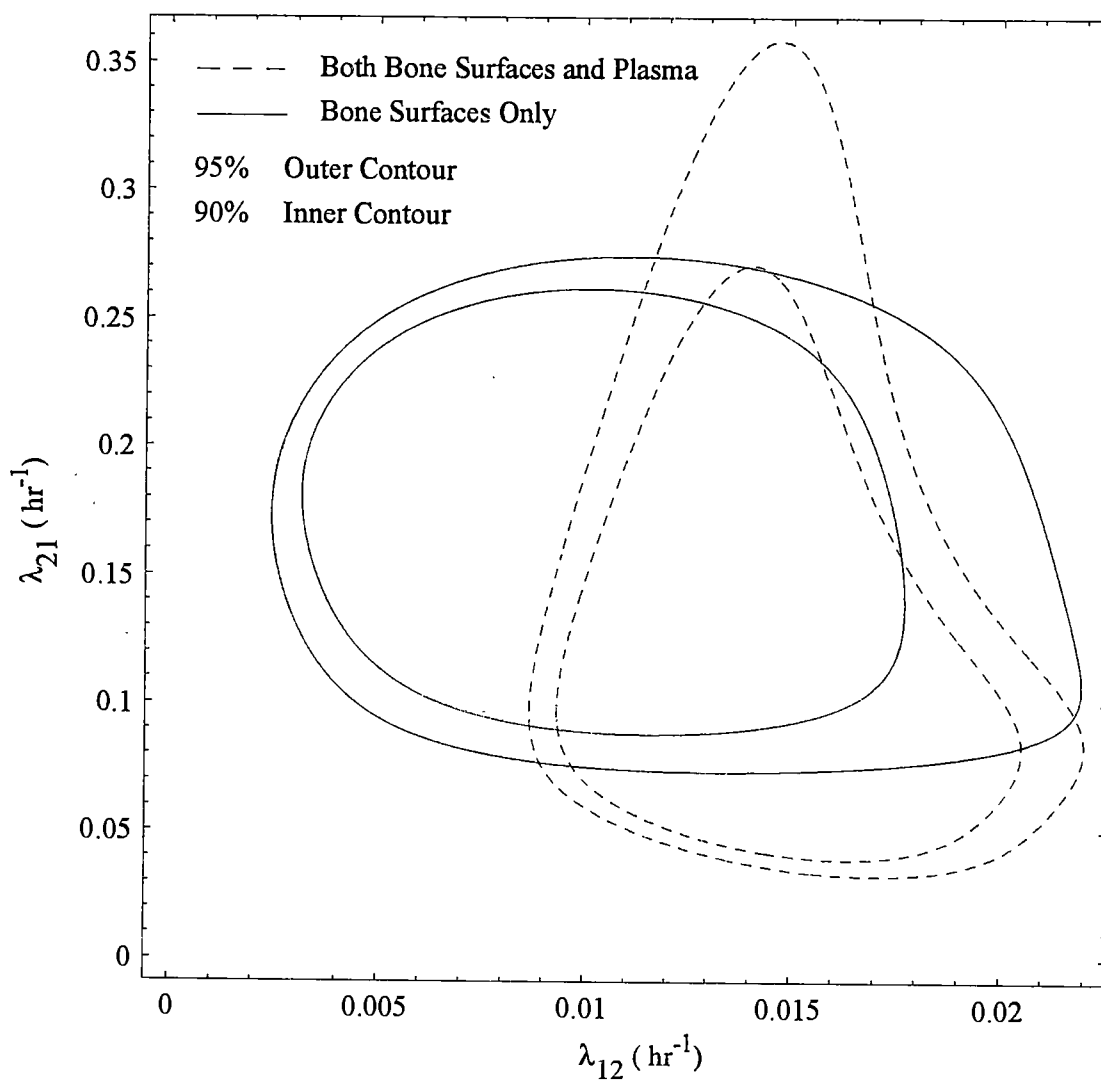


Figure 3.15. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.

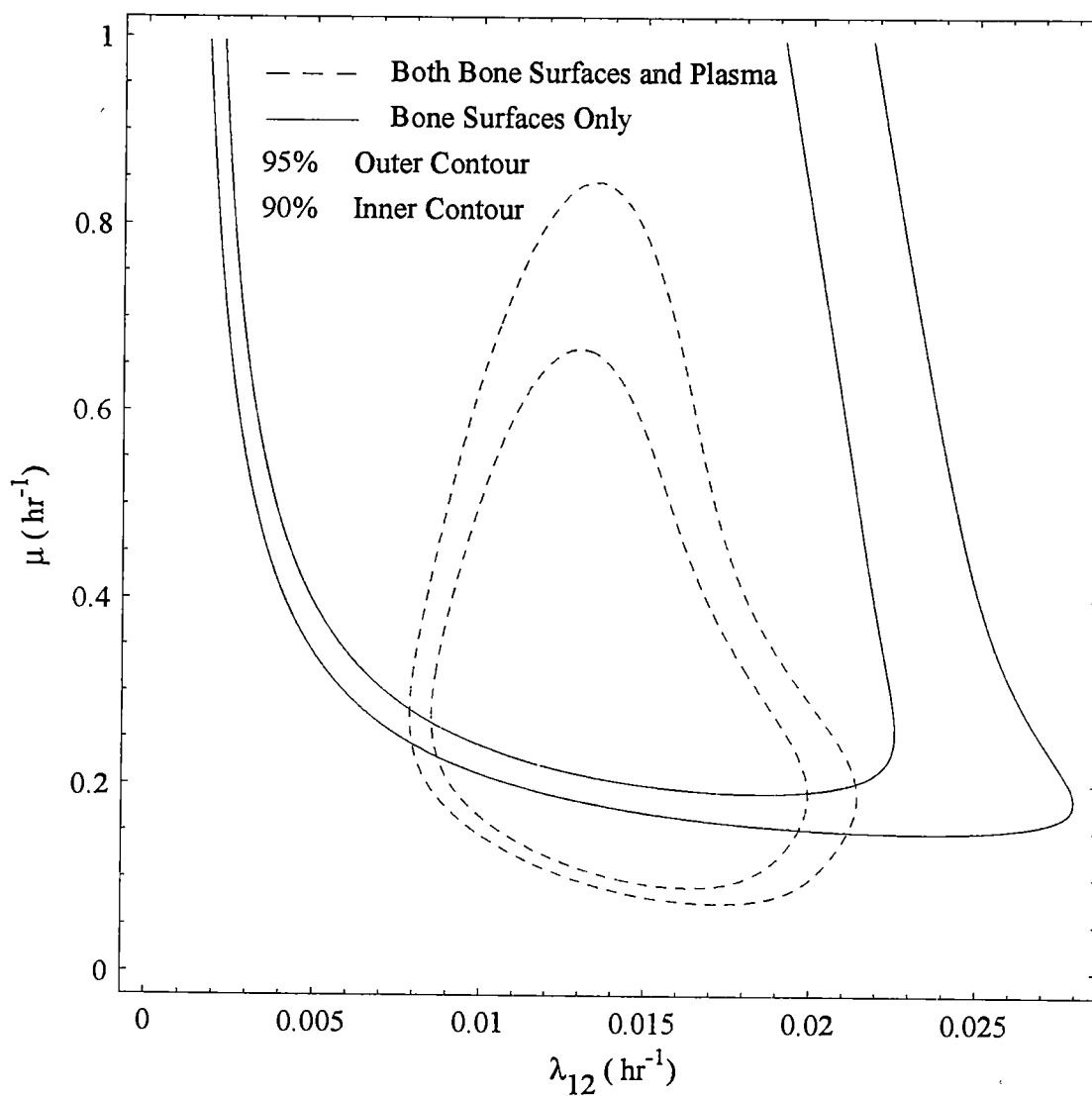


Figure 3.16. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.

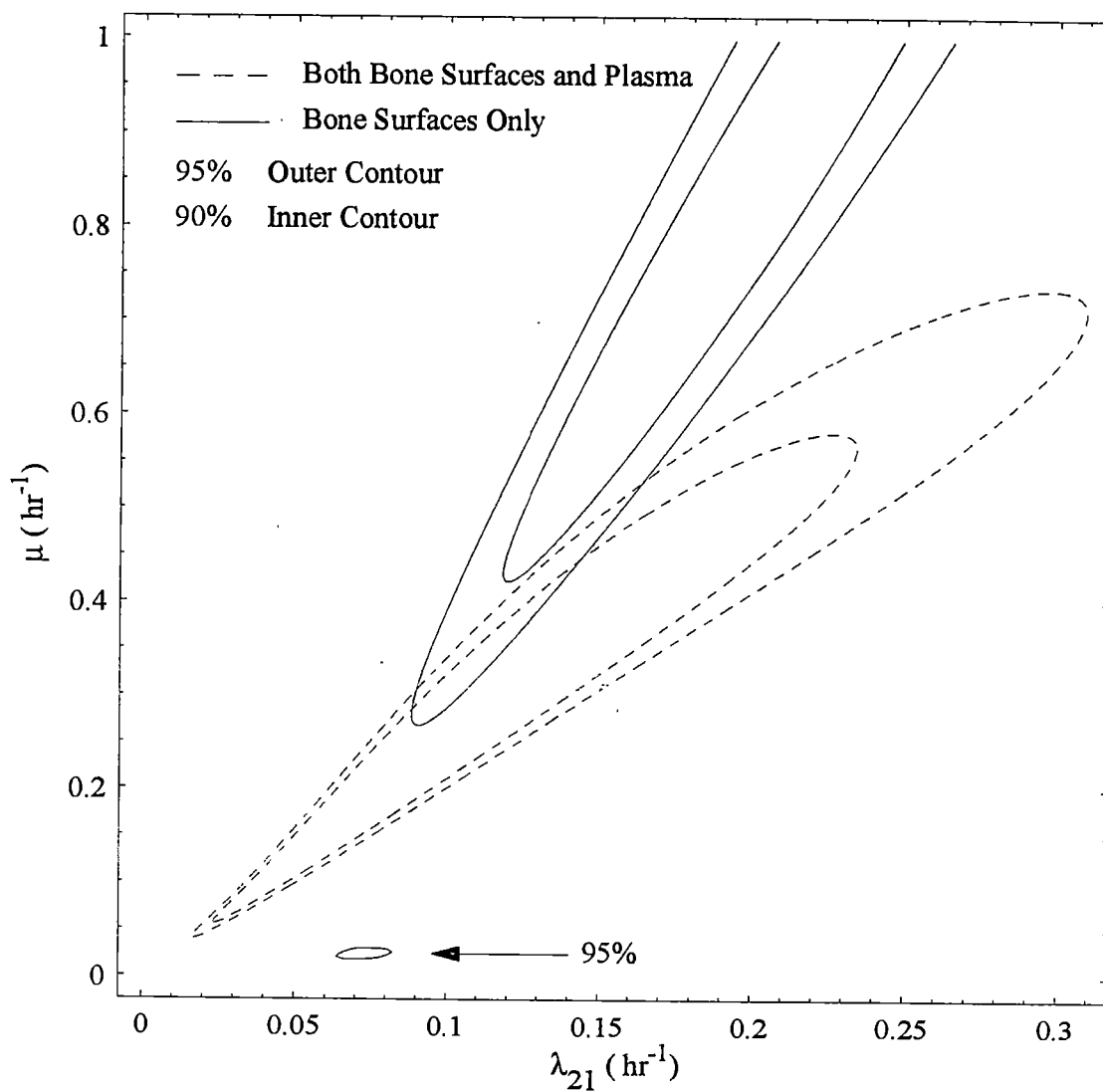


Figure 3.17. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.

Table 3.6. Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the bone surfaces ^{45}Ca data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
λ_{12} and λ_{21}	75	25
λ_{12} and μ	5.5	2.6
λ_{21} and μ	20.6	7.4

3.3.3 Only the plasma data are used

If only the plasma compartment data are used, the resulting joint posterior density with uniform priors can be simplified to:

$$p(\lambda_{12}, \lambda_{21}, \mu \mid \text{data}) \propto S_{22}(\theta)^{-5}, \quad (3.7)$$

where $S_{22}(\theta)$ was defined earlier for Eqn. (3.4). Using the same integration limits as before, the log-log plot of the normalized marginal posterior densities for the parameters is shown in Fig. 3.18. Posterior modes, means and standard deviations of the estimates are listed in Table 3.7. Unlike in the previous marginal density plots, bimodality was not observed here. However, the posterior density for λ_{12} has changed dramatically. This is similar to an earlier behavior found during the integration limits investigations, where inadequate integration limits were used.

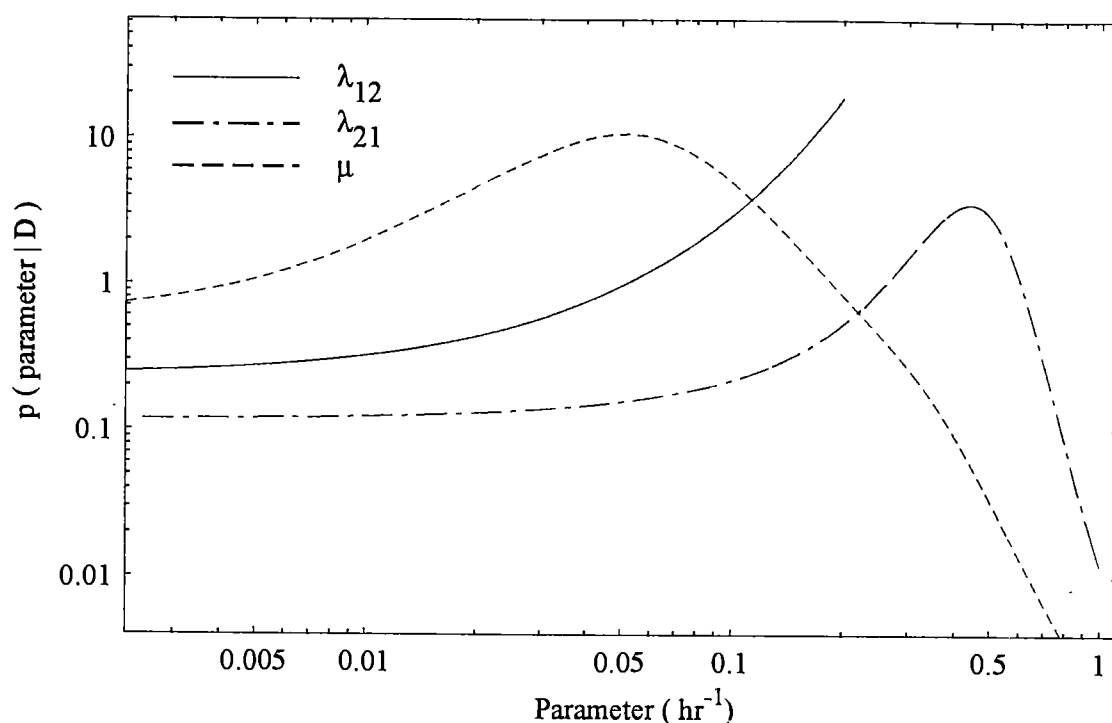


Figure 3.18. Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the plasma ^{45}Ca data and uniform priors. The means ($\mu\text{Ci}/\text{mg } ^{45}\text{Ca hour}$) are $\lambda_{12} = 0.1533 \pm 0.0405$, $\lambda_{21} = 0.4296 \pm 0.1329$ and $\mu = 0.0916 \pm 0.0773$.

Table 3.7. Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with the plasma ^{45}Ca data and uniform priors.

	λ_{12}	λ_{21}	μ
	$(\mu\text{Ci}/\text{mg } ^{45}\text{Ca hour})$		
Posterior Mean	0.1533 ± 0.0405	0.4296 ± 0.133	0.0915 ± 0.077
Posterior Mode	None	0.439	0.0525

Since parameter λ_{12} does not have a posterior mode, the solution of the differential equations was fitted to the data using only the posterior means. The poor fit to the bone surfaces data is shown in Fig. 3.19. On the other hand, the fit to the plasma data, shown in Fig. 3.20, was very good. Finally, we studied the effect of using only plasma data on HPD contour plots. Because less information is used, the precision of the estimates decreased. This translated into a larger joint posterior density with wider marginal density plots and larger HPD contours. The HPD contour z values are listed in Table 3.8. The corresponding 90 and 95 percent HPD contours comparing the estimates calculated from only the bone surface data versus from all data are plotted in Figs. 3.21 through 3.23. Like in the previous analysis using only the bone surfaces data, the resulting contours are larger, open-ended, and has larger estimation variances.

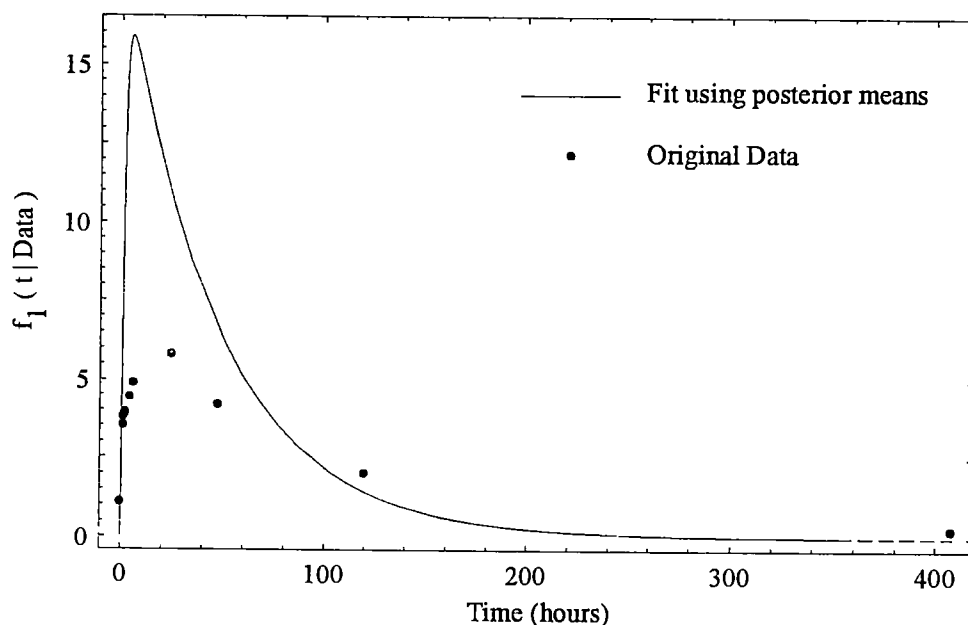


Figure 3.19. Solution of the differential equations for the parameter estimates calculated with the plasma ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data using.

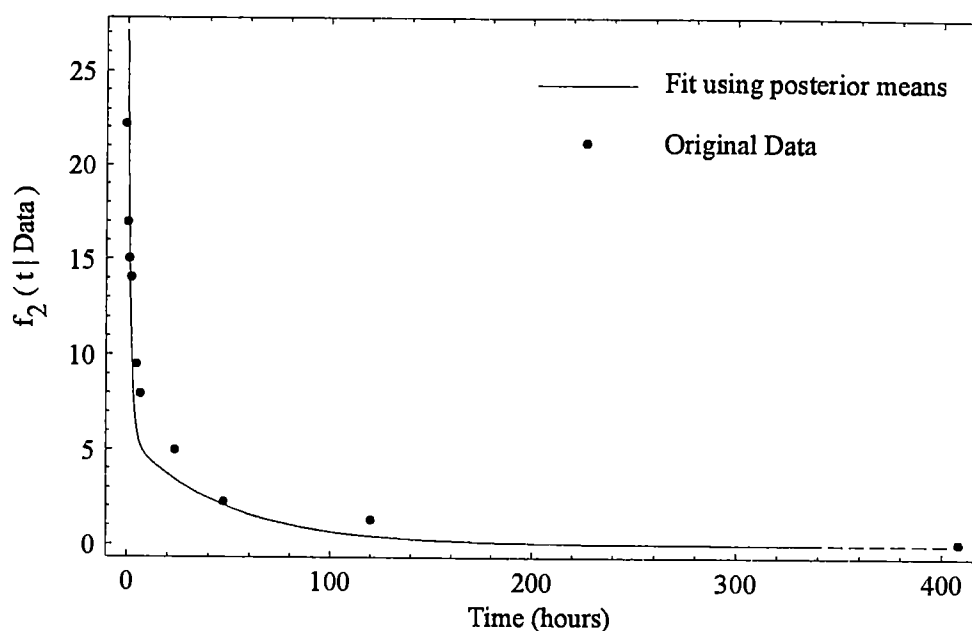


Figure 3.20. Solution of the differential equations for the parameter estimates calculated with the plasma ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

Table 3.8. Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the plasma ^{45}Ca data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
λ_{12} and λ_{21}	2.79	1.4
λ_{12} and μ	5.24	2.2
λ_{21} and μ	1.55	0.65

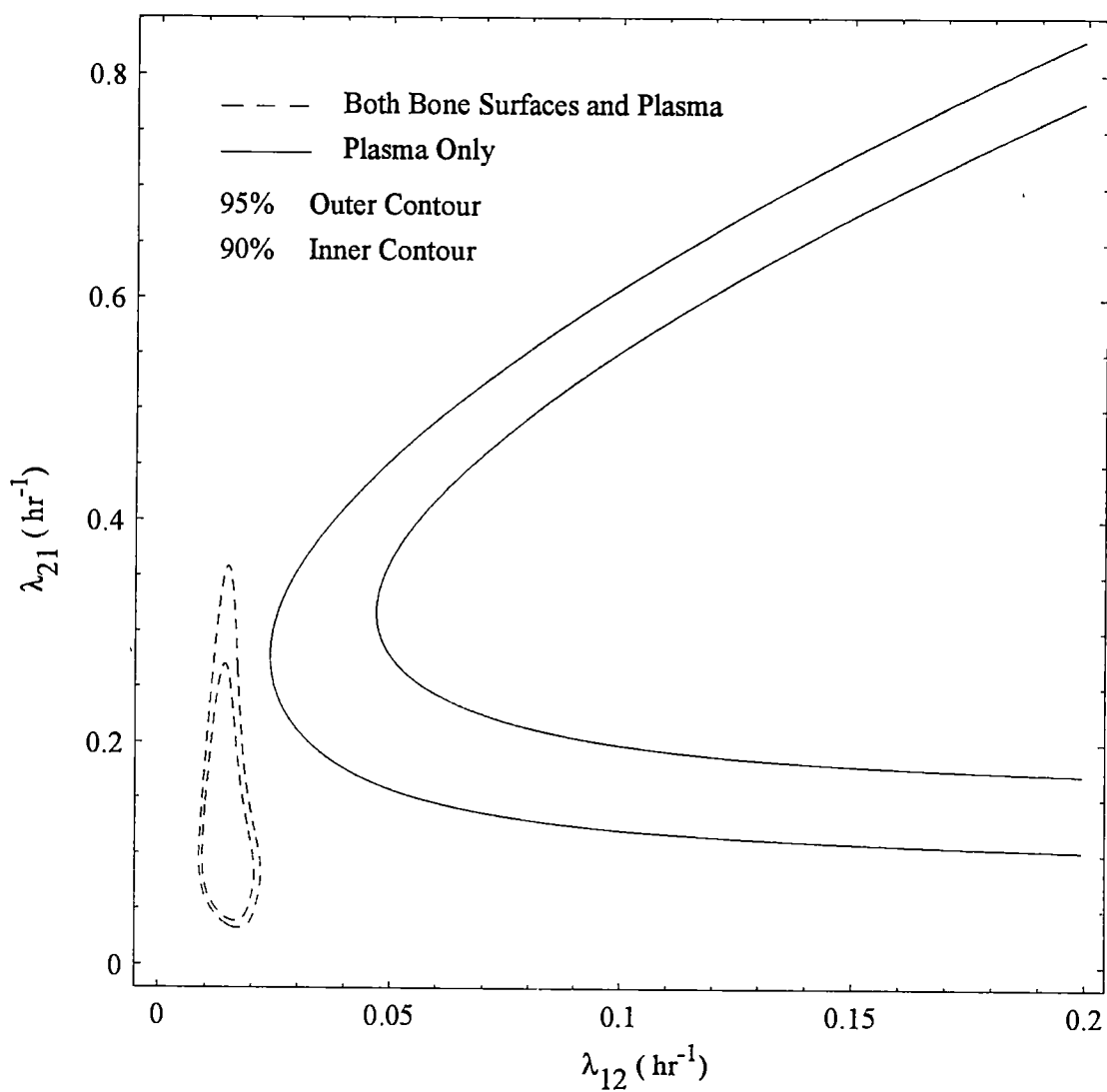


Figure 3.21. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the plasma ^{45}Ca data and uniform priors.

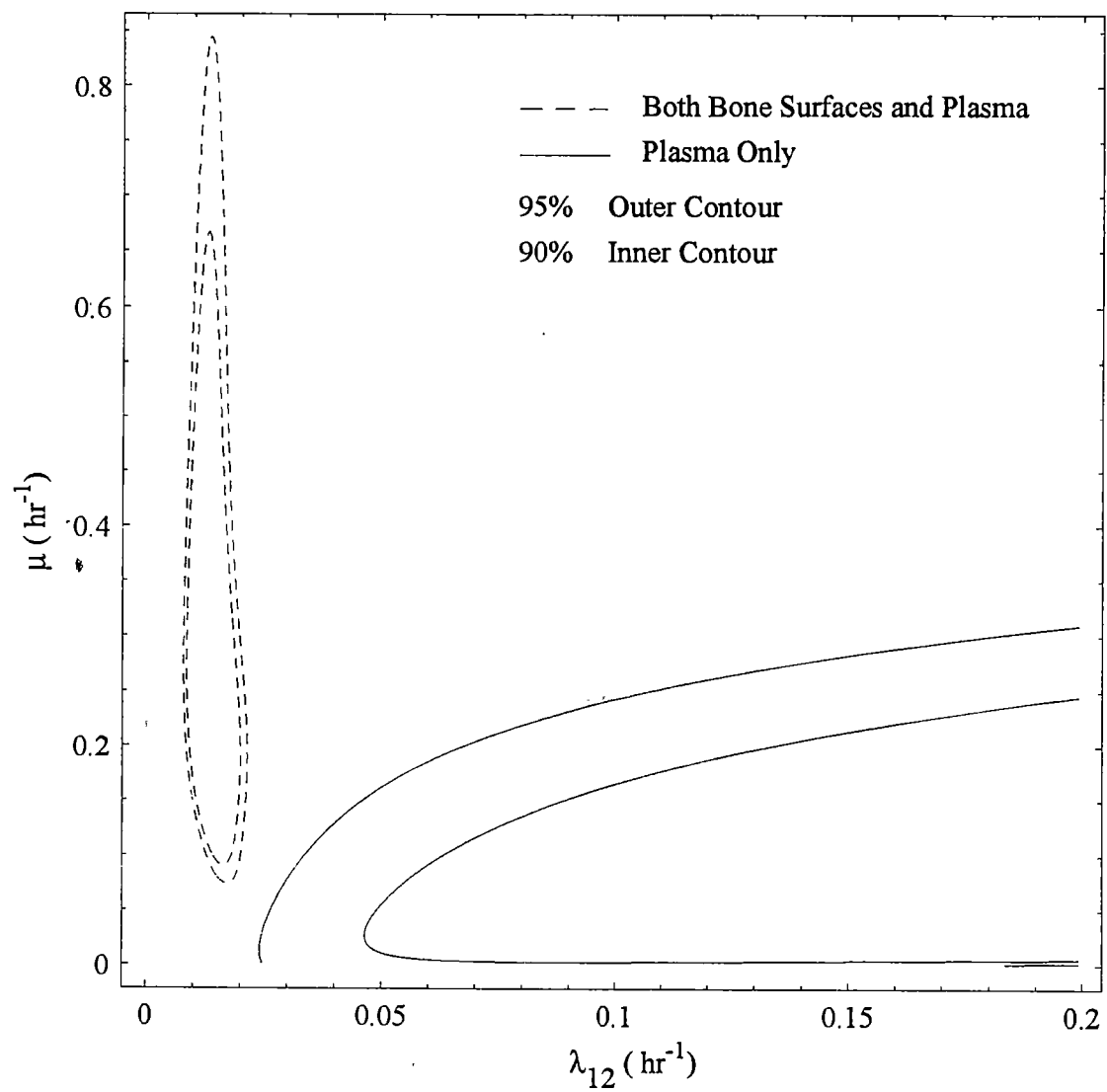


Figure 3.22. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the plasma ^{45}Ca data and uniform priors.

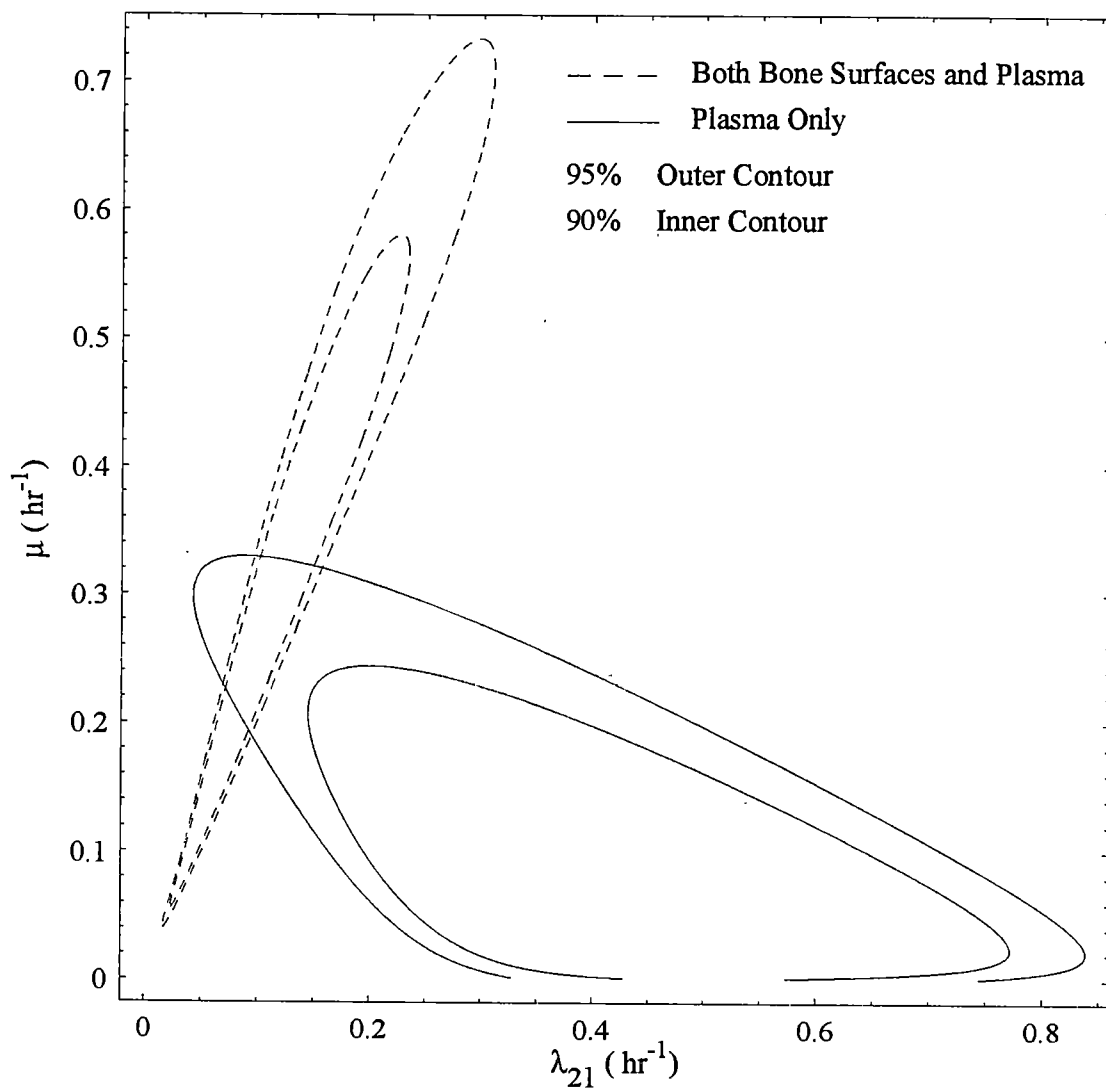


Figure 3.23. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the plasma ^{45}Ca data and uniform priors.

3.3.4 Review of the results for uniform priors with all ten data

In this section, the results of the Bayesian parameter estimation using uniform priors are reviewed. Various plots are combined together to better show the effects of reduced data. The more data one has, the more precise the estimates, which is clearly illustrated in the HPD contour plots. Parameter estimates calculated using various data sets are listed in Table 3.9. The combined normalized marginal posterior density plots for the parameters λ_{12} , λ_{21} and μ calculated using data for both compartments, bone surface only and blood plasma only are shown in Figs. 3.24 through 3.26. The combined 90 and 95 percent HPD contour plots for each parameter pairs with various data sets are shown in Figs. 3.27 through 3.29.

Table 3.9. Bayesian parameter estimates for the calcium exchange rates in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.

Parameter Estimates		Data From		
($\mu\text{Ci/mg } ^{45}\text{Ca}$ hour)		Bone Surfaces Only	Plasma Only	Both
λ_{12}	Posterior Mean	0.01132 ± 0.014	0.1522 ± 0.0405	0.01365 ± 0.00262
	Posterior Mode	0.0081	None	0.0131
λ_{21}	Posterior Mean	0.1769 ± 0.0409	0.4296 ± 0.133	0.1227 ± 0.0644
	Posterior Mode	0.192	0.439	0.0915
μ	Posterior Mean	0.7127 ± 0.199	0.0915 ± 0.077	0.3122 ± 0.146
	Posterior Mode	0.853	0.0525	0.24

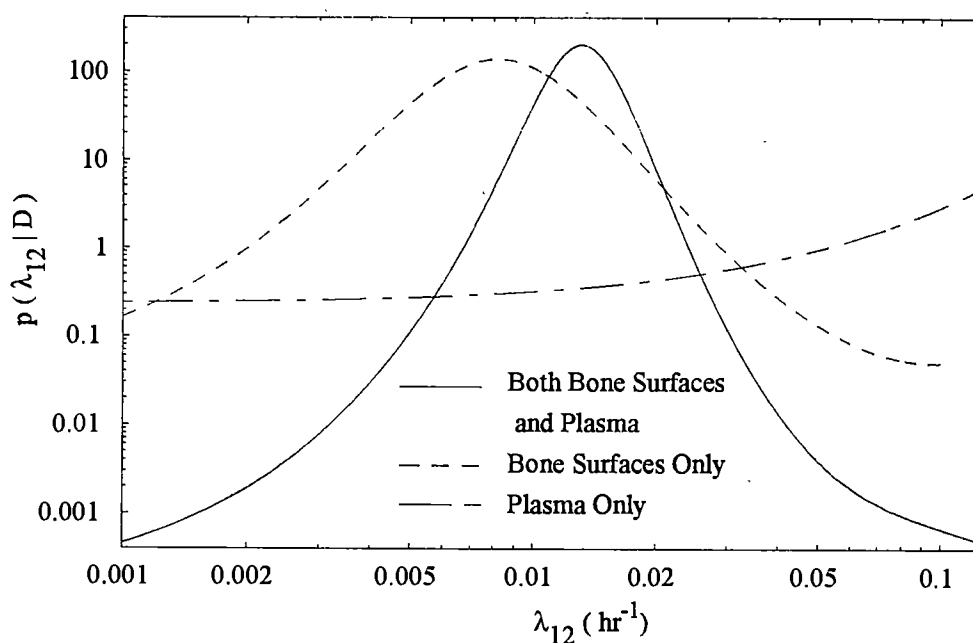


Figure 3.24. Normalized marginal posterior density for the calcium exchange rate λ_{12} in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.

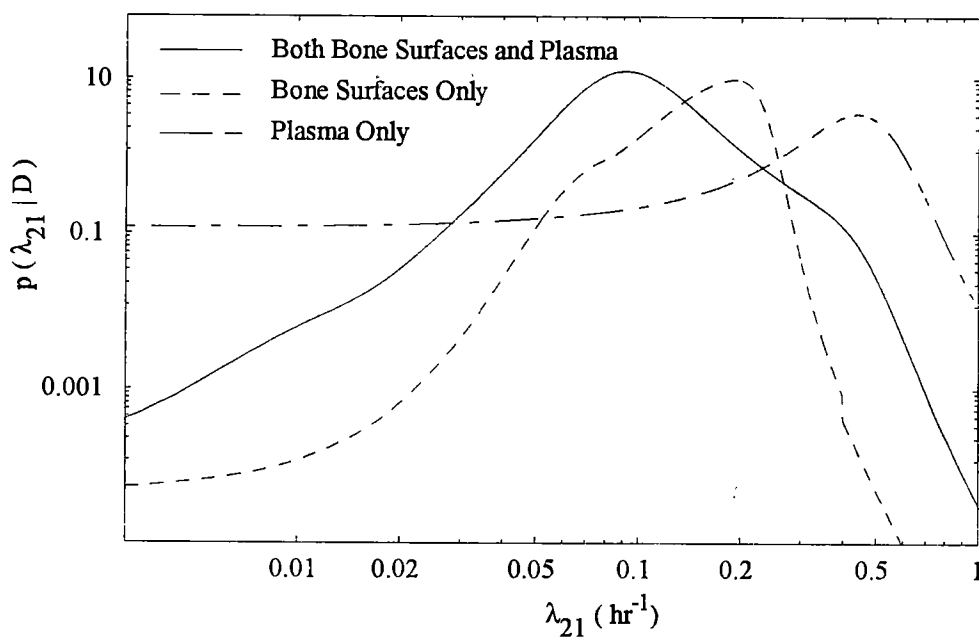


Figure 3.25. Normalized marginal posterior density for the calcium exchange rate λ_{21} in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.

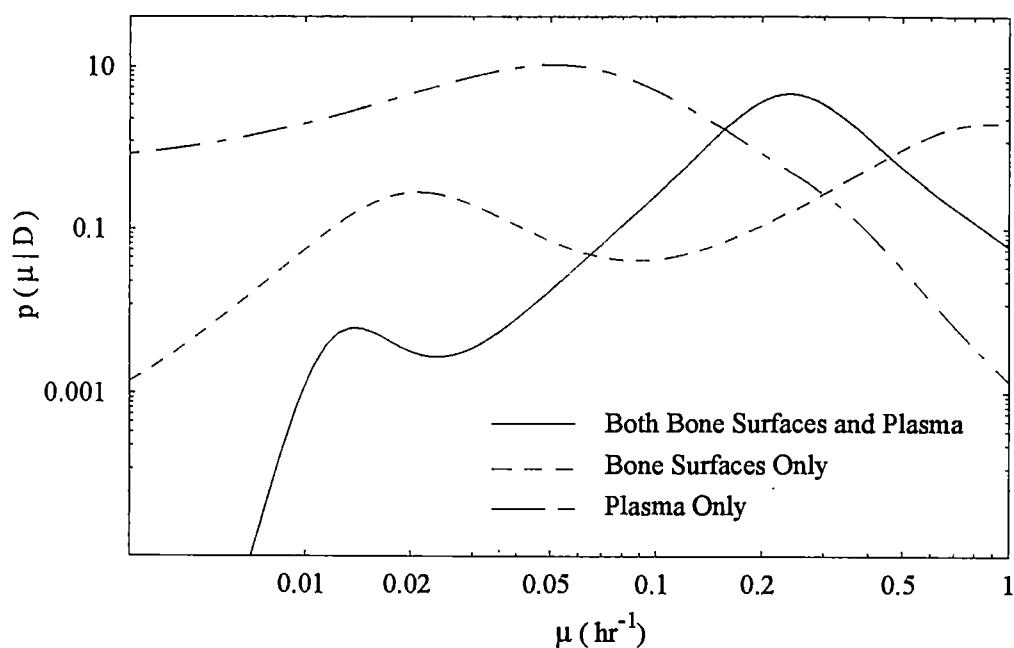


Figure 3.26. Normalized marginal posterior density for the calcium exchange rate μ in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.

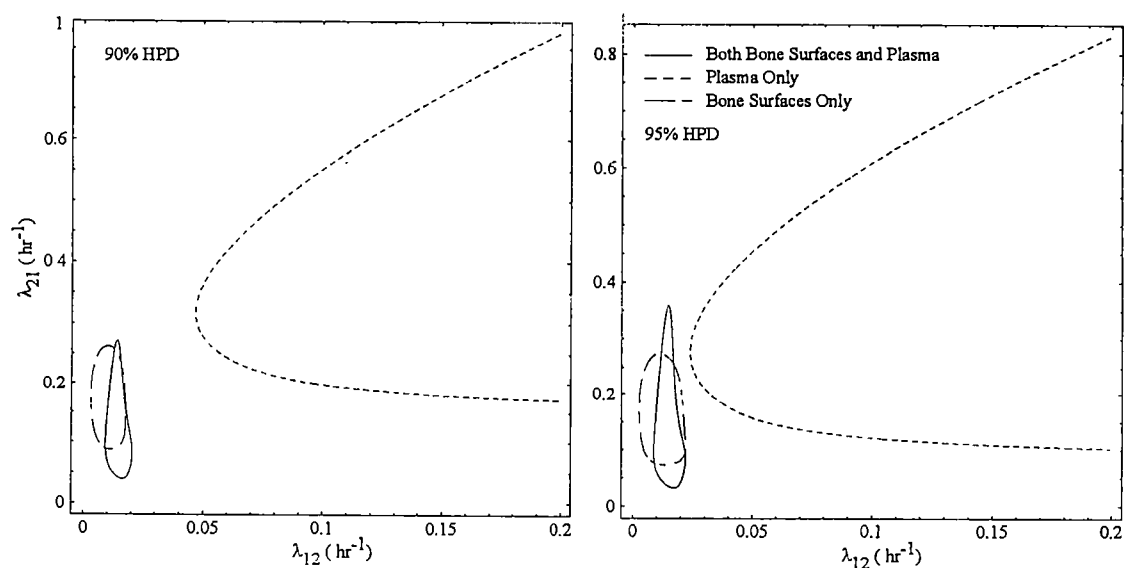


Figure 3.27. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.

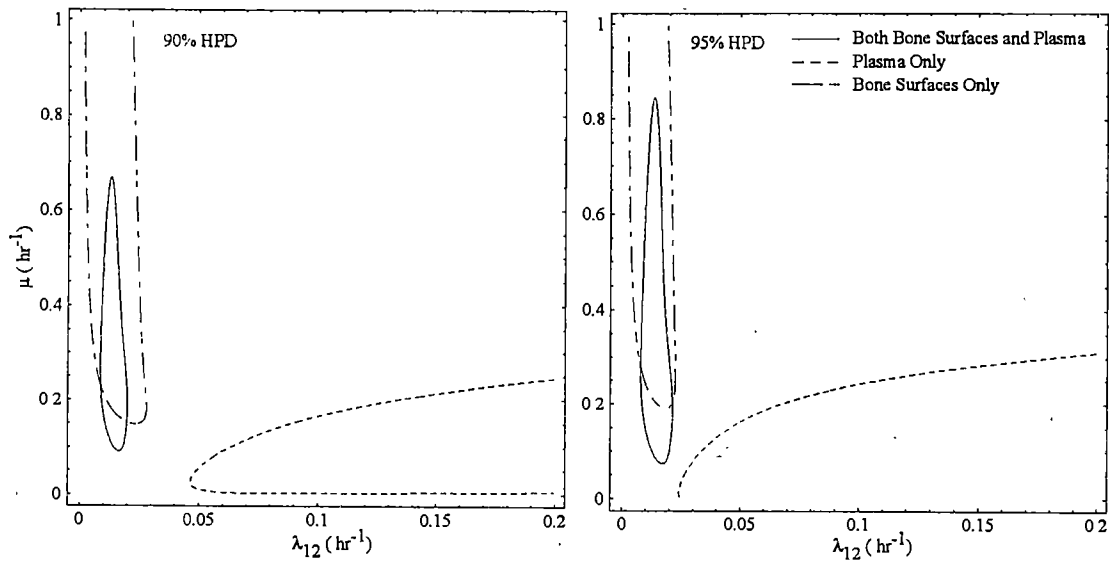


Figure 3.28. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.

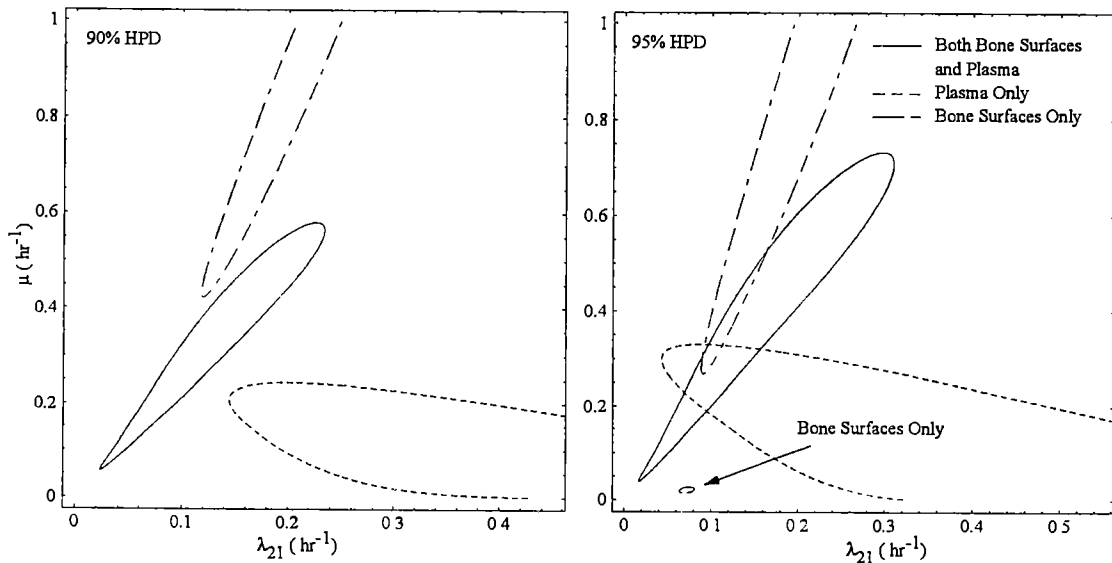


Figure 3.29. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with uniform priors and the ^{45}Ca data from bone surfaces, plasma or both.

3.4 Uniform Priors – Last Four Data Points Omitted

As previously discussed, estimation accuracy depends on the availability of the data. When only a single compartment is observed, the resulting parameter estimates were less accurate than those calculated using all available data. This made the marginal posterior densities and HPD contours larger, wider, and sometime open. Another observation scenario occurred when the observations are ceased prematurely. The effects of this type of reduced observations are investigated by repeating the previous analysis with the last four data points omitted.

3.4.1 First six bone surfaces and plasma data are used

When only the first six bone surfaces and plasma data are used, the joint posterior density with uniform priors is simplified to:

$$p(\lambda_{12}, \lambda_{21}, \mu \mid data) \propto \left[S_{11}(\theta) S_{22}(\theta) - S_{12}(\theta)^2 \right]^{-3}, \quad (3.8)$$

where

$$S_{11}(\theta) = \sum_{u=1}^6 \left[y_{u1} - f_1(\lambda_{12}, \lambda_{21}, \mu, t_u) \right]^2$$

$$S_{22}(\theta) = \sum_{u=1}^6 \left[y_{u2} - f_2(\lambda_{12}, \lambda_{21}, \mu, t_u) \right]^2$$

$$S_{12}(\theta) = S_{21}(\theta) = \sum_{u=1}^6 \left[y_{u1} - f_1(\lambda_{12}, \lambda_{21}, \mu, t_u) \right] \cdot \left[y_{u2} - f_2(\lambda_{12}, \lambda_{21}, \mu, t_u) \right]$$

Using the same integration limits as before, the normalized marginal posterior densities for the parameters with log-log scaling are shown in Fig. 3.30. The posterior modes, means and standard deviations of the estimates listed in Table 3.10.

In comparison with the marginal density plots generated using all ten data points (see Fig. 3.6), the bimodality in parameter μ has disappeared. Instead, we picked up another bimodality in parameter λ_{21} . The new bimodality is not very pronounced and like in the previous examples, only visible on log-log plots. Furthermore, the reduced data also significantly increased the variance for λ_{21} . Apart from that, the Bayesian parameter estimates for λ_{21} and μ are close to those found using all ten data points to within one standard deviation.

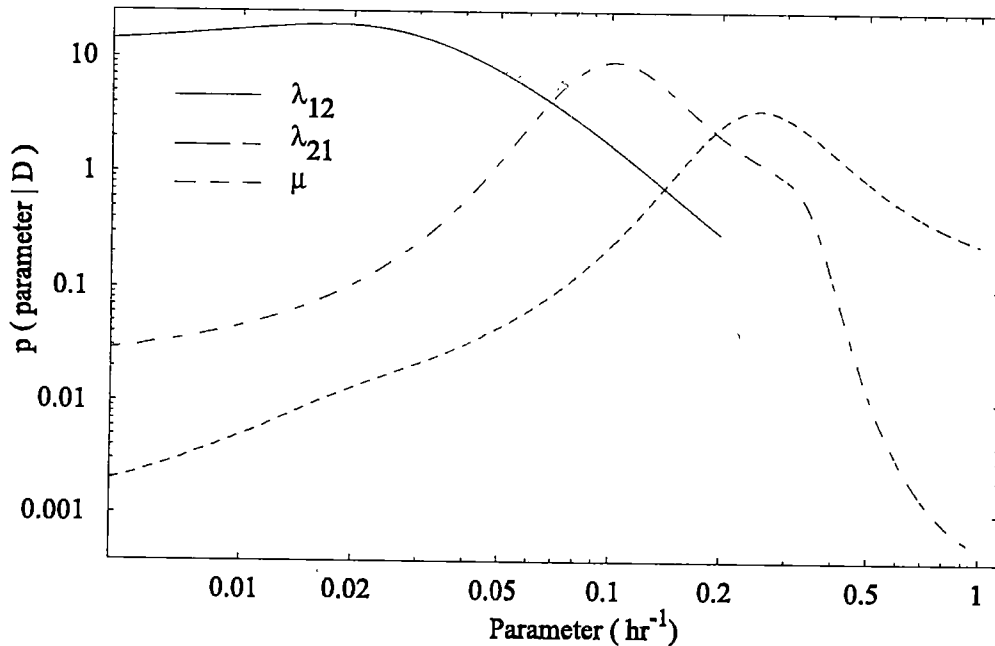


Figure 3.30. Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the first six ^{45}Ca data and uniform priors. The means ($\mu\text{Ci/mg } ^{45}\text{Ca hour}$) are $\lambda_{12} = 0.03997 \pm 0.0358$, $\lambda_{21} = 0.1454 \pm 0.0739$ and $\mu = 0.3782 \pm 0.197$.

Table 3.10. Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with the first six ^{45}Ca data and uniform priors.

	λ_{12}	λ_{21}	μ
	(μCi / mg ^{45}Ca hour)		
Posterior Mean	0.03997 ± 0.0358	0.1454 ± 0.0739	0.3782 ± 0.197
Posterior Mode	0.175	0.101	0.253

Next, the solution of the differential equations was fitted to the data using the parameter estimates calculated using the first six bone surfaces and plasma data. Plots of the fits using both posterior modes and means for bone surfaces data are shown in Fig. 3.31, and for the plasma data in Fig. 3.32. Because of the large increase in the posterior mean of λ_{12} , the fit to the bone surfaces data using the posterior means was off. In addition, the fits to the plasma data appeared to be the same as those using all available data (see Fig 3.8).

Finally, plots of the 90 and 95 percent HPD contours comparing the first six bone surfaces and plasma data versus all available data are shown in Figs. 3.33 through 3.35, with the corresponding z values listed in Table 3.11. These plots show that the effect of missing data on HPD contour plots is the same as before, enlarge and sometime open contours. This is especially true for parameter λ_{12} where large estimation variance caused by the missing data significantly elongated the contours along the λ_{12} axis.

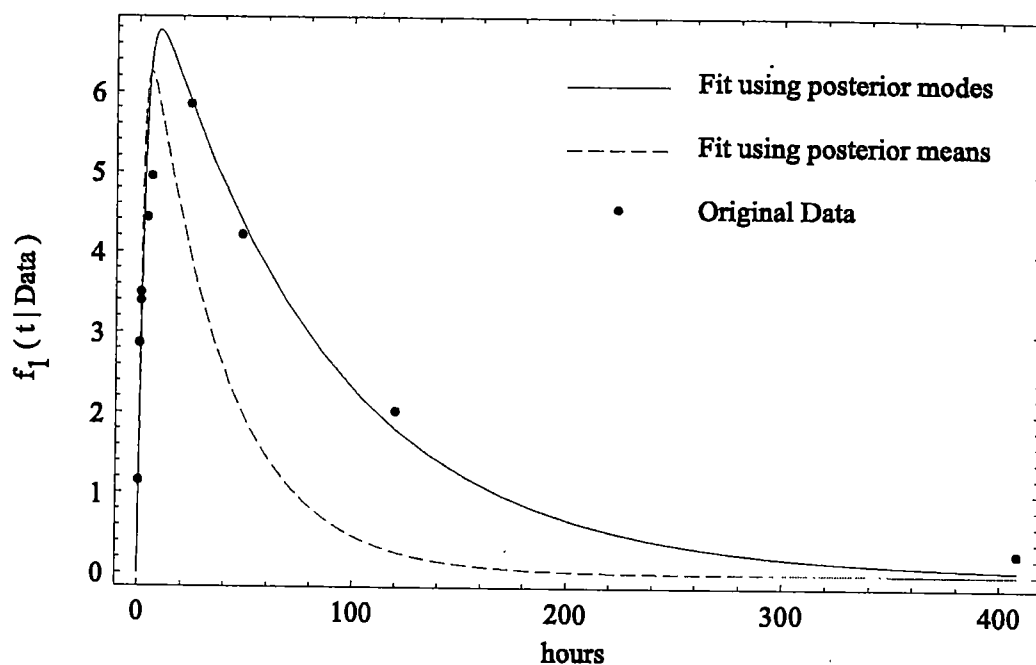


Figure 3.31. Solution of the differential equations for the parameter estimates calculated with the first six ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

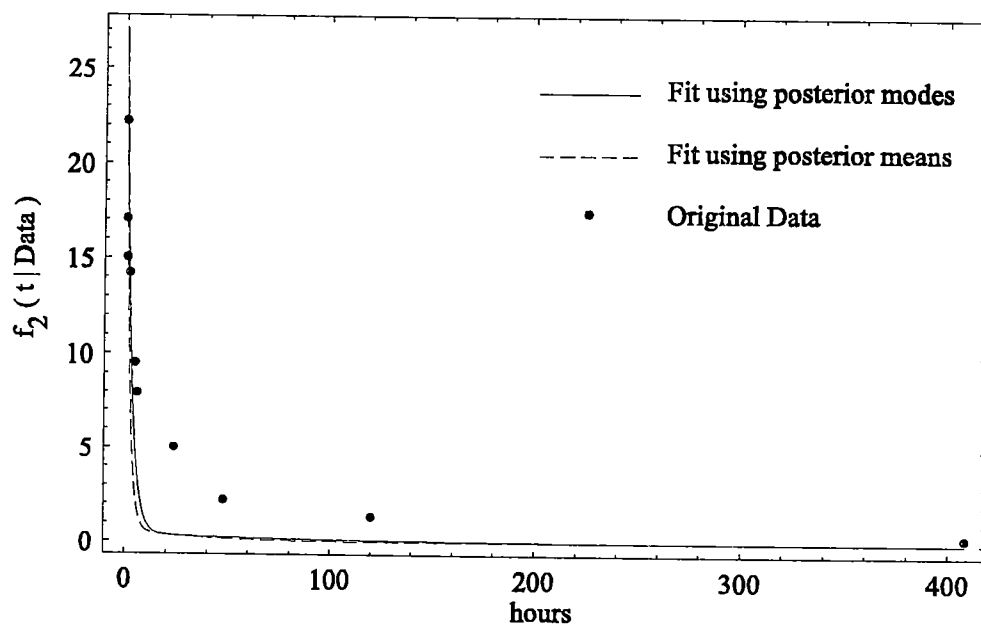


Figure 3.32. Solution of the differential equations for the parameter estimates calculated with the first six ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

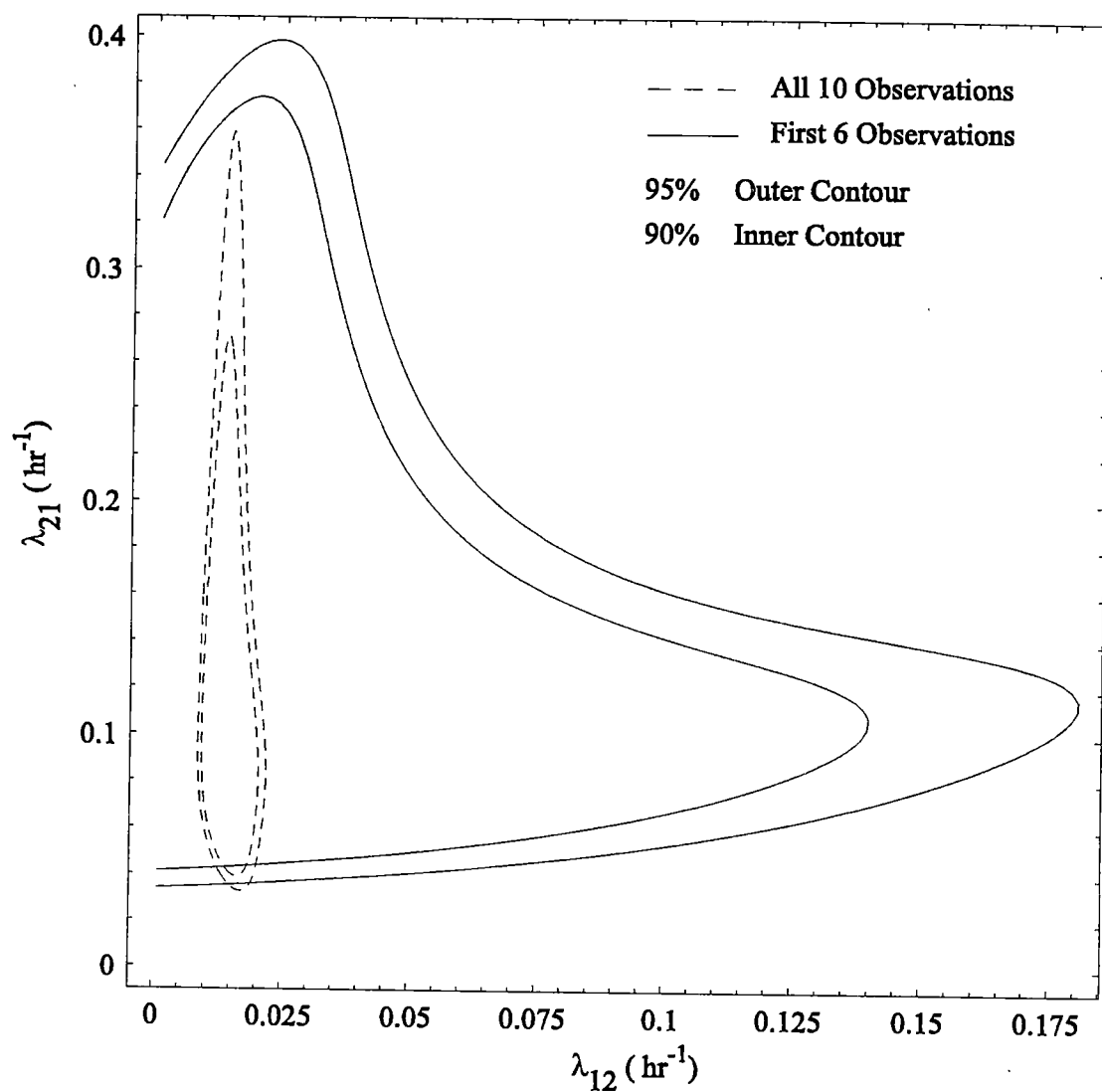


Figure 3.33. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the first six ⁴⁵Ca data and uniform priors.

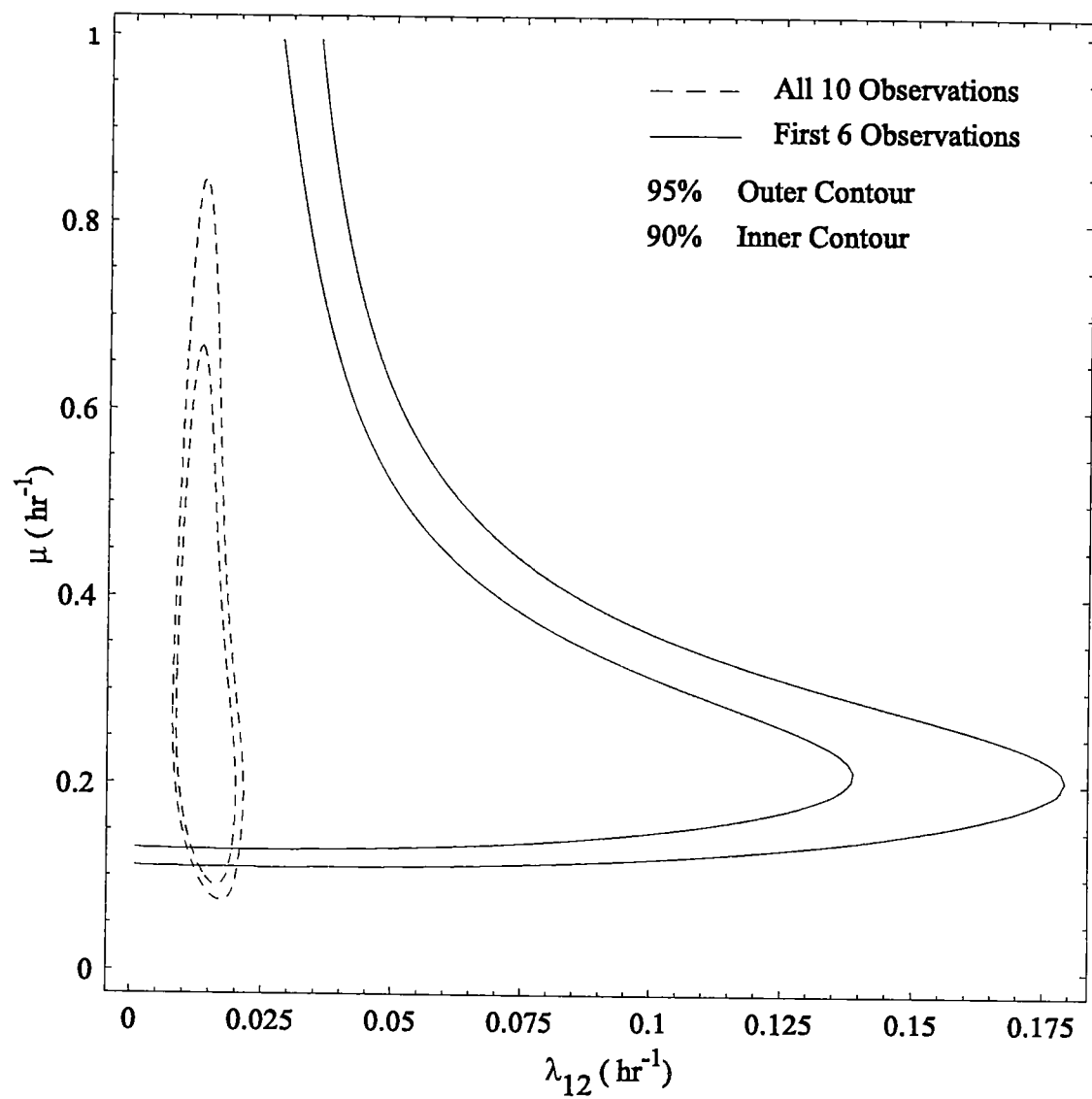


Figure 3.34. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the first six ^{45}Ca data and uniform priors.

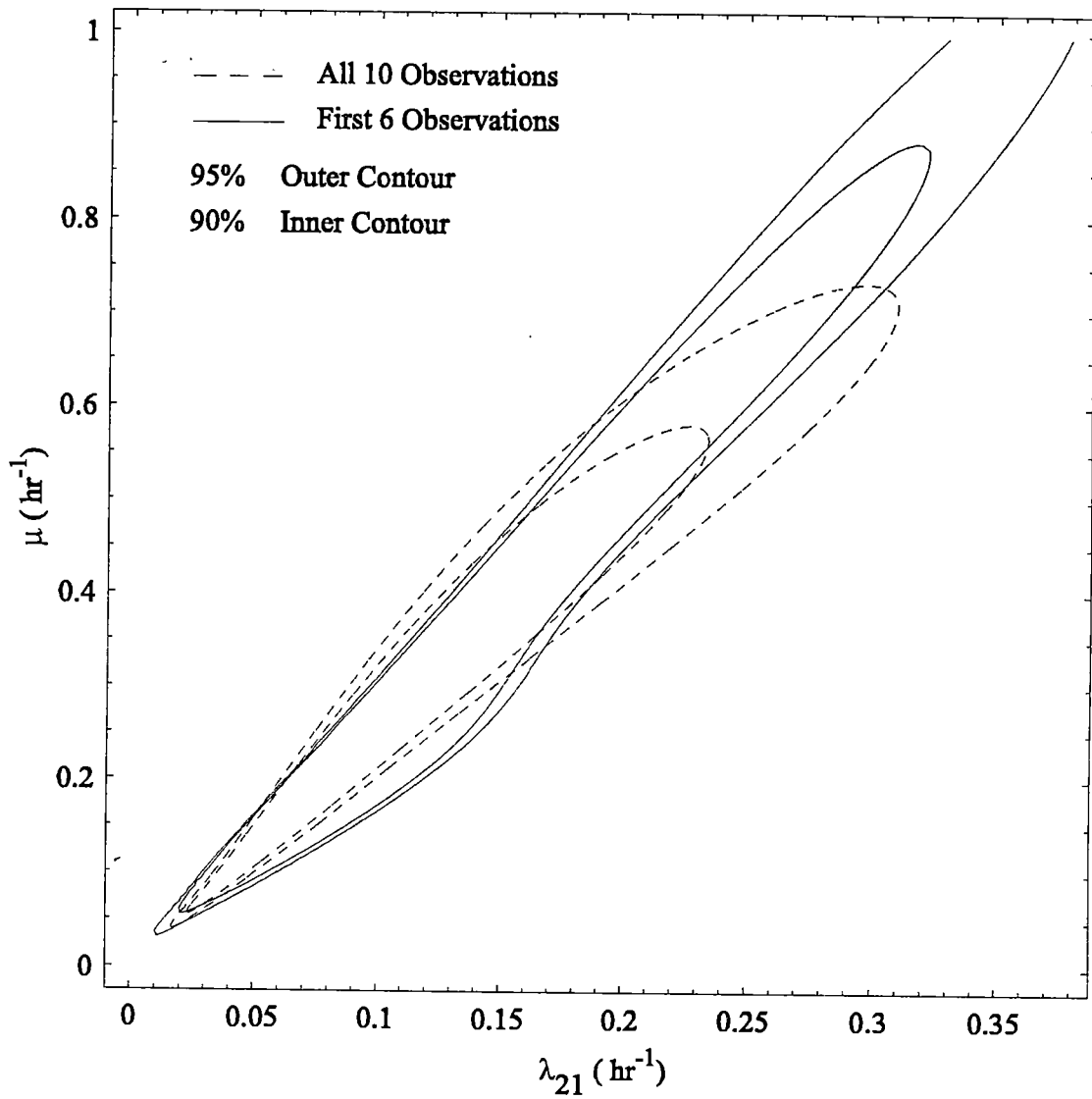


Figure 3.35. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the first six ^{45}Ca data and uniform priors.

Table 3.11. Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the first six ^{45}Ca data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
λ_{12} and λ_{21}	9.45	4.46
λ_{12} and μ	4.36	2.16
λ_{21} and μ	3.56	1.90

3.4.2 First six bone surfaces data used

If only the first six bone surfaces data are used, the resulting joint posterior density with uniform priors can be simplified to:

$$p(\lambda_{12}, \lambda_{21}, \mu \mid \text{data}) \propto S_{11}(\theta)^{-3}, \quad (3.9)$$

where $S_{11}(\theta)$ was defined earlier by Eqn. (3.8). Again, using the same integration limits as before, the normalized marginal posterior densities for the parameters are plotted in Fig. 3.36. The posterior modes, means and standard deviations of the estimated parameters are listed in Table 3.12. From the marginal density plots, bimodality was not observed, but the monotonic increase of parameter μ was observed. Like in the previous analysis, section 3.4.1, the shift in the marginal density for λ_{12} to the right resulted in a significant increase in its posterior mean and standard deviation.

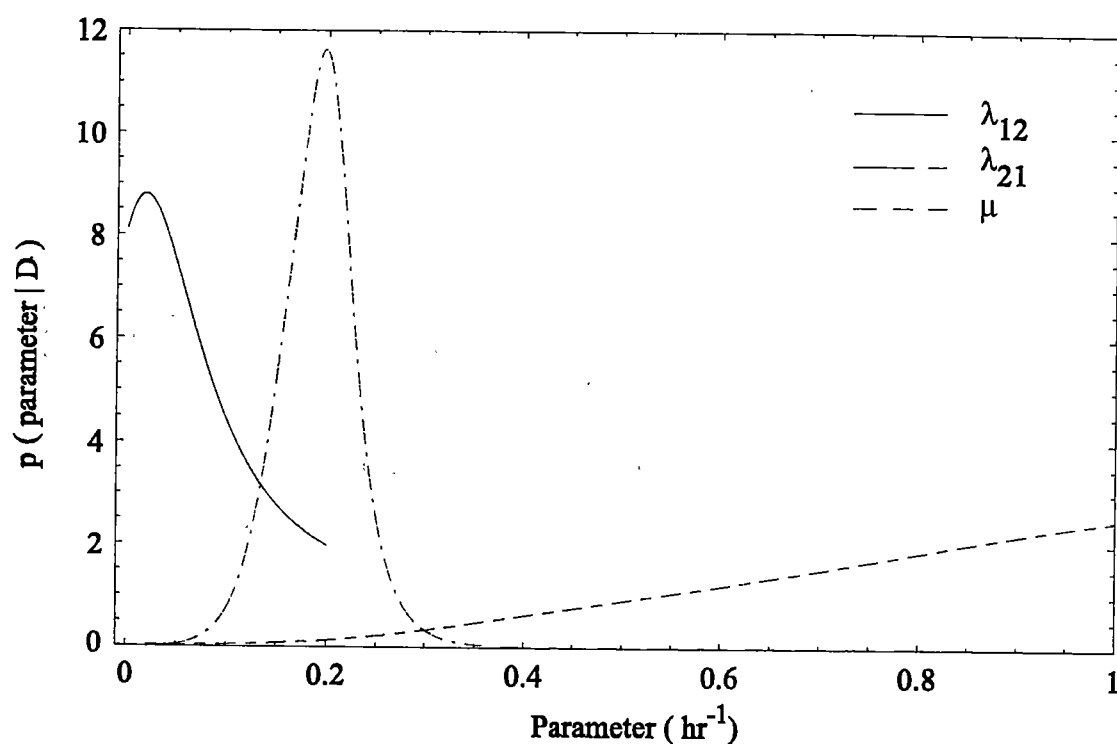


Figure 3.36. Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors. The means ($\mu\text{Ci/mg } ^{45}\text{Ca hour}$) are $\lambda_{12} = 0.07299 \pm 0.0529$, $\lambda_{21} = 0.1913 \pm 0.0398$ and $\mu = 0.7272 \pm 0.199$.

Table 3.12. Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.

	λ_{12}	λ_{21}	μ
	$(\mu\text{Ci} / \text{mg } ^{45}\text{Ca hour})$		
Posterior Mean	0.07299 ± 0.0529	0.1913 ± 0.0398	0.7272 ± 0.199
Posterior Mode	0.0181	0.1965	None

Since parameter μ does not have a posterior mode, the solution of the differential equations was fitted to the data using the calculated posterior means. Shown in Fig. 3.37 for the fit to the bone surfaces data and in Fig. 3.38 for the plasma data, both fits were poor. Interestingly, the fits to the plasma data appeared to be the same as the fits found using all of the data even though the two sets of posterior means were different.

Finally, plots of the 90 and 95 percent HPD contours comparing the estimates with the first six bone surfaces data and the estimates with all ^{45}Ca data are shown in Figs. 3.39 through 3.41. The corresponding contour z values are listed in Table 3.13. The resulting contours are significantly larger than the corresponding contours generated using all data, which signify greater estimation imprecision. The results also showed the sensitivity of the Bayesian parameter estimation technique and that omission of few data points can cause a significant shift in the estimation precision.

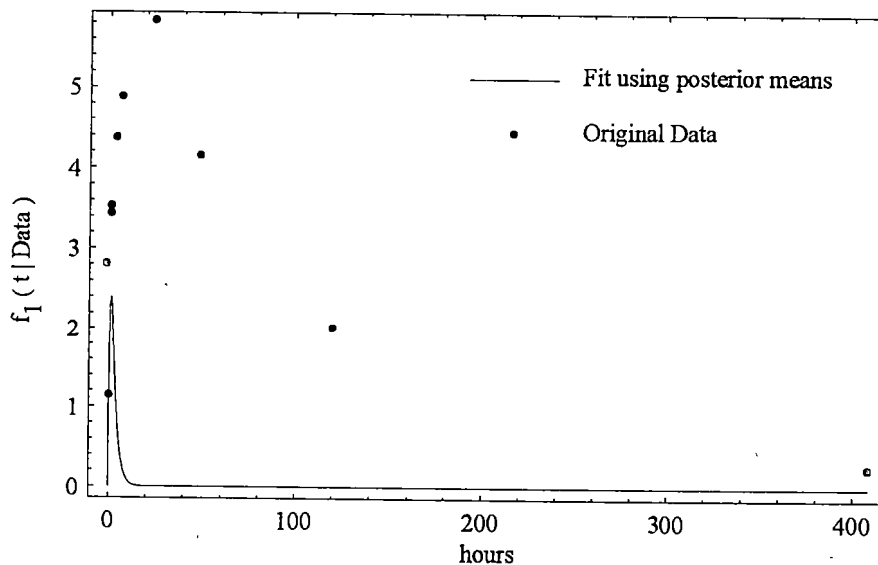


Figure 3.37. Solution of the differential equations for the parameter estimates calculated with the first six bone surfaces ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

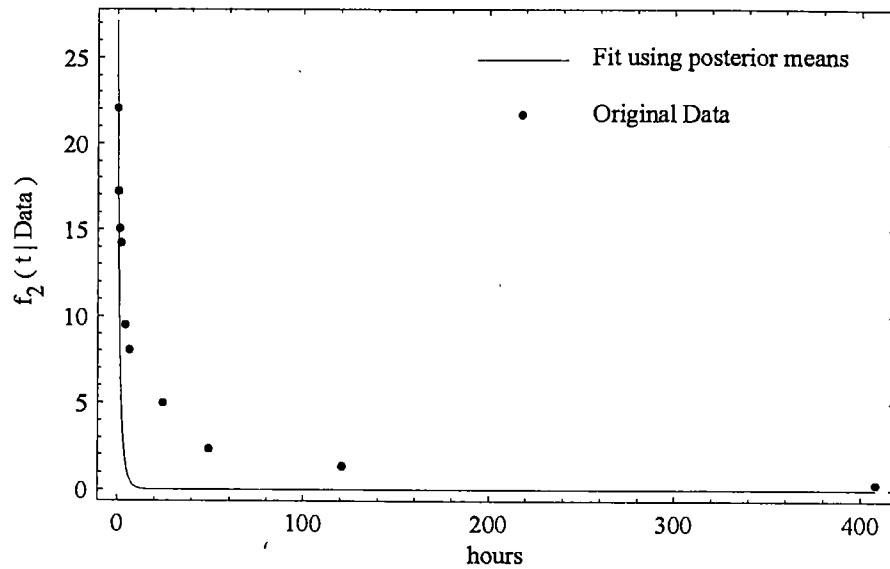


Figure 3.38. Solution of the differential equations for the parameter estimates calculated with the first six bone surfaces ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

Table 3.13. Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
λ_{12} and λ_{21}	10.5	5.9
λ_{12} and μ	3.0	1.9
λ_{21} and μ	3.6	1.74

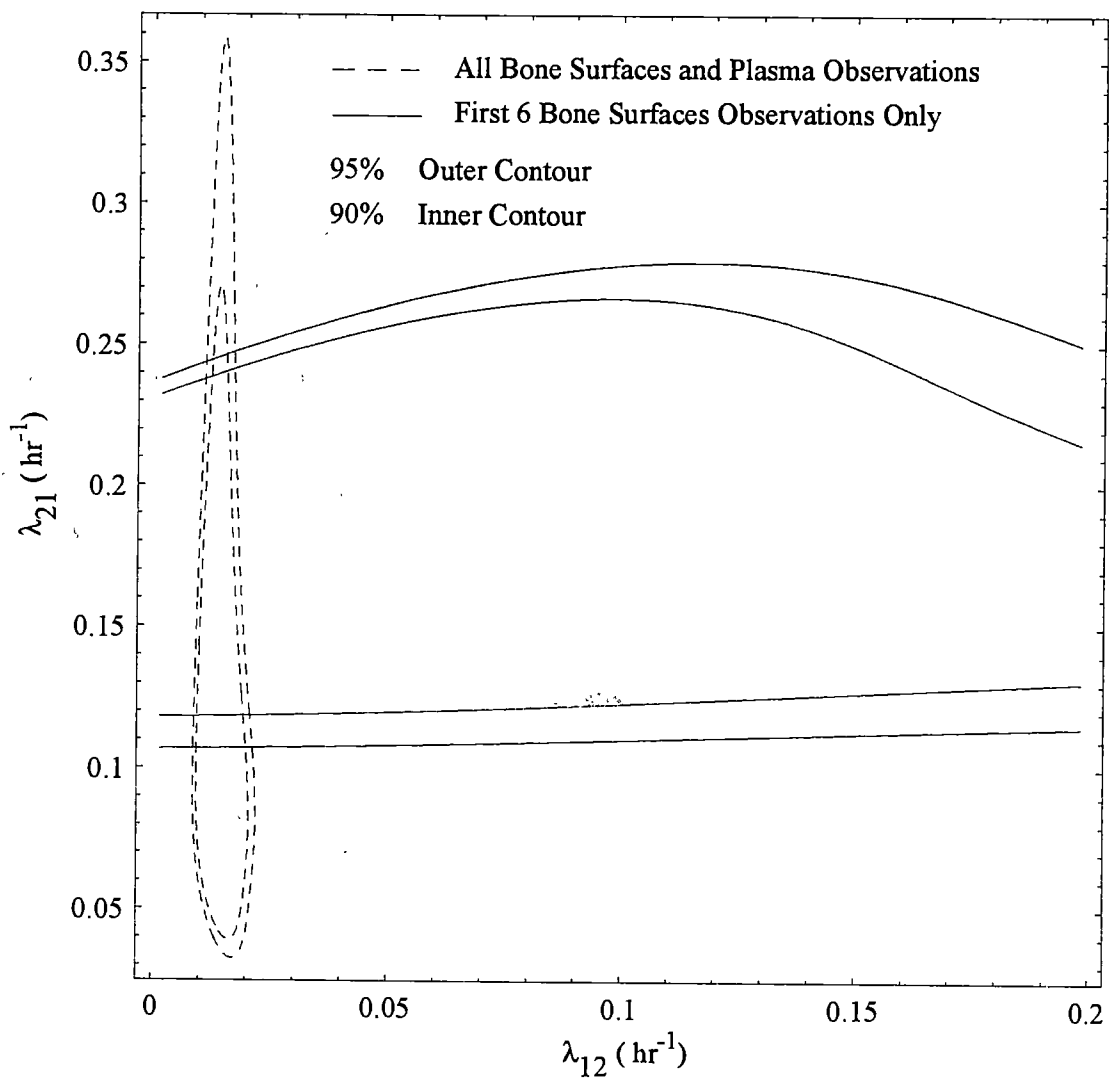


Figure 3.39. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the first six bone surfaces ⁴⁵Ca data and uniform priors.

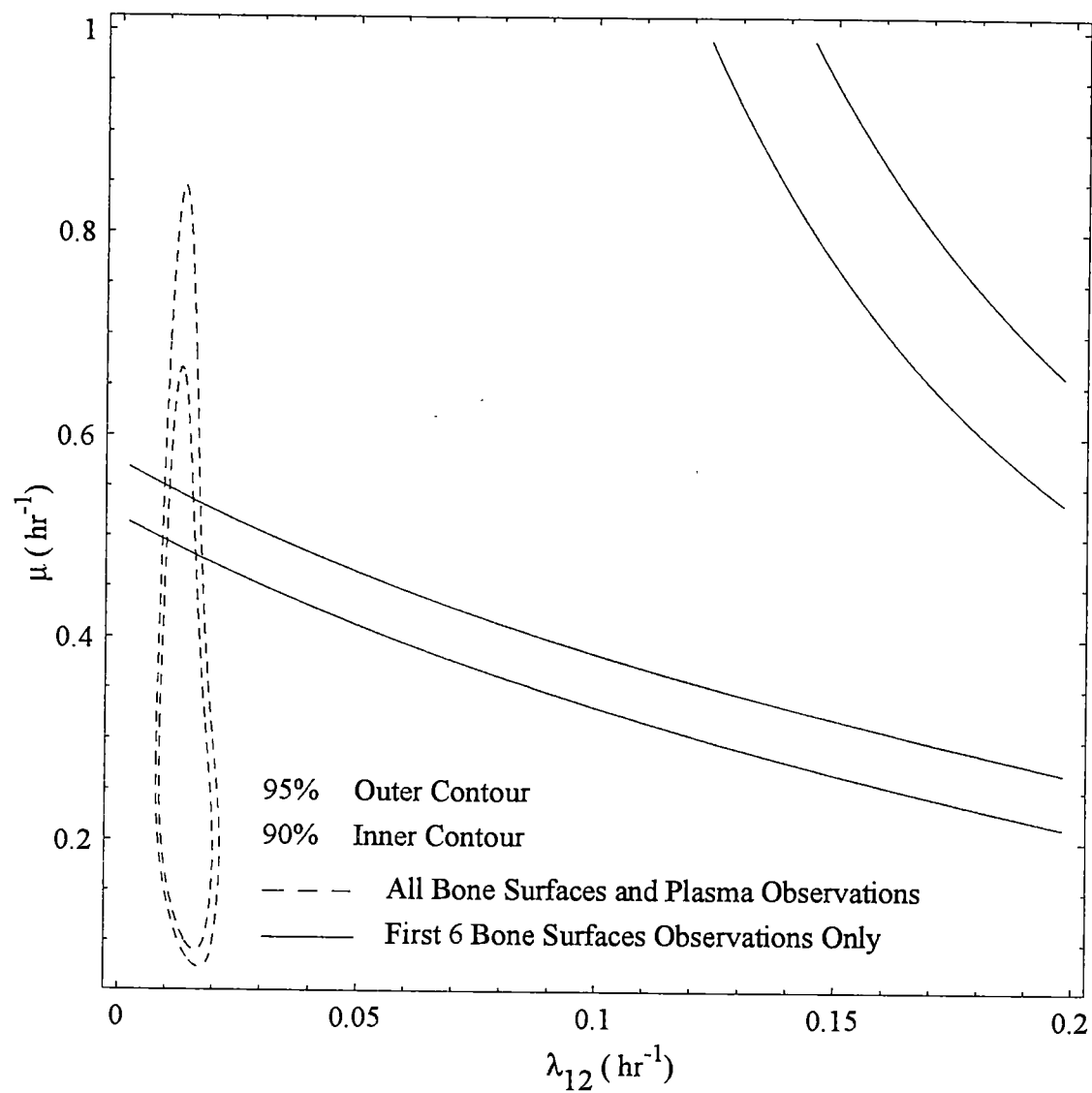


Figure 3.40. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.

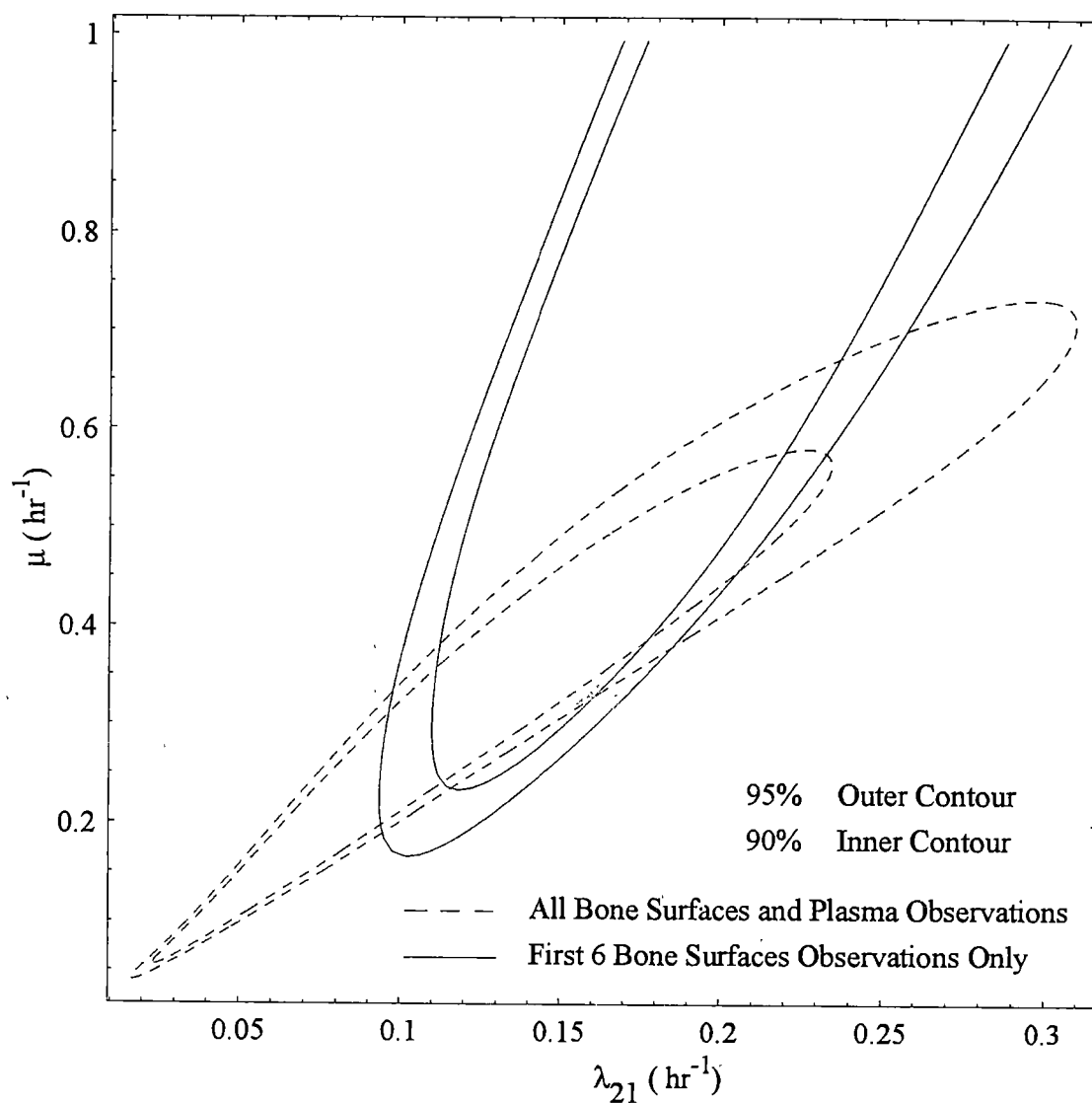


Figure 3.41. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the first six bone surfaces ^{45}Ca data and uniform priors.

3.4.3 First six plasma data used

The last analysis uses the first six plasma data, and the resulting joint posterior density with uniform priors can be written as:

$$p(\lambda_{12}, \lambda_{21}, \mu \mid data) \propto S_{22}(\theta)^{-3}, \quad (3.10)$$

where $S_{22}(\theta)$ was defined earlier for Eqn. (3.8). The normalized marginal posterior densities for the parameters are plotted in Fig. 3.42 with the Bayesian estimates listed in Table 3.14. The marginal density plots showed two interesting facts: bimodality does not exist, and the monotonic increase of the marginal density for λ_{12} . The monotonic increase, or “divergent” behavior, for λ_{12} was previously observed in section 3.3.3, using all plasma data, and its occurrence here was expected. Again, the change in the marginal density for μ is due to the reduced data.

Since parameters λ_{12} and μ have no posterior modes, the solution of the differential equations was fitted to the data using only the posterior means. Plots of the fit for the bone surfaces data are shown in Fig. 3.43 and for the plasma data in Fig. 3.44. The fits were terrible, which indicated poor estimation.

Finally, comparison of the plots of the 90 and 95 percent HPD contours for the first six plasma data versus all data are shown in Figs. 3.45 through 3.47. The corresponding contour z values are listed in Table 3.15. Again, the results were terrible. All of the contours are open and clearly reflect the poor estimation accuracy caused by insufficient data.

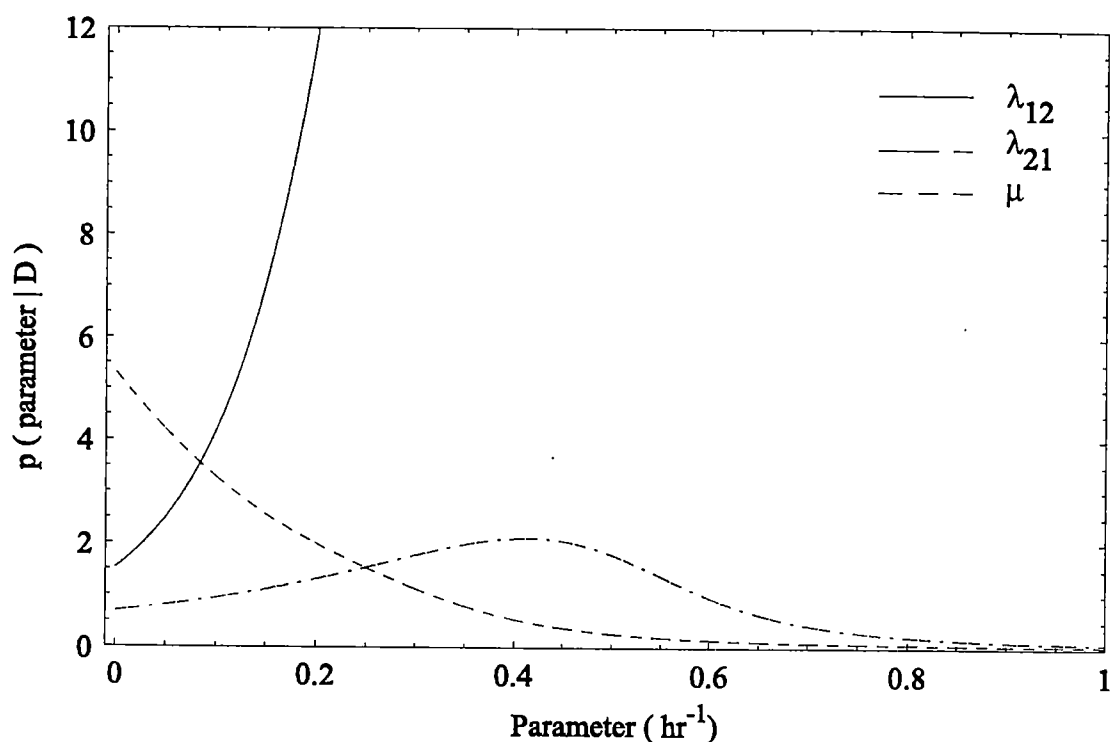


Figure 3.42. Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with the first six plasma ^{45}Ca data and uniform priors. The means ($\mu\text{Ci}/\text{mg } ^{45}\text{Ca}$ hour) are $\lambda_{12}=0.1324 \pm 0.0522$, $\lambda_{21}=0.382 \pm 0.195$ and $\mu=0.1715 \pm 0.163$.

Table 3.14. Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.

	λ_{12}	λ_{21}	μ
	$(\mu\text{Ci} / \text{mg } ^{45}\text{Ca} \text{ hour})$		
Posterior Mean	0.1324 ± 0.0522	0.3815 ± 0.195	0.1715 ± 0.163
Posterior Mode	None	0.413	None

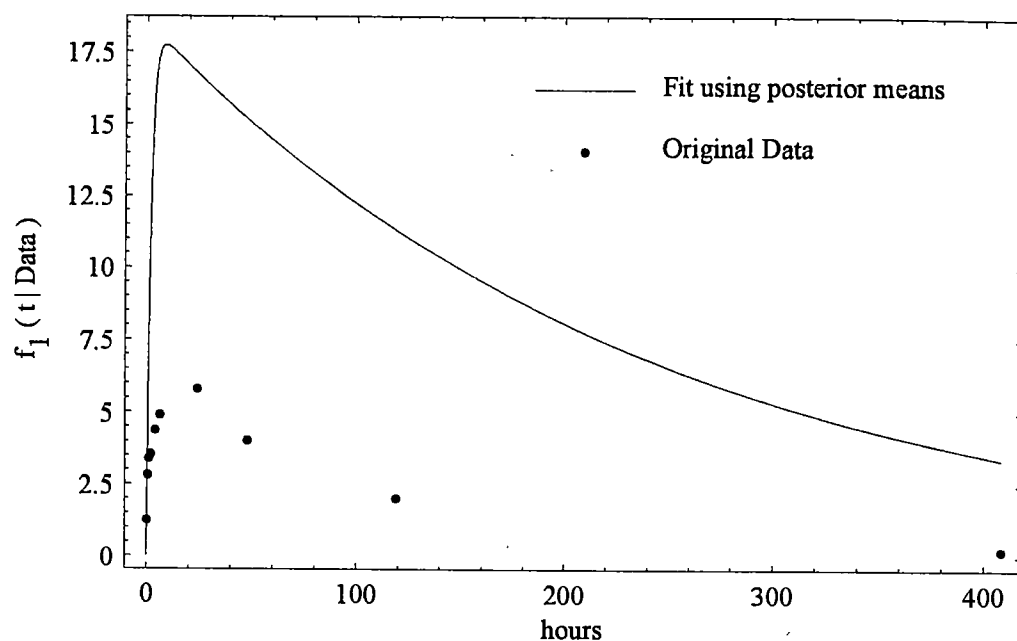


Figure 3.43. Solution of the differential equations for the parameter estimates calculated with the first six plasma ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

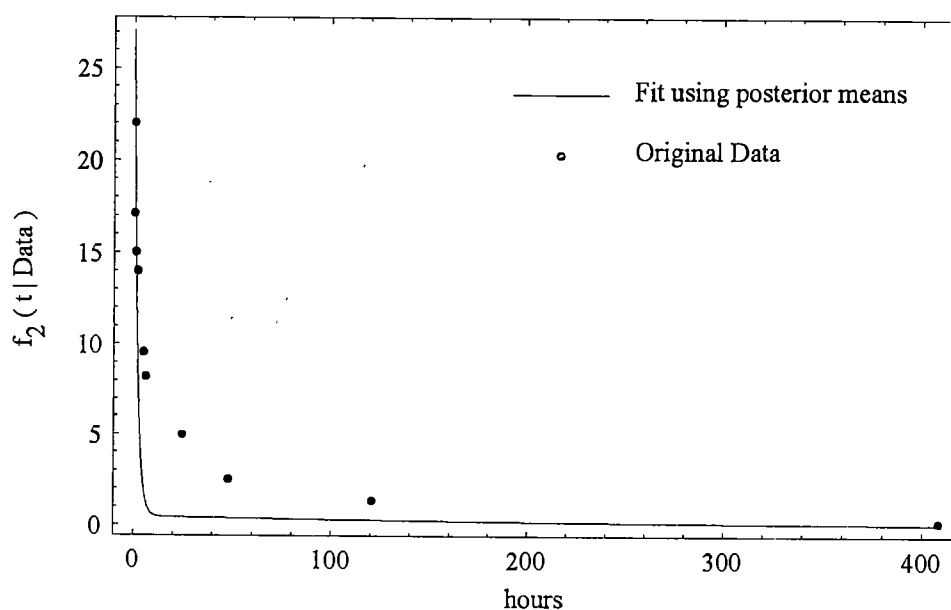


Figure 3.44. Solution of the differential equations for the parameter estimates calculated with the first six plasma ^{45}Ca data and uniform priors fitted to the beagles bone surfaces ^{45}Ca data.

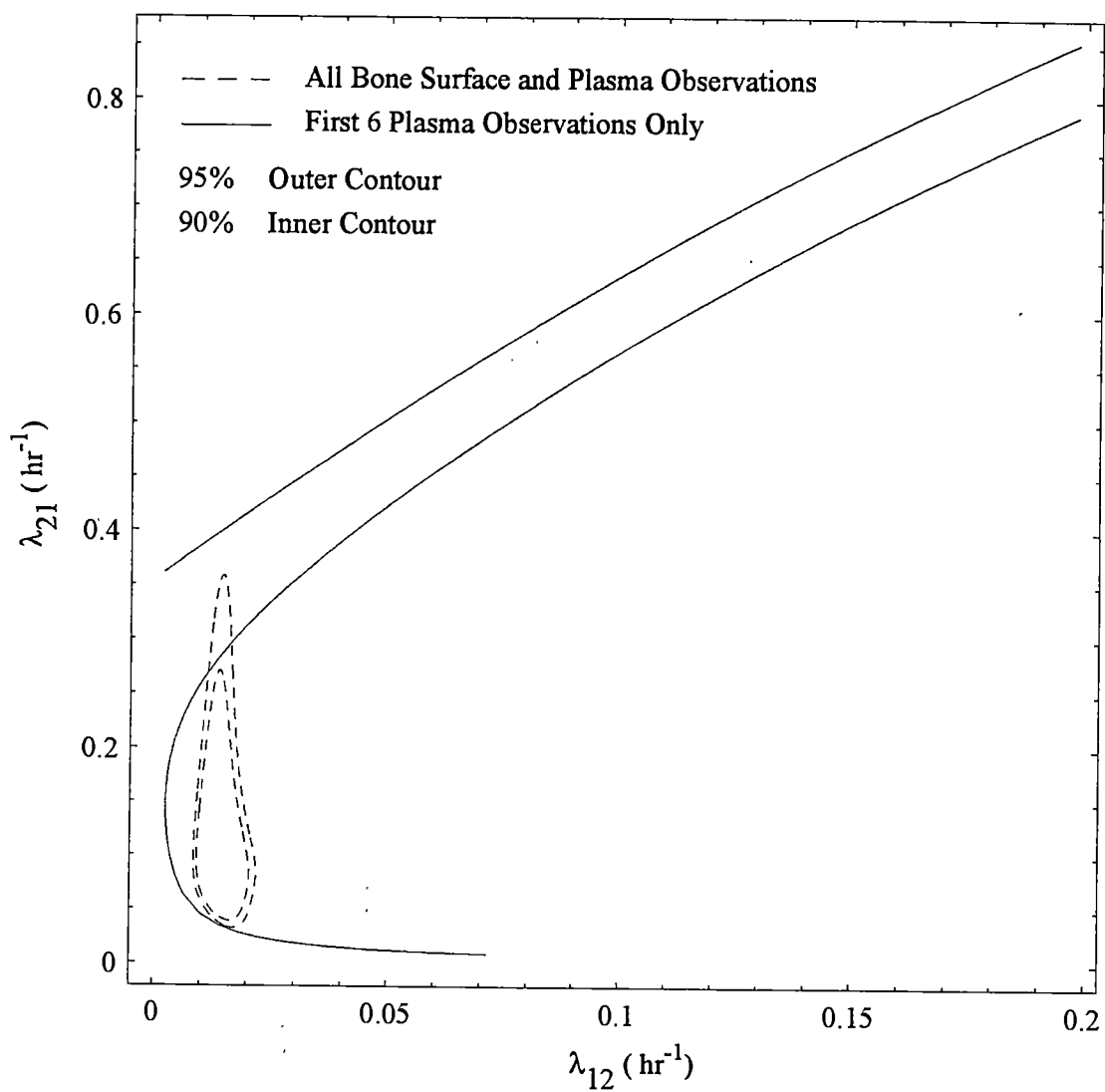


Figure 3.45. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.

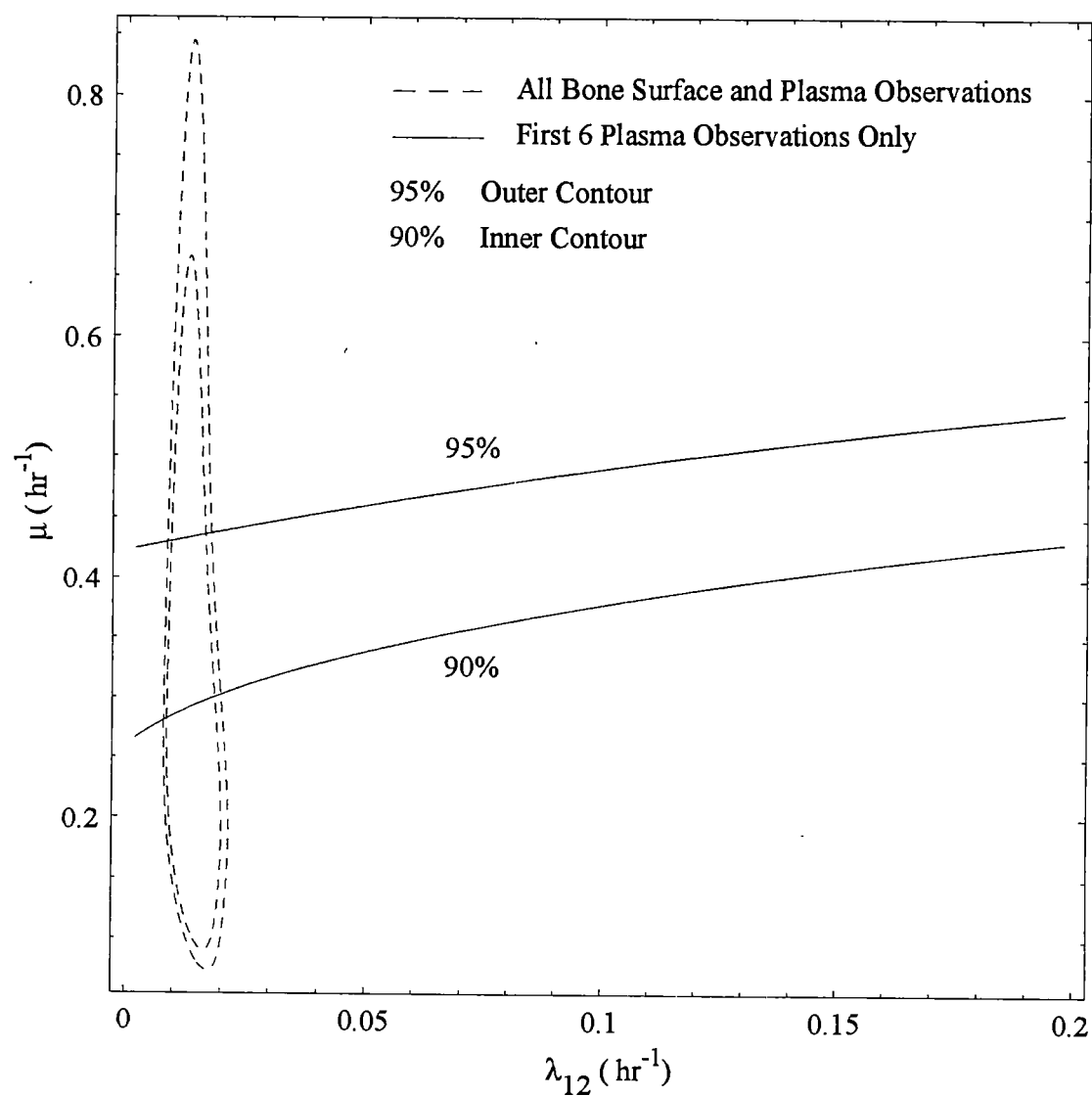


Figure 3.46. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.

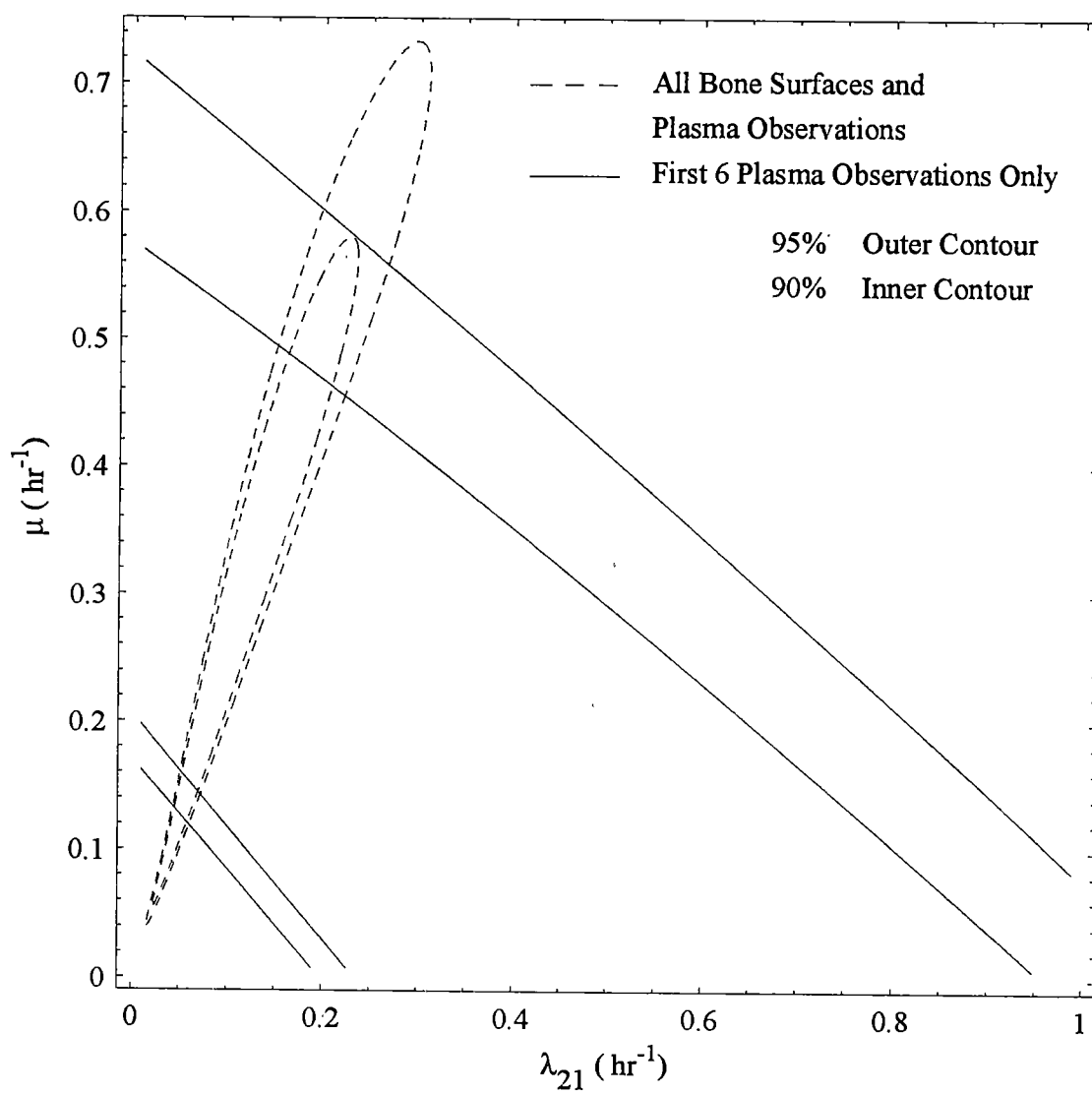


Figure 3.47. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with the first six plasma ⁴⁵Ca data and uniform priors.

Table 3.15. Ninety and ninety-five percent HPD contour z values for various combinations of the calcium exchange rates in beagles calculated with the first six plasma ^{45}Ca data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
λ_{12} and λ_{21}	3.5	2.1
λ_{12} and μ	3.1	1.4
λ_{21} and μ	0.6	0.25

3.4.4 Review of the results for uniform priors with first six data

In this section, the results of the Bayesian parameter estimation using uniform priors and first six data are reviewed. Various plots are combined together to show the effects of reduced data. Parameter estimates calculated using the various reduced data sets are listed in Table 3.16. The combined normalized marginal posterior density plots using various reduced data sets for the parameters are shown in Figs. 3.48 through 3.50. The combined 90 and 95 percent HPD contour plots for each parameter pair for the various reduced data sets are shown in Figs. 3.51 through 3.53.

Overall, the more information one has the more precise the estimates. The occurrence of bimodality and divergent behavior is due to the likelihood. It can somewhat be controlled by reducing the number of data points used, as shown in section 3.4.1, but at a cost of lower estimation accuracy. Proper priors can also be used to minimize the divergent behavior, and it will be examined in the next section.

Table 3.16. Bayesian parameter estimates for the calcium exchange rates in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.

Parameter Estimates ($\mu\text{Ci/mg } ^{45}\text{Ca}$ hour)		Data From		
		Bone Surfaces Only	Plasma Only	Both
λ_{12}	Posterior Mean	0.07299 ± 0.0529	0.1324 ± 0.0522	0.03998 ± 0.0358
	Posterior Mode	0.0181	None	0.175
λ_{21}	Posterior Mean	0.1913 ± 0.0398	0.3815 ± 0.195	0.1454 ± 0.0739
	Posterior Mode	0.1965	0.413	0.101
μ	Posterior Mean	0.7272 ± 0.199	0.1715 ± 0.163	0.3782 ± 0.1966
	Posterior Mode	None	None	0.253

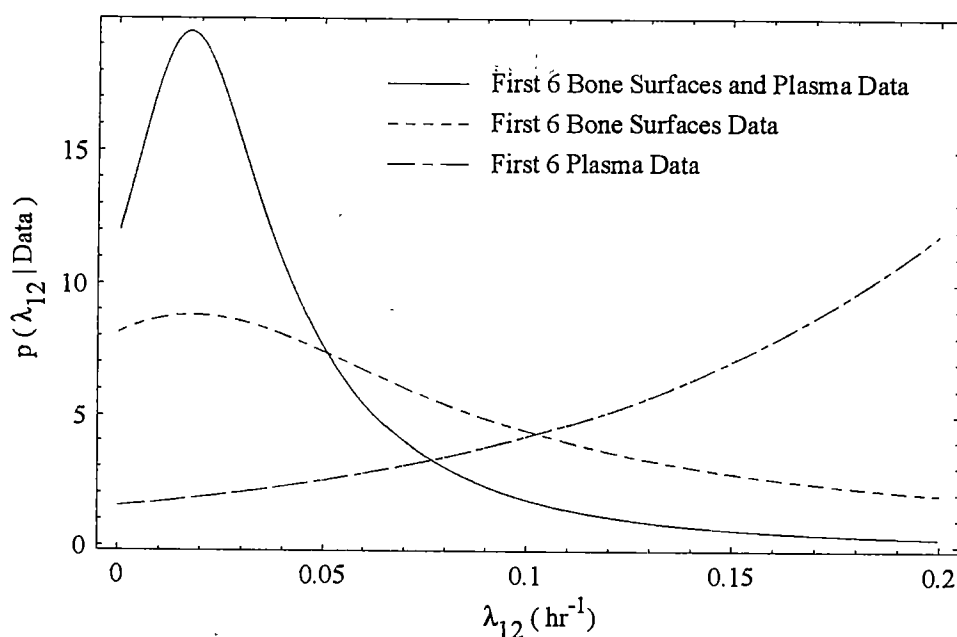


Figure 3.48. Normalized marginal posterior density for the calcium exchange rate λ_{12} in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.

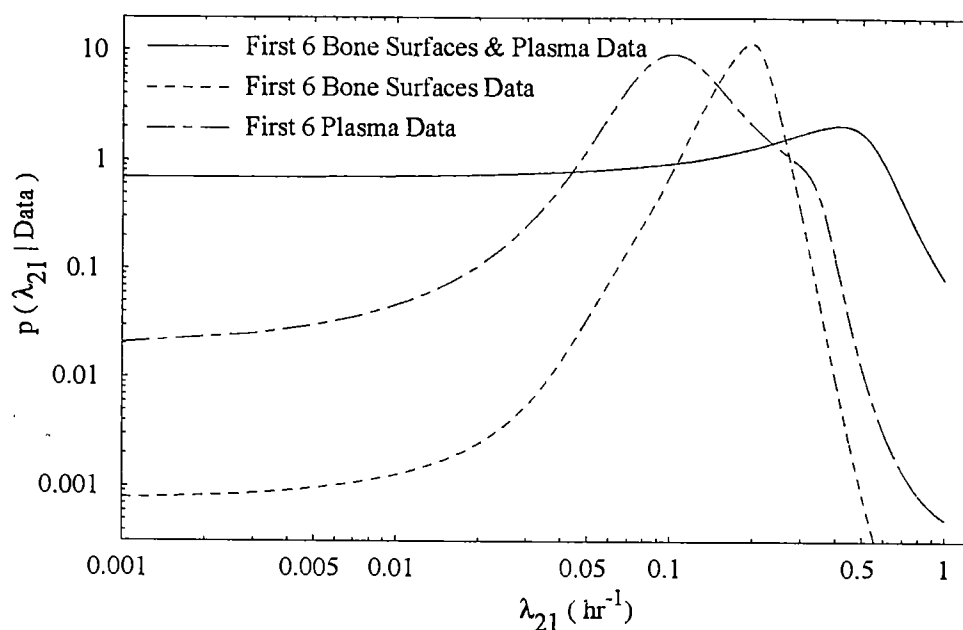


Figure 3.49. Normalized marginal posterior density for the calcium exchange rate λ_{21} in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.

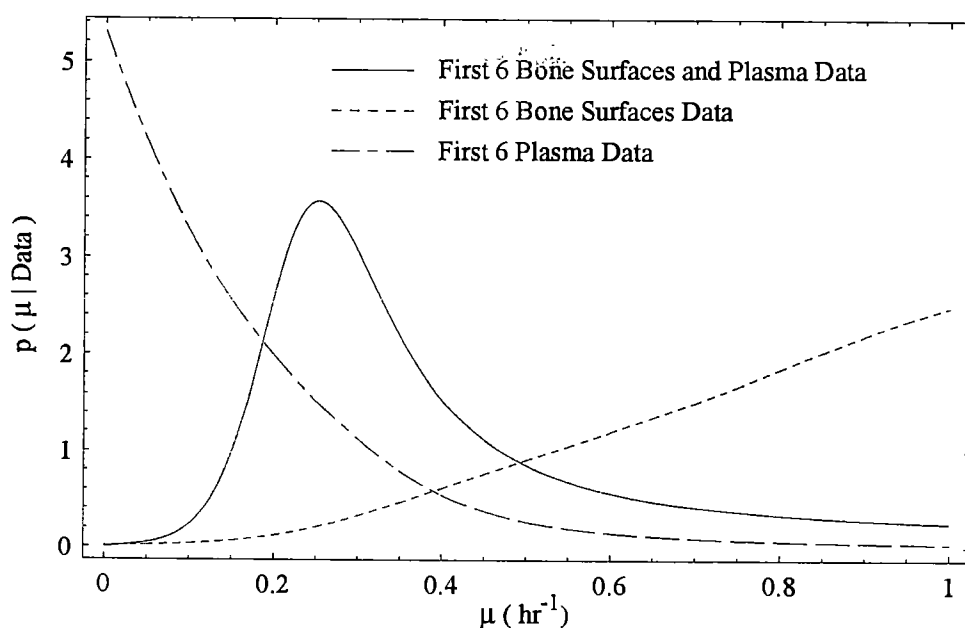


Figure 3.50. Normalized marginal posterior density for the calcium exchange rate μ in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.

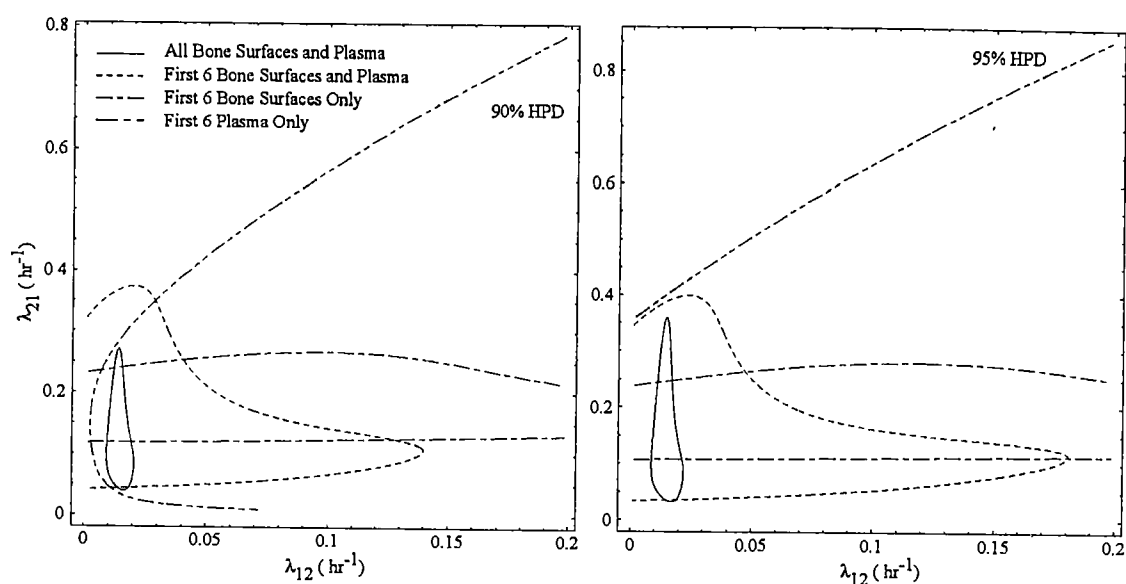


Figure 3.51. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.

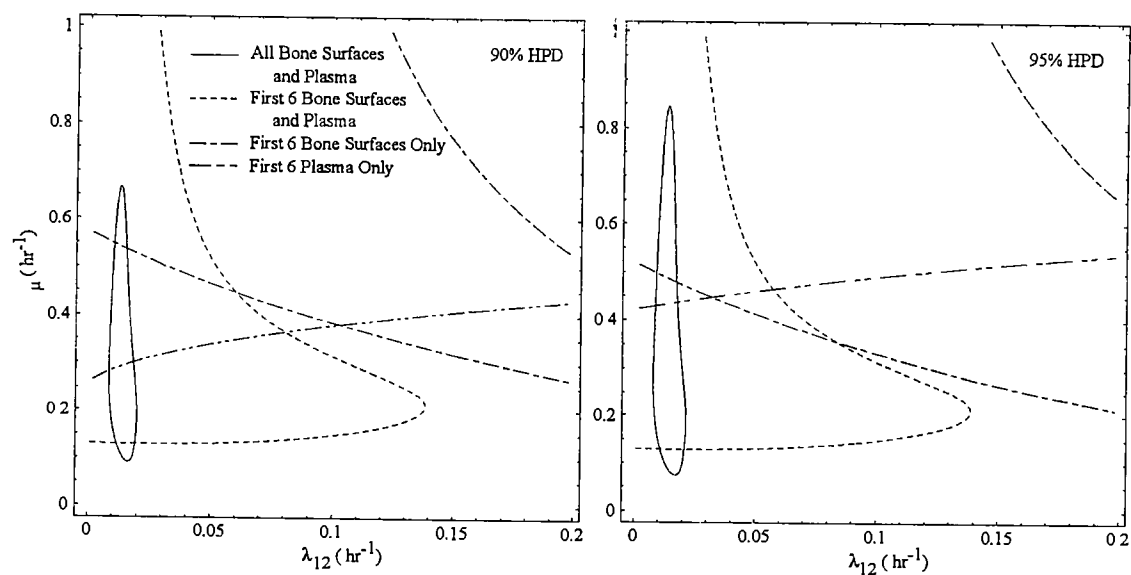


Figure 3.52. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.

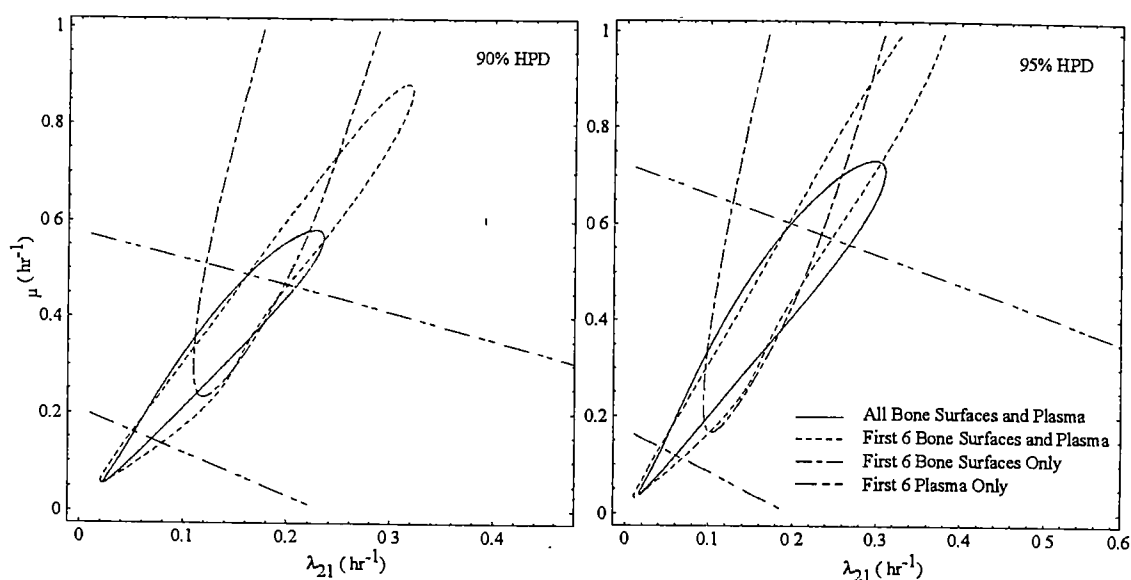


Figure 3.53. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with uniform priors and the first six ^{45}Ca data from bone surfaces, plasma or both.

3.5 Normal Priors – All Ten Data Points

In this section, Normal priors were used to minimize the “divergent” behavior of parameter λ_{12} , and to study their impacts on the bimodality and the shape of the posterior density. Since no direct prior information about the exchange of beagles bone calcium was available, the prior information was extracted from a similar analysis on Rowland’s rabbit data (Randolph, 1997). Although the rabbit analysis was already performed, it was repeated here to verify the results and to see if bimodality exist. Since the same compartmental model was used for both rabbits and beagles, this is another way of investigating the cause of bimodality. The rabbit data consisted of only four observations, and they are plotted in Fig. 3.54 and listed in Table 3.17.

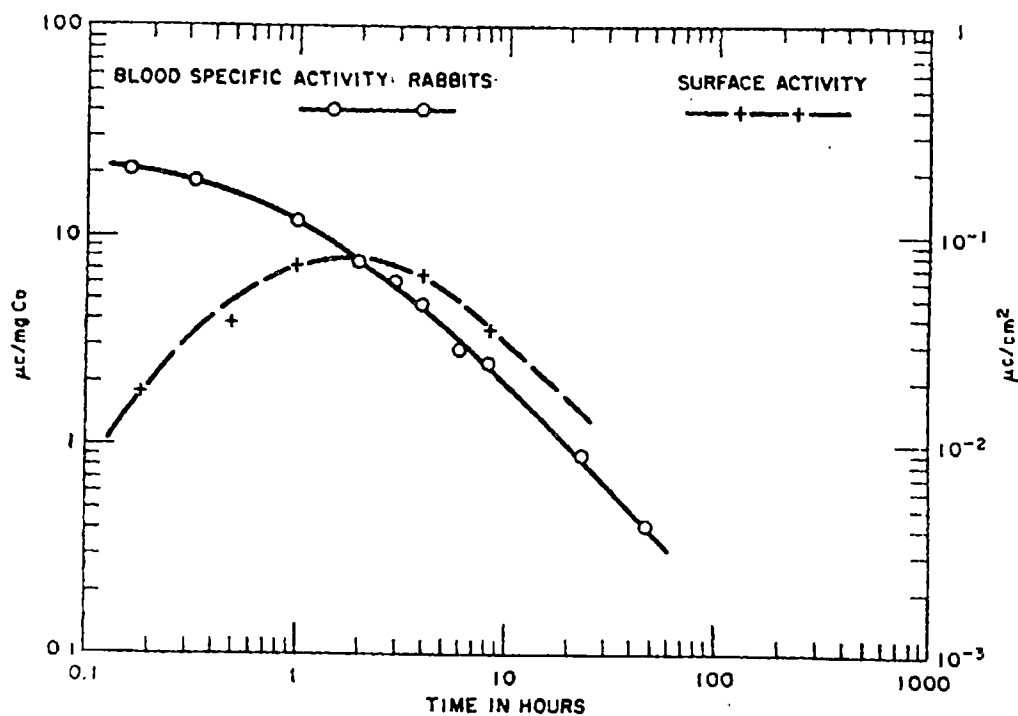


Figure 3.54. Plot of the normalized ^{45}Ca bone surfaces and plasma specific activities as a function of time in rabbits. Source: Rowland, R. E. Exchangeable Bone Calcium. Clinical Orthopedics and Related Research 49: 233-248; 1966.

Table 3.17. Normalized ^{45}Ca bone surfaces and plasma specific activities in rabbits.

Time (hours)	Bone Surfaces Activity ($\mu\text{Ci}/\text{mg } ^{45}\text{Ca}$)	Plasma Activity
0	0	20.83
0.183	1.07	21
1	7.21	13
4	6.47	5
8.5	3.57	2.5

Using the same integration limit selection process used in section 3.3, the integration limits of $0 \leq \lambda_{12}, \lambda_{21}, \mu \leq 10$ were chosen. The normalized marginal posterior densities of the rabbit ^{45}Ca exchange rates with uniform priors are plotted in Fig. 3.55 with the Bayesian estimates listed in Table 3.18. After careful examination, no bimodality was found. This is another indication that the data are the primary cause of the bimodality, if uniform priors were used.

From the plots of ^{45}Ca bone surfaces and plasma specific activities in beagles and in rabbits (see Figs. 3.2 and 3.54), the rabbits metabolic rate was judged to be about 10 times faster than beagles. To account for the relative variation between the metabolic rates in beagle and rabbit, coefficient of variation was used to determine the beagle prior standard deviation. For this model, the coefficient of variation is the ratio of the rabbit standard deviation divided by the rabbit mean.

Next, the beagle prior standard deviation was found by multiplying the coefficient of variation by the beagle prior mean and doubling the result. The doubling of the result represented the uncertainty about the factor of 10. Sample calculations for beagle prior mean and standard deviation for λ_{12} are shown with the result in Table 3.19.

Because of Bayes' theorem, constant terms can be dropped from the prior density, and the joint Normal prior can be written as:

$$p(\lambda_{12}, \lambda_{21}, \mu) \propto \text{Exp} \left\{ -\frac{1}{2} \left[\left(\frac{\lambda_{12} - \bar{x}_{12}}{\bar{\sigma}_{12}} \right)^2 + \left(\frac{\lambda_{21} - \bar{x}_{21}}{\bar{\sigma}_{21}} \right)^2 + \left(\frac{\mu - \bar{x}_{\mu}}{\bar{\sigma}_{\mu}} \right)^2 \right] \right\}, \quad (3.11)$$

where $\bar{x}$ and $\bar{\sigma}$ are the prior means and standard deviations of the estimated parameters.

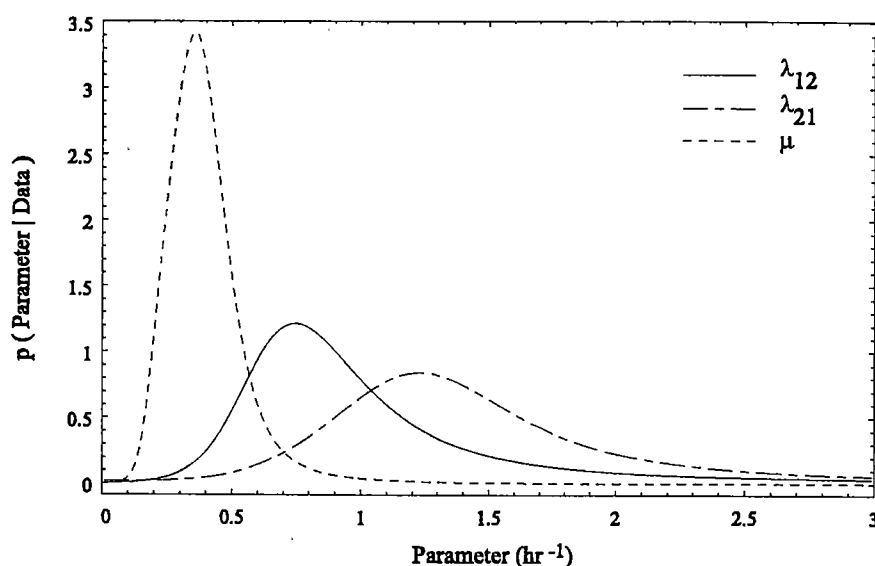


Figure 3.55. Normalized marginal posterior densities for the calcium exchange rates in rabbits calculated with all ^{45}Ca data and uniform priors. The means ($\mu\text{Ci/mg } ^{45}\text{Ca hour}$) are $\lambda_{12} = 1.4852 \pm 1.649$, $\lambda_{21} = 1.8997 \pm 1.561$ and $\mu = 0.4073 \pm 0.243$.

Table 3.18. Posterior means and standard deviations for the calcium exchange rates in rabbits calculated with all ^{45}Ca data and uniform priors.

λ_{12}	λ_{21}	μ
($\mu\text{Ci/mg } ^{45}\text{Ca hour}$)		
1.4852 ± 1.649	1.8997 ± 1.561	0.4073 ± 0.243

Table 3.19. Beagle Normal prior means and standard deviations.

λ_{12}	λ_{21}	μ
($\mu\text{Ci/mg } ^{45}\text{Ca hour}$)		
0.1485 ± 0.329	0.1899 ± 0.312	0.04073 ± 0.049

Note: Beagle prior mean for $\lambda_{12} = \frac{\text{Rabbit posterior mean for } \lambda_{12}}{10} = 0.149 \mu\text{Ci/mg } ^{45}\text{Ca hr}$

Coefficient of variation for $\lambda_{12} = \frac{\text{Rabbit posterior standard deviation for } \lambda_{12}}{\text{Rabbit posterior mean for } \lambda_{12}} = 1.1102$

Beagle prior standard deviation for $\lambda_{12} = 2 \times 0.149 \times 1.1102 = 0.329 \mu\text{Ci/mg } ^{45}\text{Ca hr}$

Substituting the prior means and standard deviations listed in Table 3.19 into Eqn. (3.11), the joint Normal prior has the form:

$$p(\lambda_{12}, \lambda_{21}, \mu) \propto \text{Exp} \left\{ -\frac{1}{2} \left[\left(\frac{\lambda_{12} - 0.149}{0.329} \right)^2 + \left(\frac{\lambda_{21} - 0.189}{0.312} \right)^2 + \left(\frac{\mu - 0.0407}{0.049} \right)^2 \right] \right\}. \quad (3.12)$$

Combining the joint Normal prior with the beagle likelihood, Eqn. (3.4), the resulting joint posterior density for the parameters λ_{12} , λ_{21} and μ can be written as:

$$p(\lambda_{12}, \lambda_{21}, \mu \mid \text{data}) \propto [S_{11}(\theta) S_{22}(\theta) - S_{12}(\theta)^2]^{-5} e^{-\frac{1}{2} \left[\left(\frac{\lambda_{12} - 0.149}{0.329} \right)^2 + \left(\frac{\lambda_{21} - 0.189}{0.312} \right)^2 + \left(\frac{\mu - 0.0407}{0.049} \right)^2 \right]}. \quad (3.13)$$

The next step is to determine the integration limits for the joint posterior density. First, the joint Normal prior density, Eqn. (3.12), is broken down into three separate densities representing each of the three parameters and plotted in Fig. 3.56:

$$f(\lambda_{12}) = e^{-\frac{1}{2} \left(\frac{\lambda_{12} - 0.149}{0.329} \right)^2}, \quad f(\lambda_{21}) = e^{-\frac{1}{2} \left(\frac{\lambda_{21} - 0.189}{0.312} \right)^2}, \quad f(\mu) = e^{-\frac{1}{2} \left(\frac{\mu - 0.0407}{0.049} \right)^2}. \quad (3.14)$$

From Fig. 3.56, the following integration limits were chosen:

$$0 \leq \lambda_{12} \leq 2; \quad 0 \leq \lambda_{21} \leq 2; \quad 0 \leq \mu \leq 0.4.$$

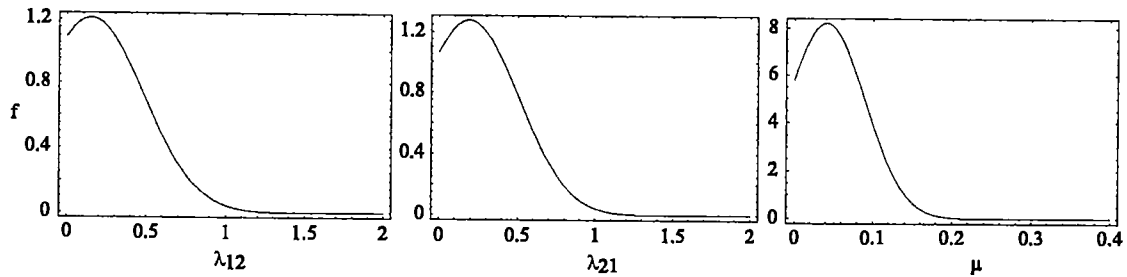


Figure 3.56. Normal prior density of λ_{12} , λ_{21} and μ calculated with rabbits ^{45}Ca data.

Using the above integration limits, log-log plots of the normalized marginal posterior densities of λ_{12} , λ_{21} and μ based on Normal priors are shown in Fig. 3.57. The posterior modes, means and standard deviations of the parameter estimates are listed in Table 3.20. The use of Normal priors eliminated the “divergent” behavior of λ_{12} . But unfortunately, the use of Normal priors also introduced bimodalities into all three parameters and made the posterior density more complicated. Like before, the differences in the peak heights are small and are only visible in log-log plots. As a result, the bimodalities can be easily missed.

When the posterior means and modes are used to calculate the residence time τ , the results were terrible, see Table 3.21. Rowland judged τ in beagles to be about 400 minutes (Rowland, 1966). The residence time calculated with posterior means gave a value of about 104 minutes, and about 912 minutes with posterior modes. For this example, the use of Normal priors did not improved the resident time estimates.

Next, the solution of the differential equations was fitted to the beagle ^{45}Ca data using the estimated parameter values. Because bimodalities were found in all three parameters, various combinations of the two peaks or modes were used in the fittings. To distinguish between them, the following terms were used. “Primary mode” represents the mode with the highest peak, and “secondary mode” represents the smaller peak. The fits using the posterior mode for λ_{12} and λ_{21} , and secondary mode for μ offered the best fits. The fits using all posterior mode were the worst. Plots of the fits, using the above combination and posterior means, to the bone surfaces data are shown in Fig. 3.58, and for the plasma data in Fig. 3.59.

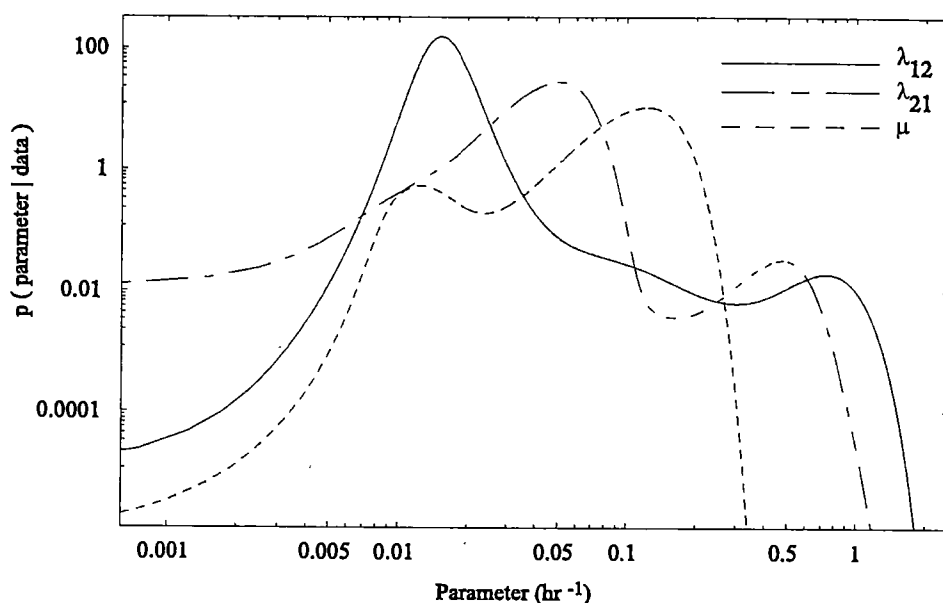


Figure 3.57. Normalized marginal posterior densities for the calcium exchange rates in beagles calculated with all ^{45}Ca data and Normal priors. The means ($\mu\text{Ci/mg } ^{45}\text{Ca hour}$) are $\lambda_{12} = 0.02464 \pm 0.0793$, $\lambda_{21} = 0.5493 \pm 0.0457$ and $\mu = 0.1239 \pm 0.0371$.

Table 3.20. Posterior modes, means and standard deviations for the calcium exchange rates in beagles calculated with all ^{45}Ca data and Normal priors.

	λ_{12}	λ_{21}	μ
	(μCi/mg $^{45}\text{Ca hour}$)		
Posterior Mean	0.02464 ± 0.0793	0.5493 ± 0.0457	0.1239 ± 0.0371
Posterior Mode	0.01522	0.05056	0.01253

Table 3.21. Comparison of residence time of calcium ions in beagles calculated with Normal priors.

	Rowland ^a	Bayesian Approach	
		Posterior Means	Posterior Modes
τ (minutes)	400	104	912

^a Rowland, R. E. Exchangeable Bone Calcium. Clin. Orth. Res. 49: 233-248; 1966.

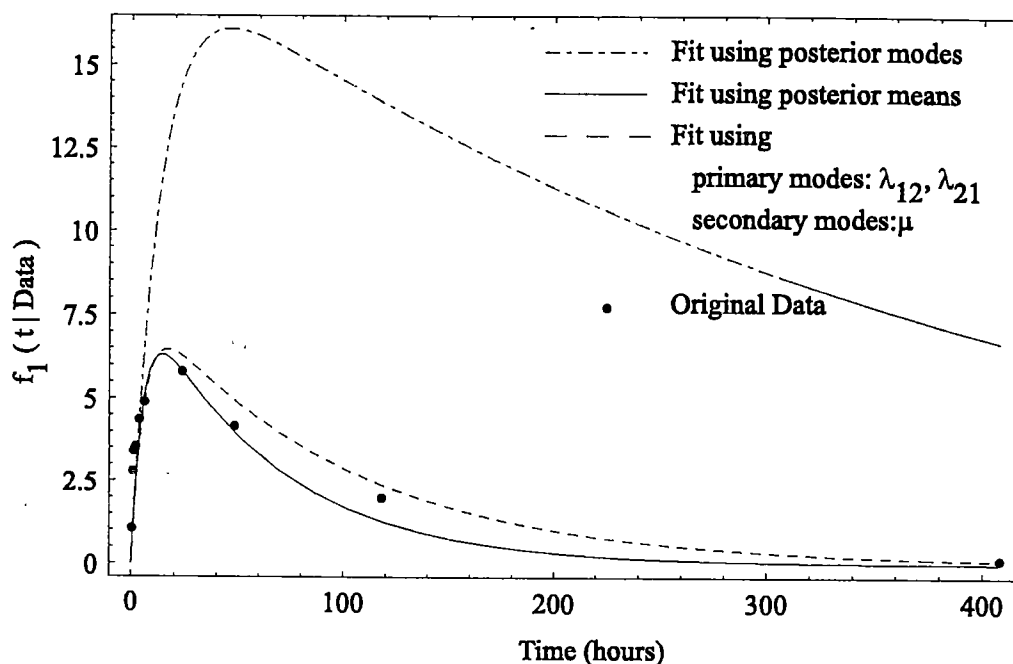


Figure 3.58. Solution of the differential equations for the parameter estimates calculated with all ^{45}Ca data and Normal priors fitted to the beagles bone surfaces ^{45}Ca data.

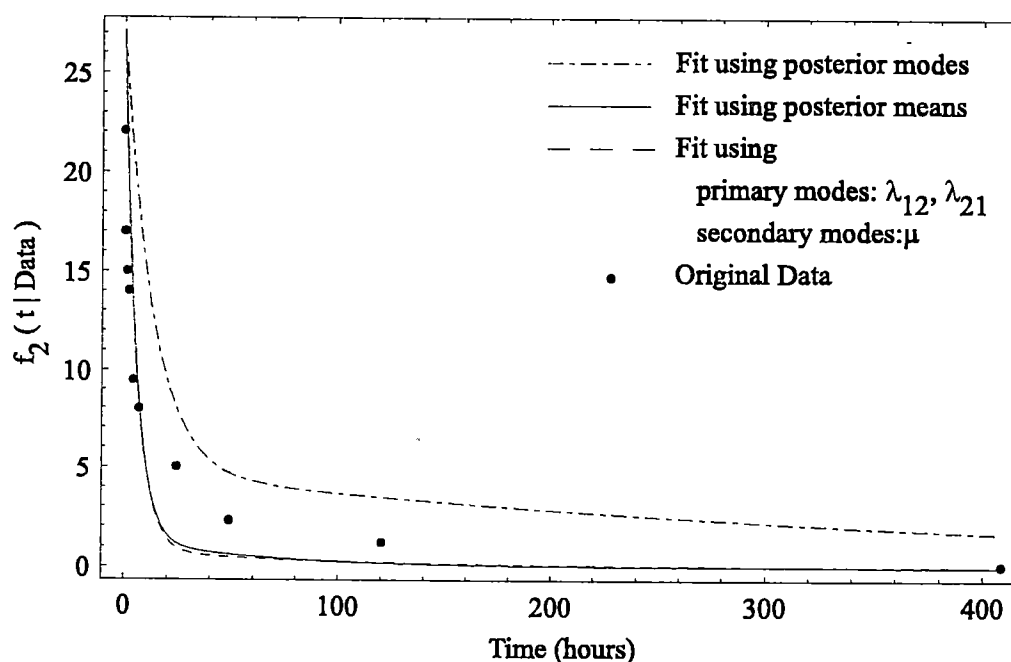


Figure 3.59. Solution of the differential equations for the parameter estimates calculated with all ^{45}Ca data and Normal priors fitted to the beagles plasma ^{45}Ca data.

Finally, the 90 and 95 percent HPD contour z values comparing the results with uniform priors versus Normal priors are listed in Table 3.22. The corresponding HPD contours are plotted in Figs. 3.60 through 3.62. Overall, the contours generated using Normal priors are more compact than the ones generated using uniform priors, which indicated greater precision. However, this contradicts the marginal posterior density plots, where the presence of bimodality could signify estimation inaccuracy.

In conclusion, we learned that the Bayesian parameter estimation technique is sensitive to the data and that the bimodality is due to the likelihood, if uniform priors were used. The use of prior information, such as Normal priors, can improve estimation precision; but it can also introduce additional bimodalities into the system as we have seen here. From the HPD contour plots, the benefit of Normal priors is clear despite of the bimodalities found in the marginal posterior densities. Finally, further improvement in the estimation precision can be achieved with better prior information and/or different prior density.

Table 3.22. Ninety and ninety-five percent HPD contours z values for various combinations of the calcium exchange rates in beagles calculated with all ^{45}Ca data and Normal priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
λ_{12} and λ_{21}	292	145
λ_{12} and μ	127	70
λ_{21} and μ	88	42

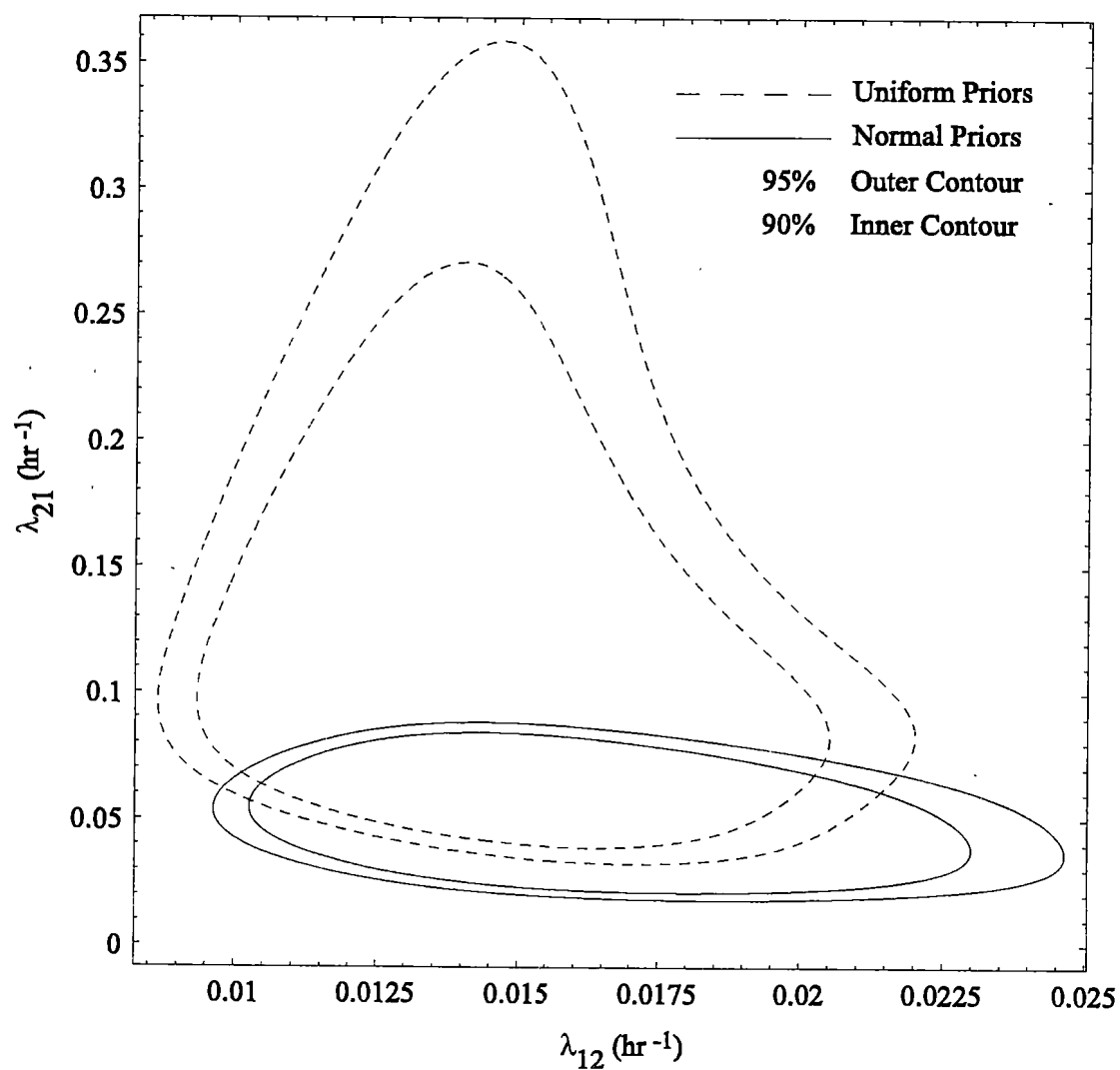


Figure 3.60. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and λ_{21} in beagles calculated with all ⁴⁵Ca data and Normal priors.

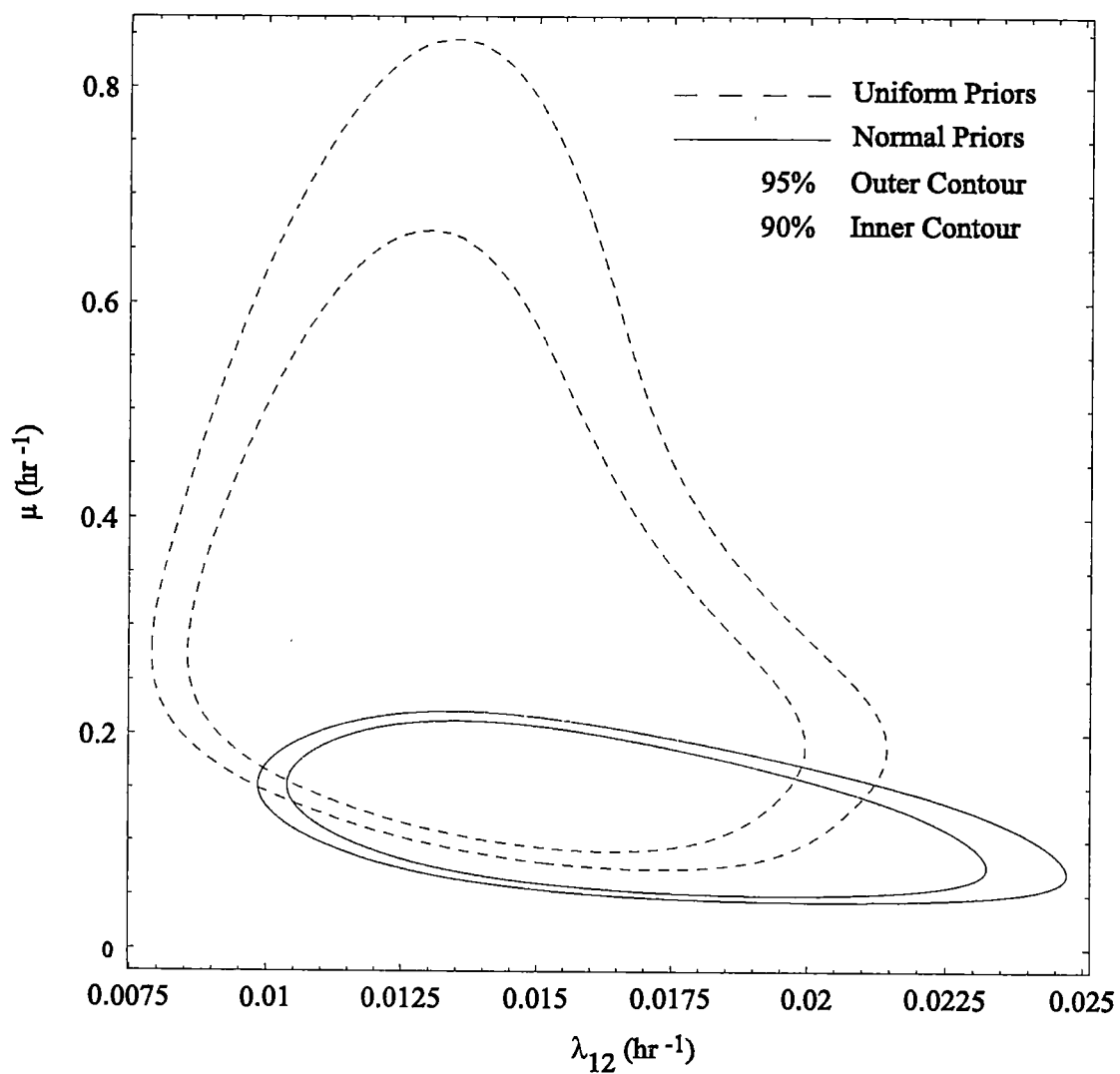


Figure 3.61. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{12} and μ in beagles calculated with all ⁴⁵Ca data and Normal priors.

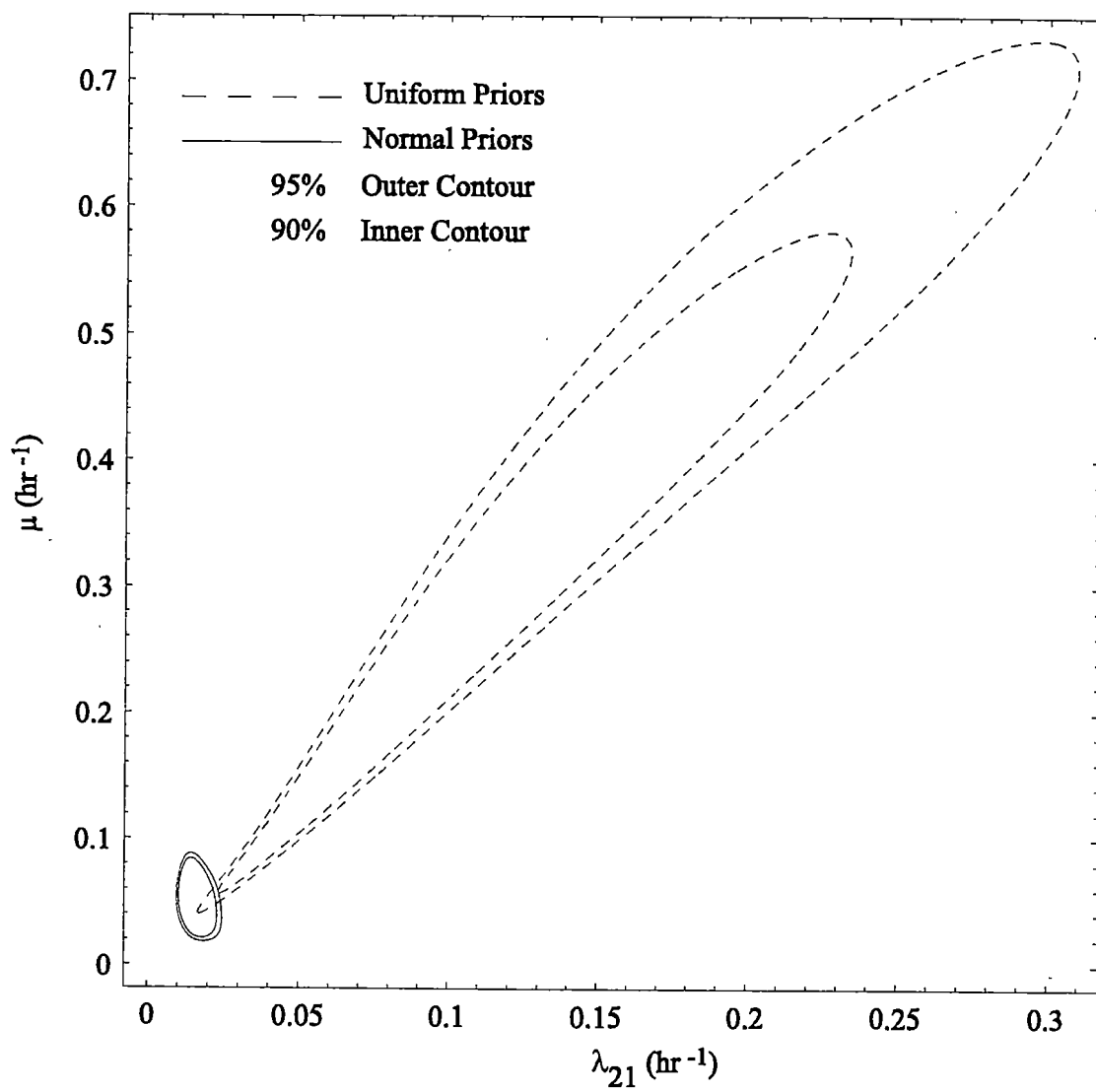


Figure 3.62. Ninety and ninety-five percent HPD contours for the calcium exchange rates λ_{21} and μ in beagles calculated with all ⁴⁵Ca data and Normal priors.

CHAPTER 4

LOCAL HUMAN CEREBRAL METABOLISM OF GLUCOSE

The next biokinetic model examined is the local human cerebral metabolism of glucose. This model uses ^{18}F labeled glucose or ^{18}F -fluorodeoxyglucose (FDG) and positron emission tomography (PET) to obtain in-vivo quantification of local tissue radioactivity. Discussions about the mathematical model and the clinical data are presented in sections 4.1 and 4.2, respectively. Results of the analysis using clinical data are presented in section 4.3. This is followed by the discussions and analyses of the simulated FDG PET data in section 4.4.

4.1 *Mathematical Model*

The local cerebral metabolism of glucose, or its radiopharmaceutical counterpart FDG, can be described by a three-compartment catenary system (Huang *et al.*, 1980). A catenary system is a system in which the compartments are arranged in a linear array so that each compartment exchanges only with the immediate adjacent compartments. Shown in Fig. 4.1, the compartments represent the concentrations of FDG in plasma (C_P), FDG in cerebral tissue (C_E), and FDG-6-P in cerebral tissue (C_M). The last compartment, C_M , represents the first stage of glucose metabolism, where glucose or FDG reacts with adenosine triphosphate (ATP) to form glucose-6-phosphate (FDG-6-phosphate or FDG-6-P). Since the human body can not metabolize FDG-6-phosphate any further, the model ends here.

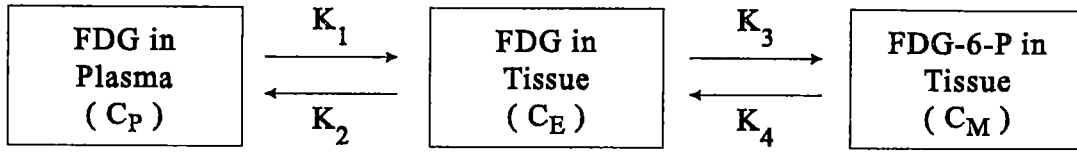


Figure 4.1. A three-compartment catenary system describing the local human cerebral metabolism of ^{18}F -fluorodeoxyglucose (FDG).

The boundary between FDG in plasma and FDG in cerebral tissue is a physical one, called the blood-brain barrier. The movements of FDG across it are denoted by K_1 and K_2 . However, the boundary separating FDG and FDG-6-P in tissue is not a physical one, but rather a chemical one represented by the parameters K_3 and K_4 . Since PET can not distinguish between FDG and FDG-6-P, lumping of the C_E and C_M observations occurs. This will be discussed in more detail in section 4.2.

Assuming the compartments are well-mixed, homogeneous and have constant FDG exchange and metabolism rates, the differential equations describing the above system is given by Eqn. (4.1):

$$\begin{aligned}
 \frac{dC_P}{dt} &= -K_1 C_P + K_2 C_E \\
 \frac{dC_E}{dt} &= K_1 C_P - (K_2 + K_3) C_E + K_4 C_M \\
 \frac{dC_M}{dt} &= K_3 C_E - K_4 C_M
 \end{aligned} \tag{4.1}$$

The differential equations are linear and homogeneous and can be solved using the matrix method. Assuming an initial plasma FDG concentration of x_0 , the solution to the above differential equations is:

$$\begin{aligned}
C_P(\bar{K}, t) &= \frac{K_2 K_4 x_o}{m_2} + \frac{K_1 (K_1 + K_2 + \lambda_3) x_o}{\lambda_2 m_3} e^{\lambda_2 t} - \frac{K_1 (K_2 K_4 + K_1 \lambda_3) x_o}{\lambda_3 m_3 (K_1 + \lambda_3)} e^{\lambda_3 t} \\
C_E(\bar{K}, t) &= \frac{K_1 K_4 x_o}{m_2} + \frac{K_1 (K_4 + \lambda_2) x_o}{\lambda_2 m_3} e^{\lambda_2 t} - \frac{K_1 (K_4 + \lambda_3) x_o}{\lambda_3 m_3} e^{\lambda_3 t} \\
C_M(\bar{K}, t) &= \frac{K_1 K_3 x_o}{m_2} + \frac{K_1 K_3 \lambda_3 x_o}{m_2 m_3} e^{\lambda_2 t} - \frac{K_1 K_3 x_o}{\lambda_3 m_3} e^{\lambda_3 t}
\end{aligned} \tag{4.2}$$

where

$$\bar{K} = K_1, K_2, K_3, K_4$$

$$m_1 = K_1 + K_2 + K_3 + K_4$$

$$m_2 = K_1 K_3 + K_1 K_4 + K_2 K_4$$

$$m_3 = \sqrt{m_1^2 - 4m_2}$$

$$\lambda_2, \lambda_3 = \frac{1}{2}(-m_1 \pm m_3)$$

4.2 Clinical Data

We obtained the clinical FDG PET data from the University of Tennessee Medical Center in Knoxville (Smith, 1997). Listed in Table 4.1, the data consist of 14 observations for the concentrations of FDG in plasma and FDG/FDG-6-P in tissue. Due to the current technical limitation of PET, the data has the following two characteristics.

The first characteristic is the spillover factor, a detector specific factor related to the scanning resolution. Illustrated in Fig. 4.2, this factor is small and is ignored by most investigators (Huang *et al.*, 1980). For this analysis, a 10% plasma spillover factor will be

Table 4.1. Clinical FDG PET data in plasma and in cerebral gray matter tissue in human.
Source: Dr. Gary Smith, Department of Nuclear Medicine, University of Tennessee
Medical Center in Knoxville, 1997.

Time (minutes)	Plasma Activity (y_{u1}) ^a	Cerebral Gray Matter Activity (y_{u2}) ^{a,b}
	(counts per second/pixel)	
0.00	0.28312	0.022133
0.33	0.24034	0.0095083
0.67	0.10309	0.036216
1.00	0.03525	0.016425
1.67	0.035391	0.020681
2.67	0.026204	0.023384
3.67	0.032618	0.022551
6.67	0.027097	0.026685
11.67	0.023454	0.035063
16.67	0.020009	0.042288
21.67	0.021686	0.047085
26.67	0.017526	0.043846
31.67	0.014054	0.056481
36.67	0.014042	0.061099
46.67	0.013588	0.068573

^a 10% Plasma spillover factor is assumed.

^b Made up of both FDG and FDG-6-phosphate activities.

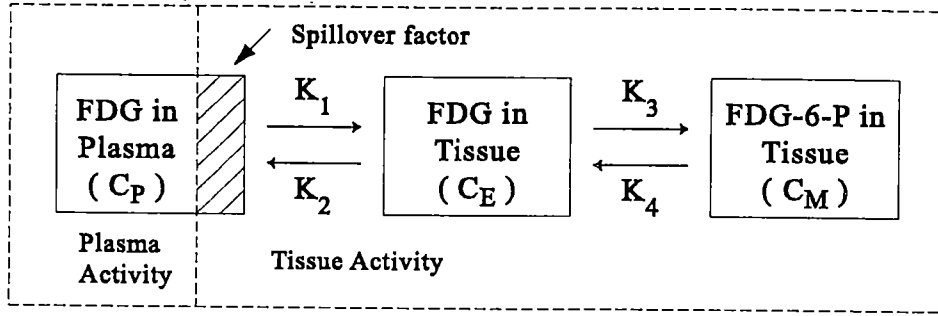


Figure 4.2. Three-compartment catenary system describing the local human cerebral metabolism of ^{18}F -fluorodeoxyglucose with spillover factor and compartmental lumping.

used (Smith, 1997). Therefore, the plasma FDG activities listed in Table 4.1 represent only 90% of the actual plasma FDG activity with the remainder 10% reported as FDG/FDG-6-P activity in tissue.

The second characteristics is PET's inability to distinguish between FDG and FDG-6-P. Since both compounds are radioactively identical and both are found in tissue. Because there is no physical barrier separating FDG and FDG-6-P, it is currently impossible to separate the two counts. Therefore, the activities for tissue's FDG and FDG-6-P are lumped together as one, tissue activity.

4.3 Analysis of Clinical Data

Considering a 10% plasma spillover factor, 14 data points, lumping of C_E and C_M compartments and uniform priors, the joint posterior density for the parameters is:

$$p(K_1, K_2, K_3, K_4 | \text{data}) \propto \left[S_{11}(\theta) S_{22}(\theta) - S_{12}(\theta)^2 \right]^{-7}, \quad (4.3)$$

where

$$S_{11}(\theta) = \sum_{u=1}^{14} [\gamma_{u1} - 0.9 \cdot C_P(\bar{K}, t_u)]^2$$

$$S_{22}(\theta) = \sum_{u=1}^{14} [\gamma_{u2} - 0.1 \cdot C_P(\bar{K}, t_u) - C_E(\bar{K}, t_u) - C_M(\bar{K}, t_u)]^2$$

$$S_{12}(\theta) = S_{21}(\theta)$$

$$= \sum_{u=1}^{14} [\gamma_{u1} - 0.9 \cdot C_P(\bar{K}, t_u)] \cdot [\gamma_{u2} - 0.1 \cdot C_P(\bar{K}, t_u) - C_E(\bar{K}, t_u) - C_M(\bar{K}, t_u)]$$

To obtain the marginal posterior densities, integration of the joint posterior density is needed. The integration limits were calculated from the information about the published average rate constants calculated by Huang *et al.* and are listed in Table 4.2.

Table 4.2. Published average FDG metabolism rates in human cerebral gray matter, and the extrapolated integration limits for Bayesian analysis.

Parameter	Published Average Values ^a	Integration Limits ^b
	(1/min)	
K ₁	0.102 ± 0.028	0 ≤ K ₁ ≤ 0.4
K ₂	0.13 ± 0.066	0 ≤ K ₂ ≤ 0.8
K ₃	0.062 ± 0.019	0 ≤ K ₃ ≤ 0.4
K ₄	0.0068 ± 0.0014	0 ≤ K ₄ ≤ 0.02

^a Source: Huang *et al.* Non-Invasive Determination of Local Cerebral Metabolic Rate of Glucose in Man. American Journal Physiology 238:E69-E82, 1980.

^b Upper integration limit = Published Value + (10 × Published Standard Deviation).

Using the above integration limits, the normalized marginal posterior densities of the parameters with uniform priors are plotted in Fig. 4.3, with the Bayesian estimates listed in Table 4.3. From the marginal density plots, two interesting features can be seen for parameter K_2 : “divergent” behavior and bimodality. They were the results of the likelihood. It will be shown in the next section that they are due to the data, which can be attributed to either patient movements during PET imaging or physiological problems or both. As for the large probability density values at $K_3 = 0.4$ and $K_4 = 0.02$, they are also influenced by the data and to some extent by the current integration limits. They could be reduced by increase the integration limits, but at a possible cost of higher posterior means and variances.

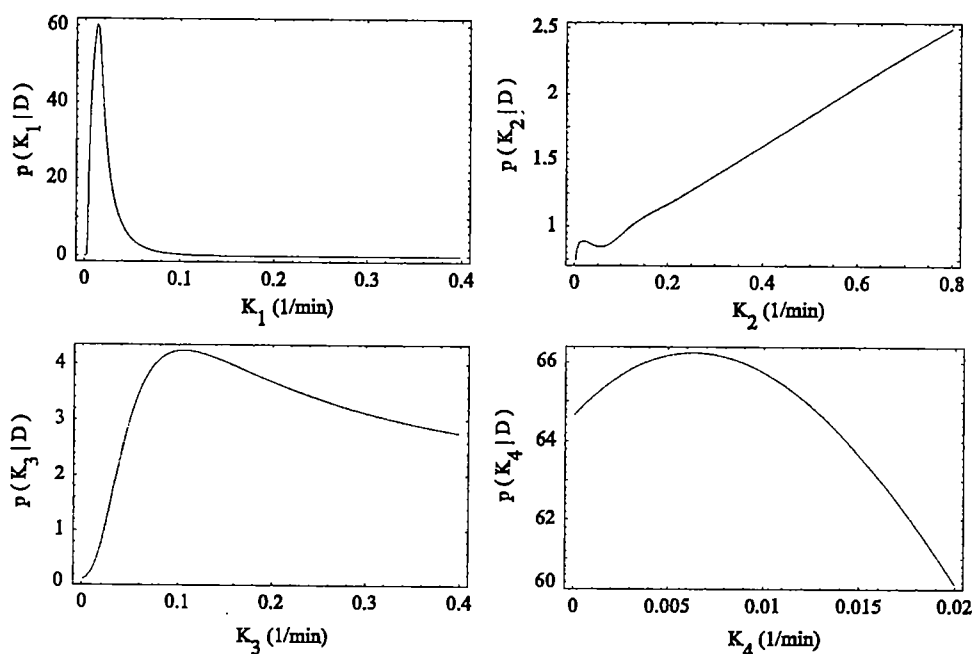


Figure 4.3. Normalized marginal posterior densities for human cerebral gray matter glucose metabolism rates calculated with clinical FDG PET data and uniform priors. The means are (min^{-1}): $K_1 = 0.0256 \pm 0.021$, $K_2 = 0.474 \pm 0.22$, $K_3 = 0.161 \pm 0.076$ and $K_4 = 0.00977 \pm 0.0057$.

Table 4.3. Posterior modes, means and standard deviations for the human cerebral gray matter glucose metabolism rates calculated with clinical FDG PET data and uniform priors.

Parameter	Posterior Mean	Posterior Mode
	(1 / min)	
K_1	0.0256 ± 0.021	0.01365
K_2	0.474 ± 0.22	None
K_3	0.161 ± 0.076	0.1055
K_4	0.00977 ± 0.0057	0.006305

Since parameter K_2 does not have a posterior mode, the solution of the differential equations was fitted to the data using only the posterior means. Plots of the fit to the plasma FDG data are shown in Fig. 4.4, and to the tissue FDG/FDG-6-P data in Fig. 4.5. The fits were poor. The first explanation is that the 10% spillover factor is incorrect. However, the fits using zero spillover factor and the published average rate constants were not any better (see Figs. 4.6 and 4.7). The second explanation is that there are unknown problems with the data, and it will be discussed in more detail in section 4.4.

The posterior density has four parameters and a contour plot is two-dimensional; therefore, six parameter pairs are needed to cover all of the possibilities: $K_1 - K_2$, $K_1 - K_3$, $K_1 - K_4$, $K_2 - K_3$, $K_2 - K_4$ and $K_3 - K_4$. The 90 and 95 percent HPD are plotted in Figs. 4.8 through 4.13, with the corresponding contours z values listed in Table 4.4. There is evidence of imprecise estimation in every plot. All of the contours were open, and two of them, (K_2, K_3) and (K_2, K_4) , exhibited quite interesting contours.

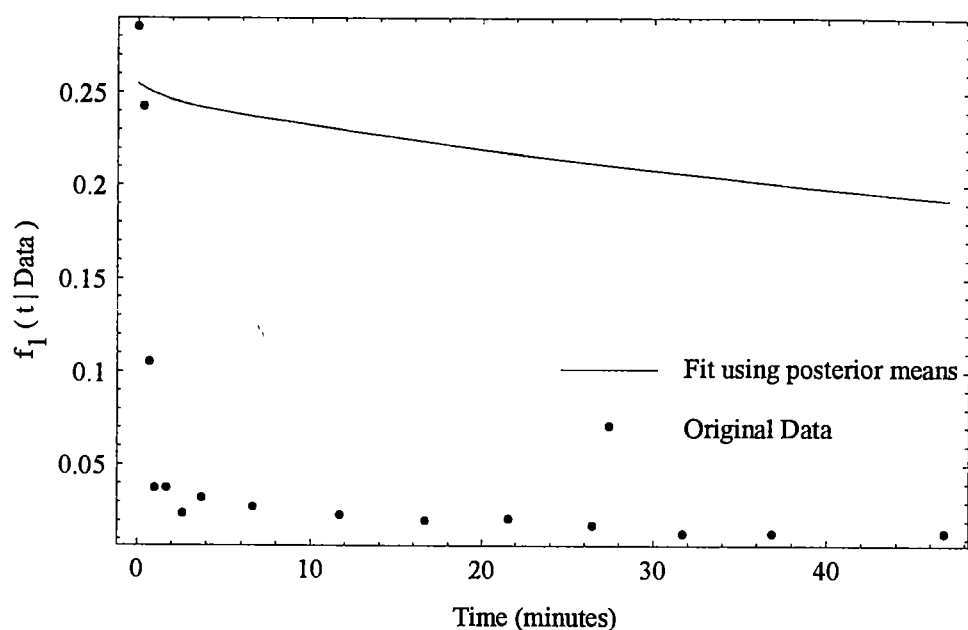


Figure 4.4. Solution of the differential equations for the parameter estimates calculated with clinical FDG PET data and uniform priors fitted to the human cerebral plasma FDG data.

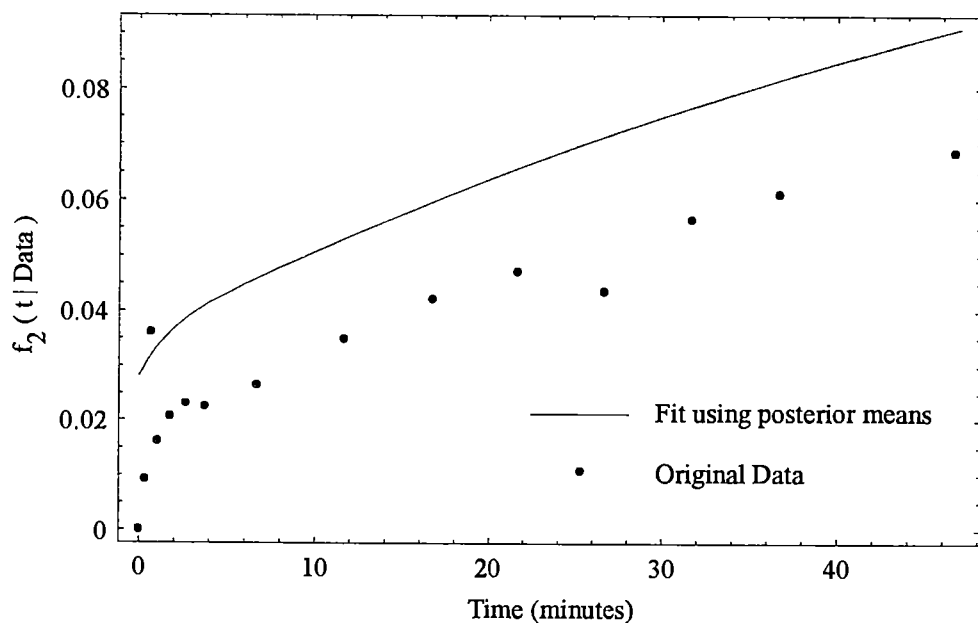


Figure 4.5. Solution of the differential equations for the parameter estimates calculated with clinical FDG PET data and uniform priors fitted to the human cerebral gray matter tissue FDG and FDG-6-P data.

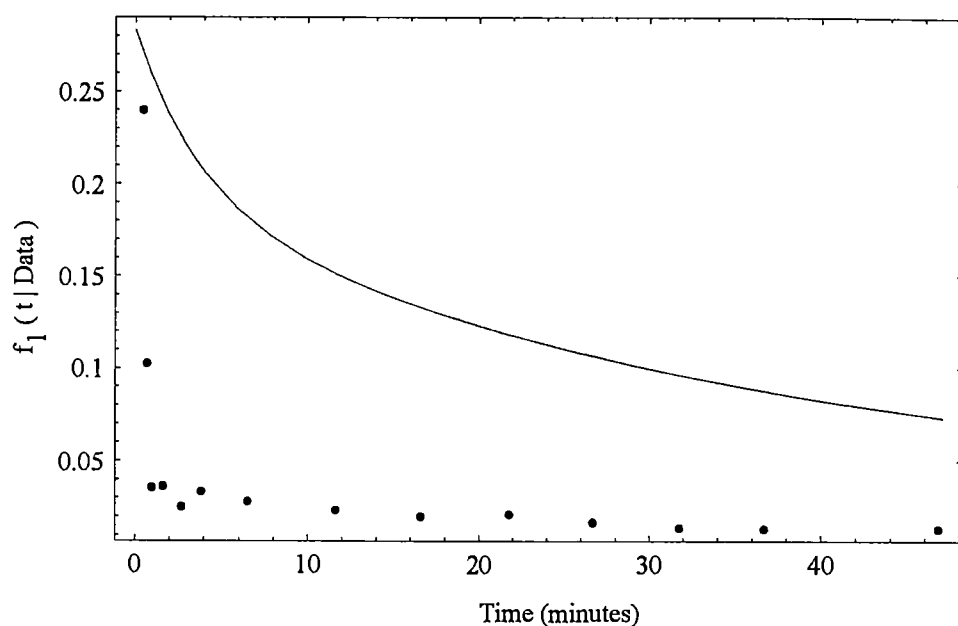


Figure 4.6. Solution of the differential equations fitted to the human cerebral plasma FDG data using the published average rate constants with no spillover factor.

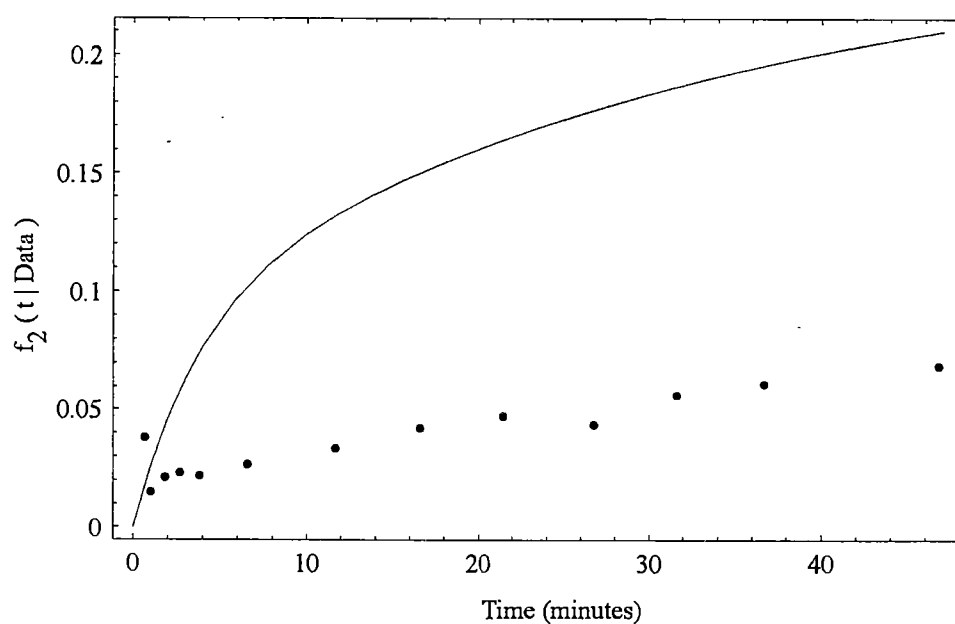


Figure 4.7. Solution of the differential equations fitted to the human cerebral gray matter tissue FDG and FDG-6-P data using the published average rate constants with no spillover factor.

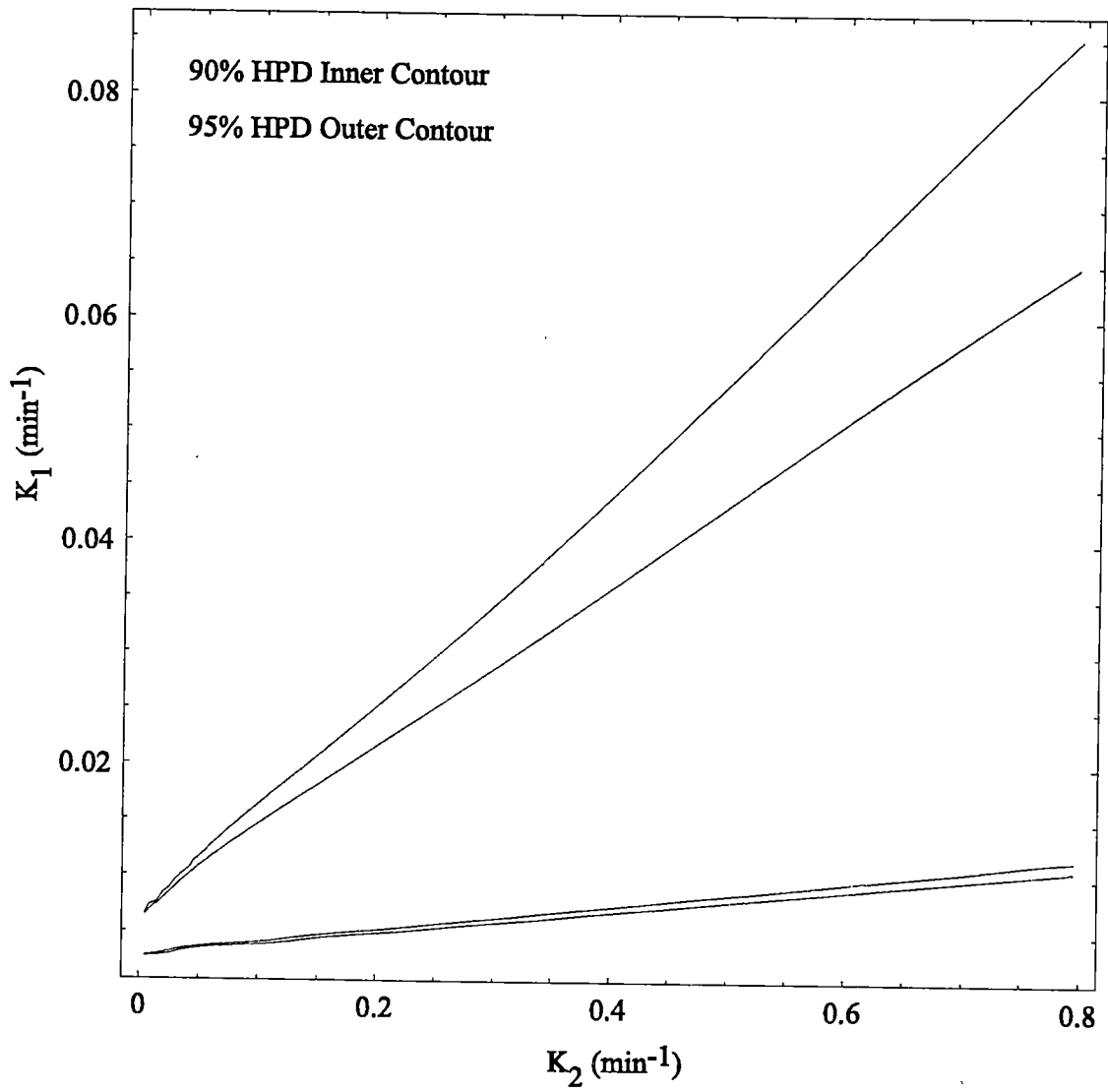


Figure 4.8. Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_2 calculated with clinical FDG PET data and uniform priors.

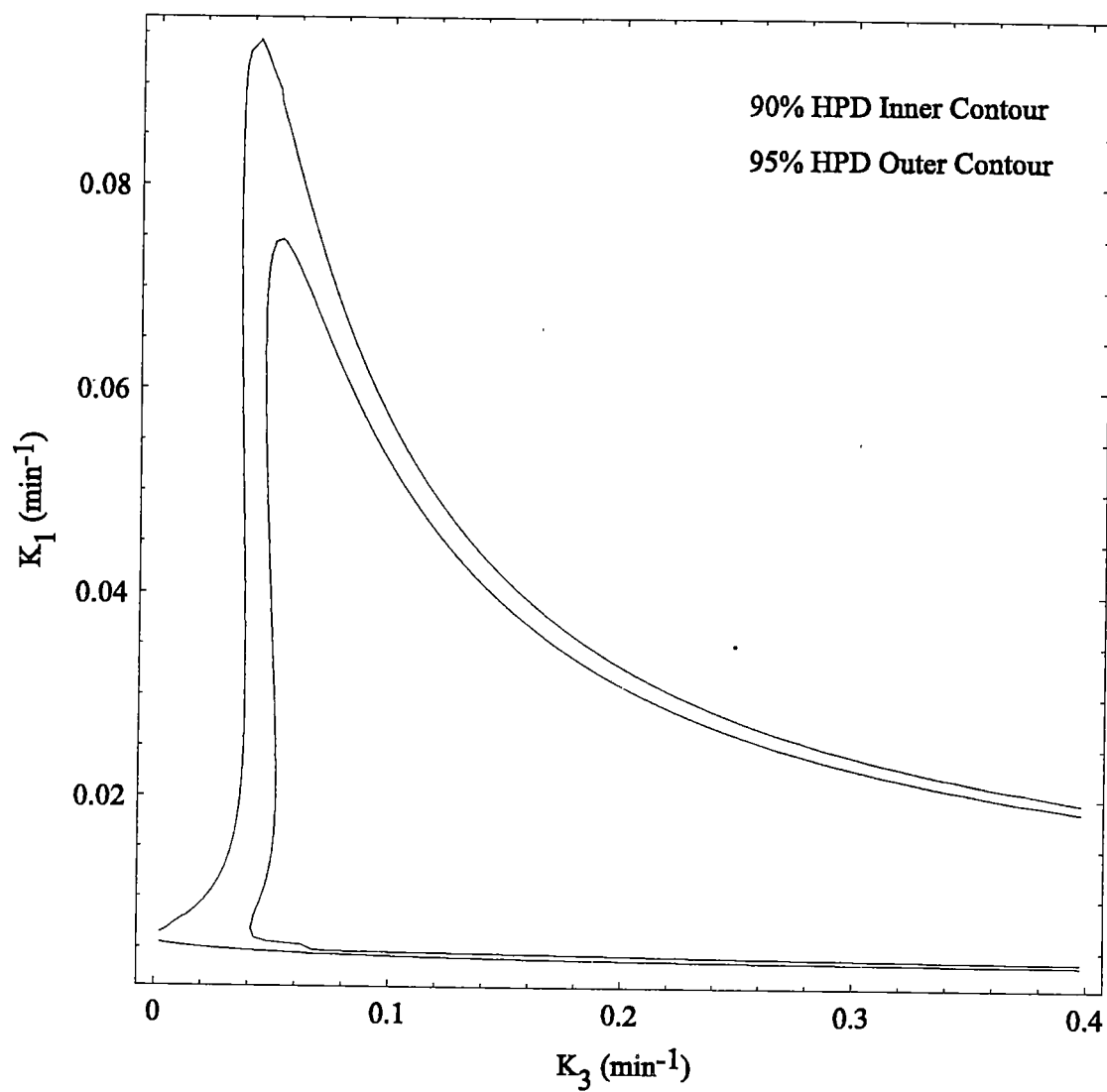


Figure 4.9. Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_3 calculated with clinical FDG PET data and uniform priors.

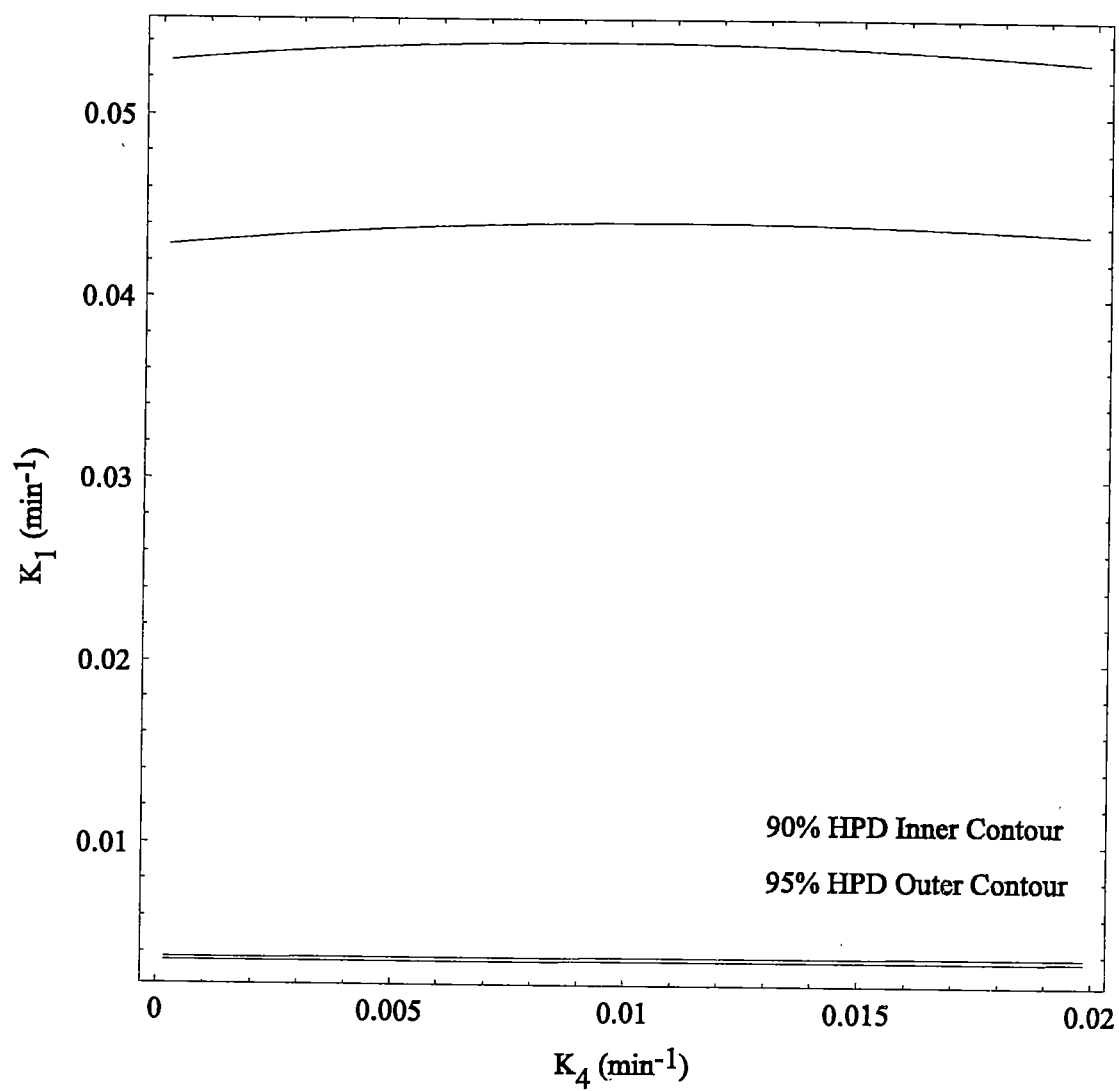


Figure 4.10. Ninety and ninety-five percent HPD contours for human cerebral gray matter glucose metabolism rates K_1 and K_4 calculated with clinical FDG PET data and uniform priors.

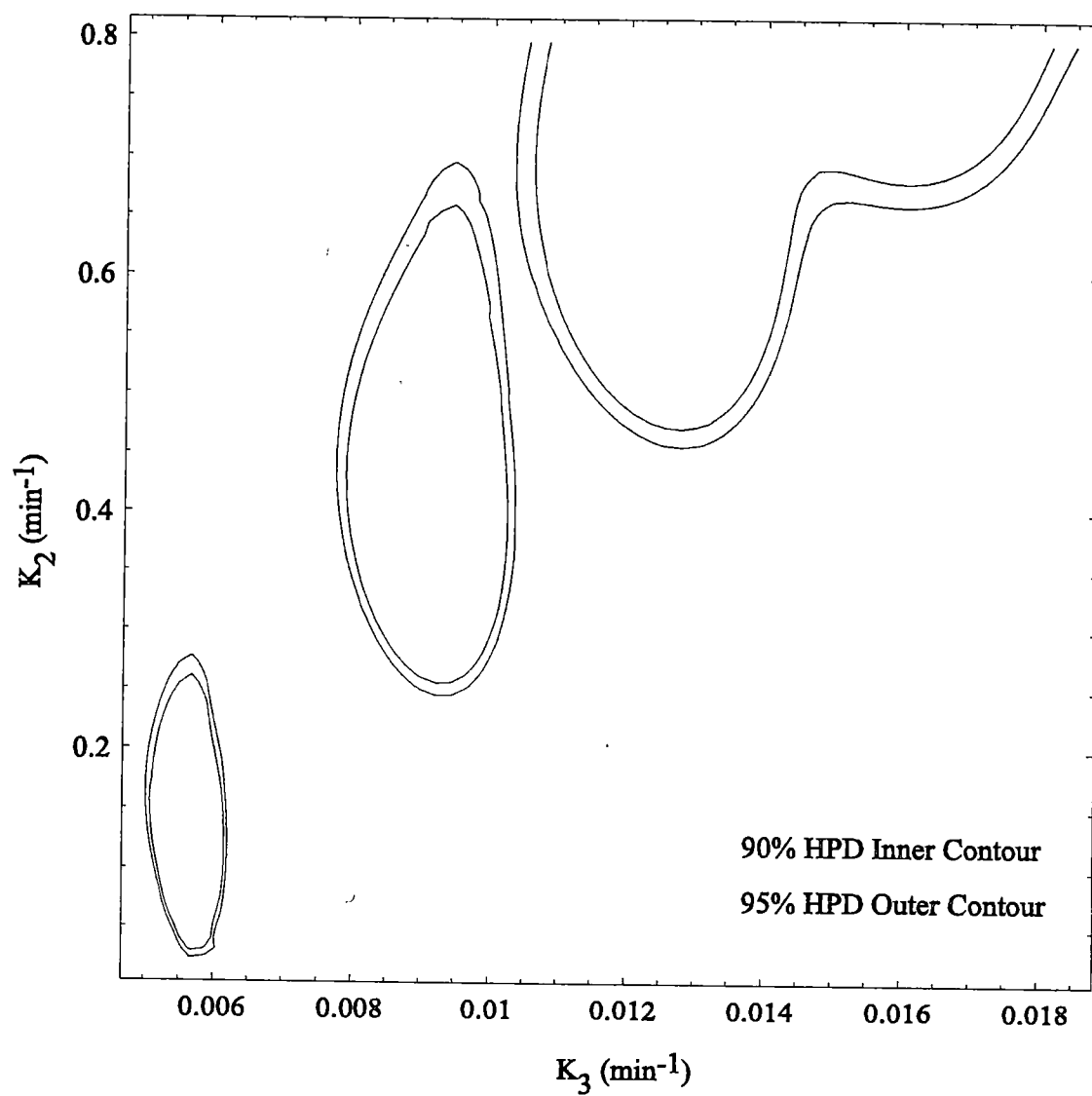


Figure 4.11. Ninety and ninety-five percent HPD contours for human cerebral gray matter glucose metabolism rates K_2 and K_3 calculated with clinical FDG PET data and uniform priors.

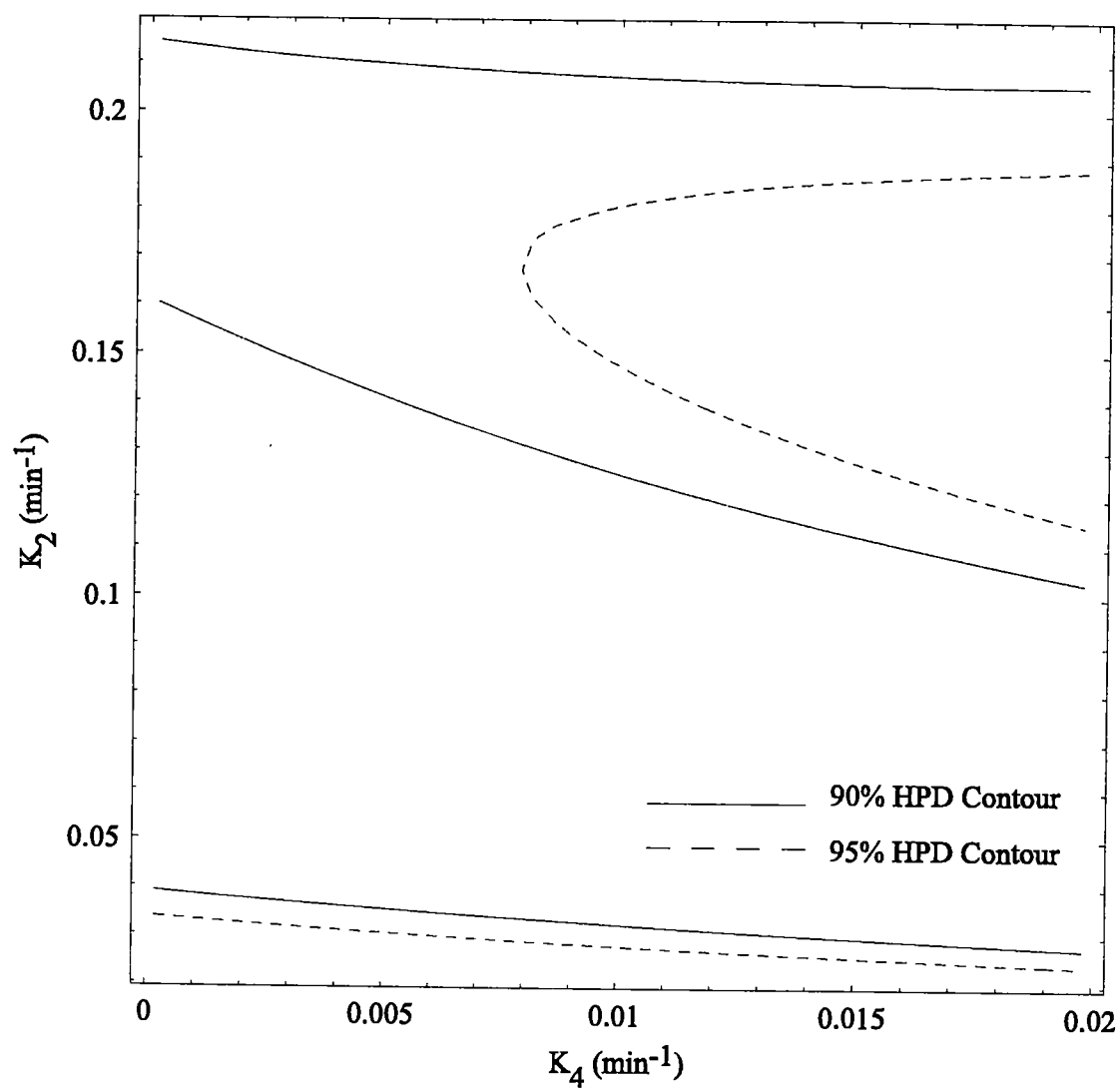


Figure 4.12. Ninety and ninety-five percent HPD contours for human cerebral gray matter glucose metabolism rates K_2 and K_4 calculated with clinical FDG PET data and uniform priors.

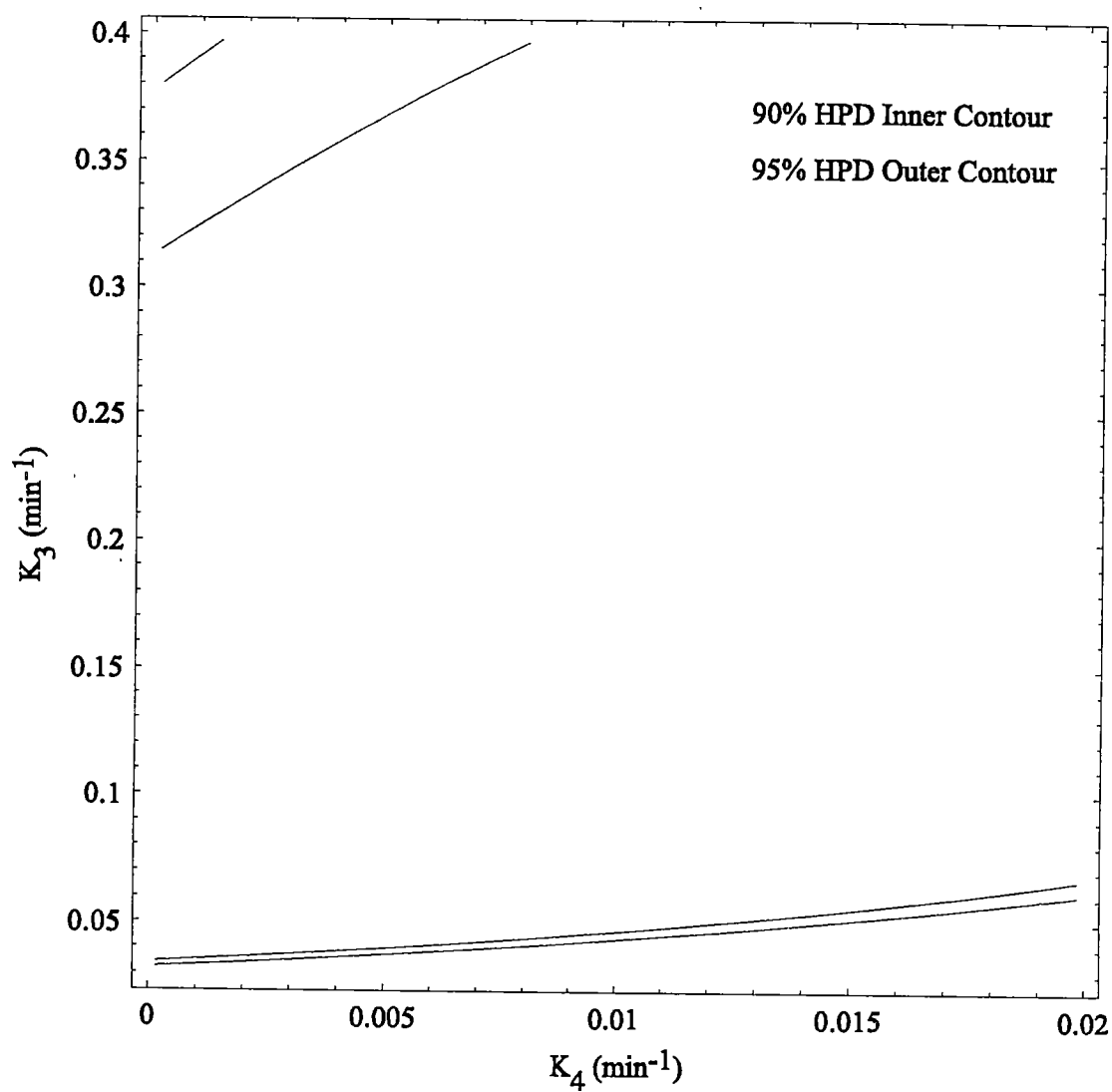


Figure 4.13. Ninety and ninety-five percent HPD contours for human cerebral gray matter glucose metabolism rates K_3 and K_4 calculated with clinical FDG PET data and uniform priors.

Table 4.4. Ninety and ninety-five percent HPD contour z values for various combinations of the human cerebral gray matter glucose metabolism rates calculated with clinical FDG PET data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
K_1 and K_2	9.7	4.5
K_1 and K_3	32	17
K_1 and K_4	307	174
K_2 and K_3	2.6	1.8
K_2 and K_4	52	49
K_3 and K_4	141	130

4.4 Analysis of Simulated Data

In section 4.3, we pointed out that the Bayesian estimation of cerebral FDG metabolism rates using clinical data was imprecise. To see if the clinical data were the culprit, three FDG PET data sets were simulated using the following assumptions: initial plasma activity of 0.283 cps/pixel, 14 observations, 10% plasma spill-over factor, lumping of the observations for the tissue compartments, and 5, 10, and 25% noise.

First, we substituted the published average rate constants (see Table 4.2) into the solution of the differential equations (Eqn. 4.2) to calculate the expected FDG activities for the plasma and tissue compartments at each of the 14 observation periods. Next, the standard deviation for the expected FDG activity is calculated using the desired percent noise level and the coefficient of variation:

Standard deviation = Percent random noise x Expected value.

Finally, assuming Normal error, the data are simulated using the *Mathematica*[®] (Wolfram, 1998) commands listed in Appendix B. The simulated data with 5, 10, and 25% random Normal noise are listed in Table 4.5.

Using the same integration limits as before in section 4.3, the normalized marginal posterior densities of K_1 , K_2 , K_3 and K_4 for the three simulated data sets are shown in Figs. 4.14 through 4.17. Posterior modes, means and standard deviations of the estimates are listed in Table 4.6. Overall, the results were good. No bimodality was found. However, large probability density values at $K_4 = 0.02$ were found the marginal density plots. This can be solved by increase the current integration limits.

The analysis showed that the clinical data were the primary cause of bimodality and the “divergent” behavior of the posterior density found in section 4.3. The results also showed the close relationships between data precision and the estimates. Estimation precision can also be increased if individual tissue compartment observations were used. Unfortunately, this is not possible due to the current limitations of the PET FDG imaging.

Next, the solution of the differential equations was fitted to the simulated data using the above estimates. Since the posterior mode of K_4 does not exist for 10 and 25% noise data, only the posterior means were used to fit the 10 and 25% noise data. Plots of the fits using the above estimates for the simulated plasma and tissue observations are shown in Figs. 4.18 through 4.23. The results were much improved from the clinical data analysis.

Table 4.5. Local human cerebral gray matter FDG PET data sets simulated using the published average rate constants with 5, 10 and 25% noise.

Time (min)	Plasma Activity (cps/pixel)			Tissue Activity (cps/pixel)		
	5% Noise	10% Noise	25% Noise	5% Noise	10% Noise	25% Noise
0	0.283	0.283	0.283	0	0	0
0.33	0.251718	0.265285	0.230550	0.038396	0.037211	0.035754
0.67	0.215370	0.228715	0.276844	0.044123	0.046293	0.054254
1.00	0.223473	0.231607	0.211110	0.052203	0.049631	0.046122
1.67	0.214501	0.223029	0.263448	0.065194	0.058478	0.051758
2.67	0.203709	0.209644	0.170133	0.082669	0.084410	0.067106
3.67	0.187607	0.191851	0.185513	0.089911	0.093660	0.095072
6.67	0.161114	0.152366	0.148769	0.120286	0.112577	0.103480
11.67	0.152582	0.140875	0.130000	0.148575	0.139785	0.178933
16.67	0.128204	0.119206	0.106350	0.165110	0.163266	0.112659
21.67	0.110076	0.106593	0.122211	0.178269	0.178781	0.176500
26.67	0.100308	0.098982	0.111328	0.185946	0.185587	0.149264
31.67	0.085757	0.087245	0.112476	0.202862	0.200672	0.202885
36.67	0.082555	0.079475	0.094049	0.205300	0.202237	0.161306
46.67	0.068249	0.068799	0.078765	0.217953	0.216558	0.264059

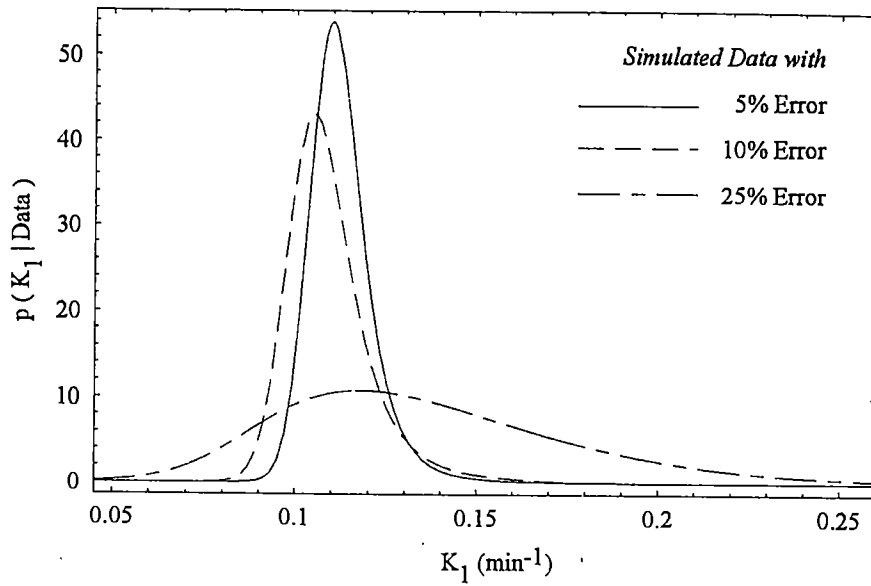


Figure 4.14. Normalized marginal posterior density for the human cerebral gray matter glucose metabolism rate K_1 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise. The means (min^{-1}) are: 5% noise = 0.1127 ± 0.00925 , 10% noise = 0.1094 ± 0.0121 and 25% Noise = 0.01368 ± 0.0412 .

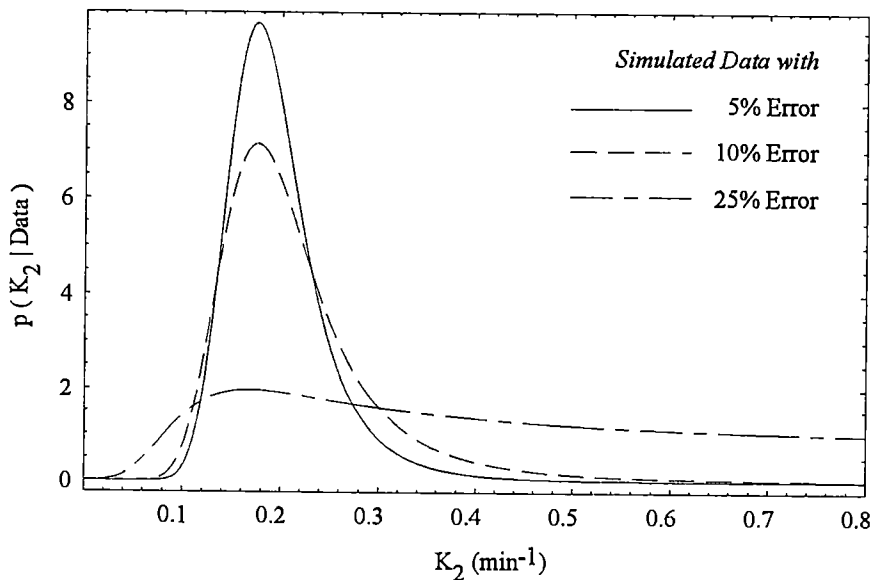


Figure 4.15. Normalized marginal posterior density for the human cerebral gray matter glucose metabolism rate K_2 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise. The means (min^{-1}) are: 5% noise = 0.198 ± 0.0575 , 10% noise = 0.2192 ± 0.0893 and 25% noise = 0.3914 ± 0.208 .

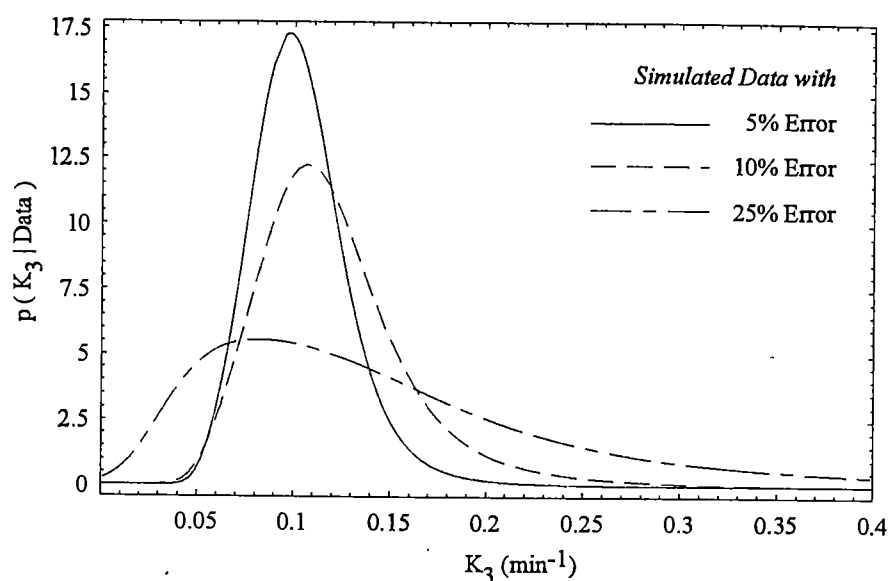


Figure 4.16. Normalized marginal posterior density for the human cerebral gray matter glucose metabolism rate K_3 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise. The means (min⁻¹) are: 5% noise = 0.1035 ± 0.0258 , 10% noise = 0.1205 ± 0.0398 and 25% noise = 0.1402 ± 0.0829 .

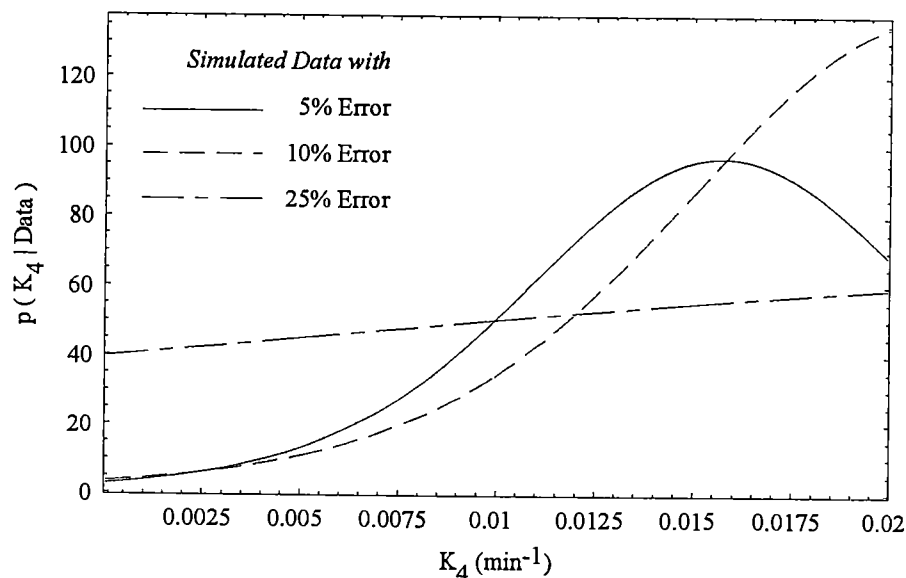


Figure 4.17. Normalized marginal posterior density for the human cerebral gray matter glucose metabolism rate K_4 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise. The means (min⁻¹) are: 5% noise = 0.01378 ± 0.00407 , 10% noise = 0.0148 ± 0.00414 and 25% noise = 0.01067 ± 0.00572 .

Table 4.6. Posterior modes, means and standard deviations for the human cerebral gray matter glucose metabolism rates calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.

	Parameter	5% Noise	10% Noise	25% Noise
Posterior Mean (l/min)	K_1	0.1137 ± 0.00618	0.1094 ± 0.0226	0.1368 ± 0.0322
	K_2	0.198 ± 0.0358	0.2192 ± 0.117	0.3914 ± 0.193
	K_3	0.1035 ± 0.0187	0.1205 ± 0.0393	0.1402 ± 0.08
	K_4	0.01378 ± 0.00306	0.0148 ± 0.00548	0.01067 ± 0.00552
Posterior Mode (l/min)	K_1	0.1098	0.1048	0.1179
	K_2	0.1749	0.1751	0.1674
	K_3	0.09725	0.1049	0.08185
	K_4	0.01571	None	None

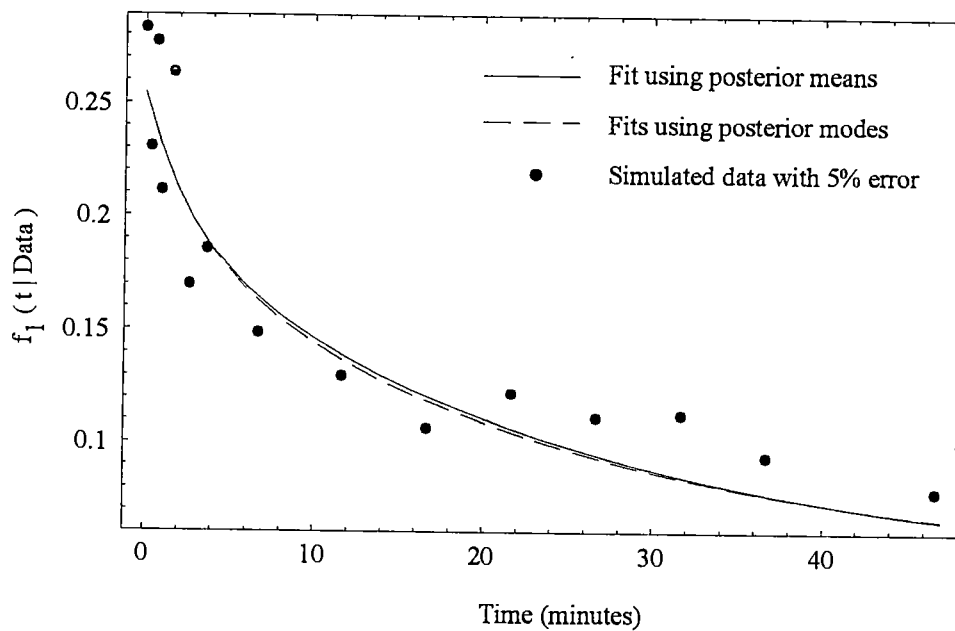


Figure 4.18. Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 5% noise and uniform priors fitted to the simulated human cerebral plasma FDG data.

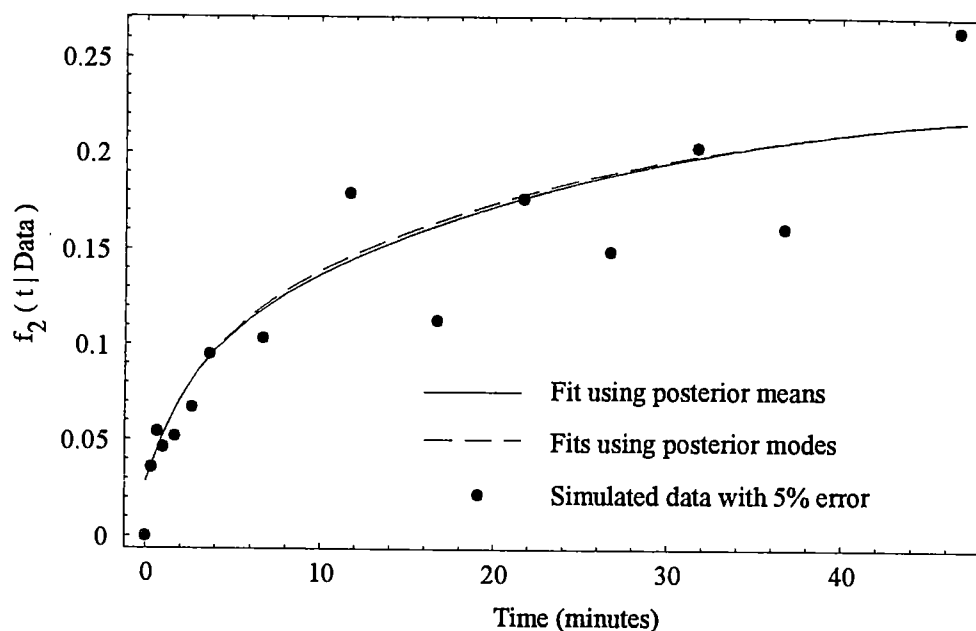


Figure 4.19. Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 5% noise and uniform priors fitted to the simulated human cerebral gray matter tissue FDG and FDG-6-P data.

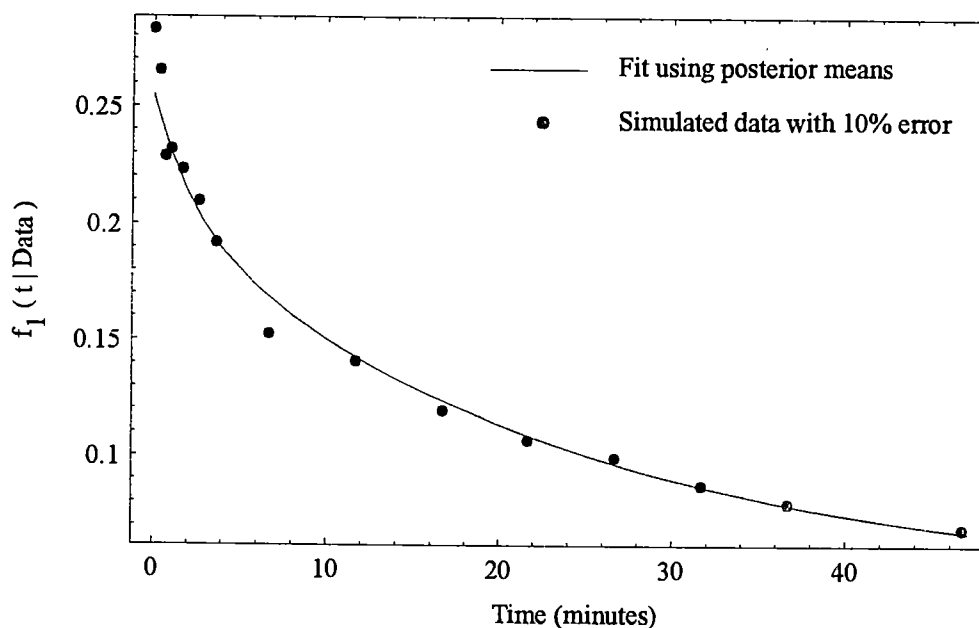


Figure 4.20. Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 10% noise and uniform priors fitted to the simulated human cerebral plasma FDG data.

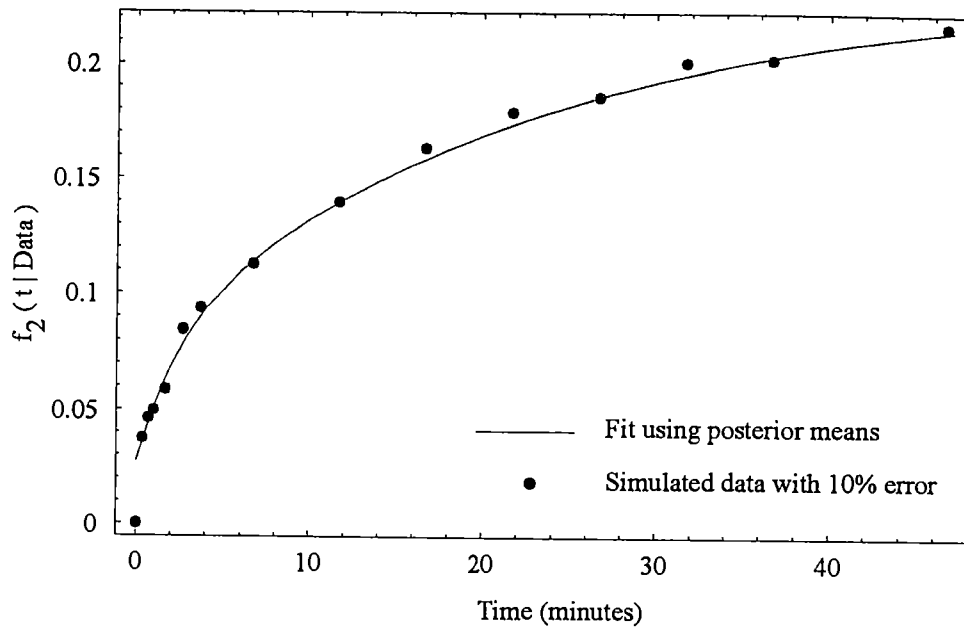


Figure 4.21. Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 10% noise and uniform priors fitted to the simulated human cerebral gray matter tissue FDG and FDG-6-P data.

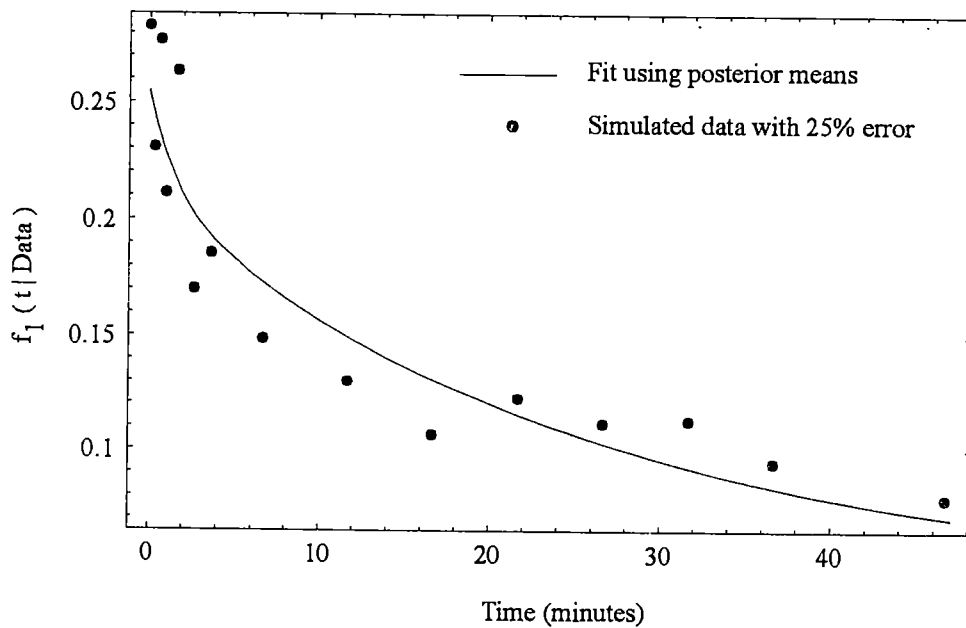


Figure 4.22. Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 25% noise and uniform priors fitted to the simulated human cerebral plasma FDG data.

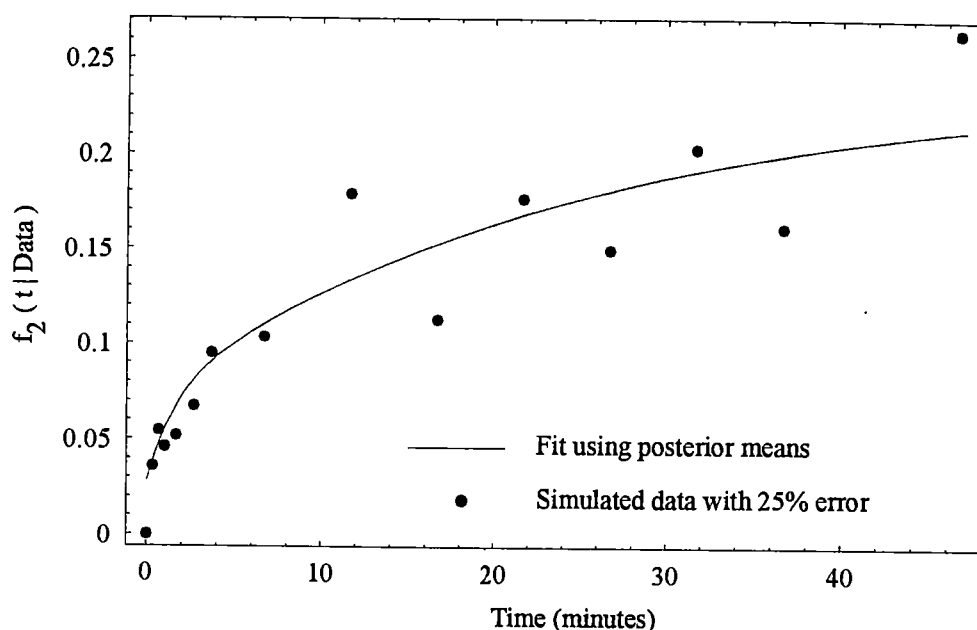


Figure 4.23. Solution of the differential equations for the parameter estimates calculated with simulated human cerebral FDG PET data set with 25% noise and uniform priors fitted to the simulated human cerebral gray matter tissue FDG and FDG-6-P data.

Finally, the 90 and 95 percent HPD contours and the published average rate constants are plotted in Figs. 4.24 through 4.29. The corresponding contours z values are listed in Table 4.7. The results were good, and showed that as the amount of noise increases, the contour gets larger and can become open-ended. In conclusion, the Bayesian technique worked for the simulated data, which assumed the specified model (see Fig. 4.2). Furthermore, the clinical data, which did not work, may not follow the specified model or it may have unknown errors. Therefore, additional analysis into the model and clinical data are needed to determine the validity of the specified model.

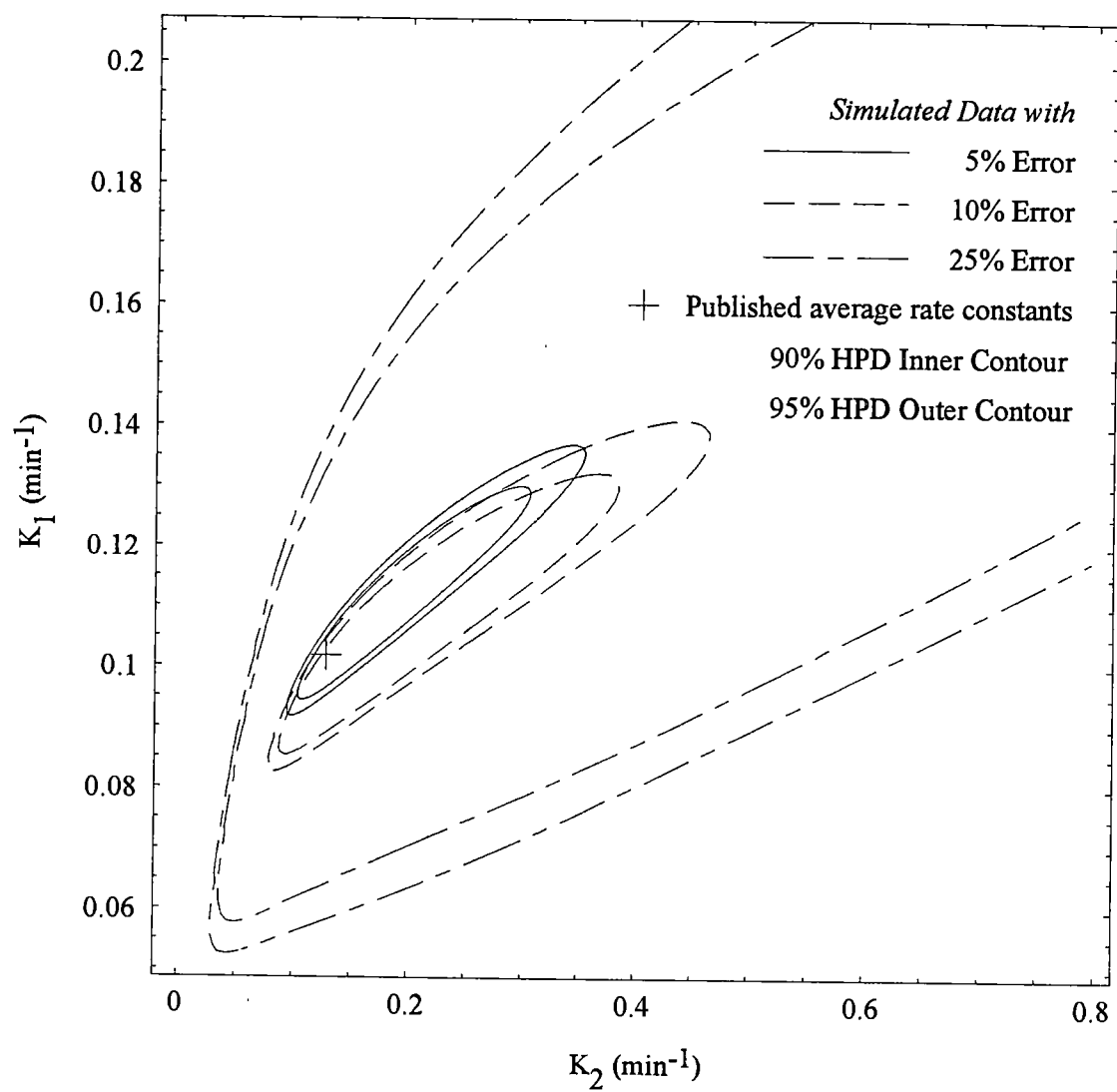


Figure 4.24. Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_2 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.

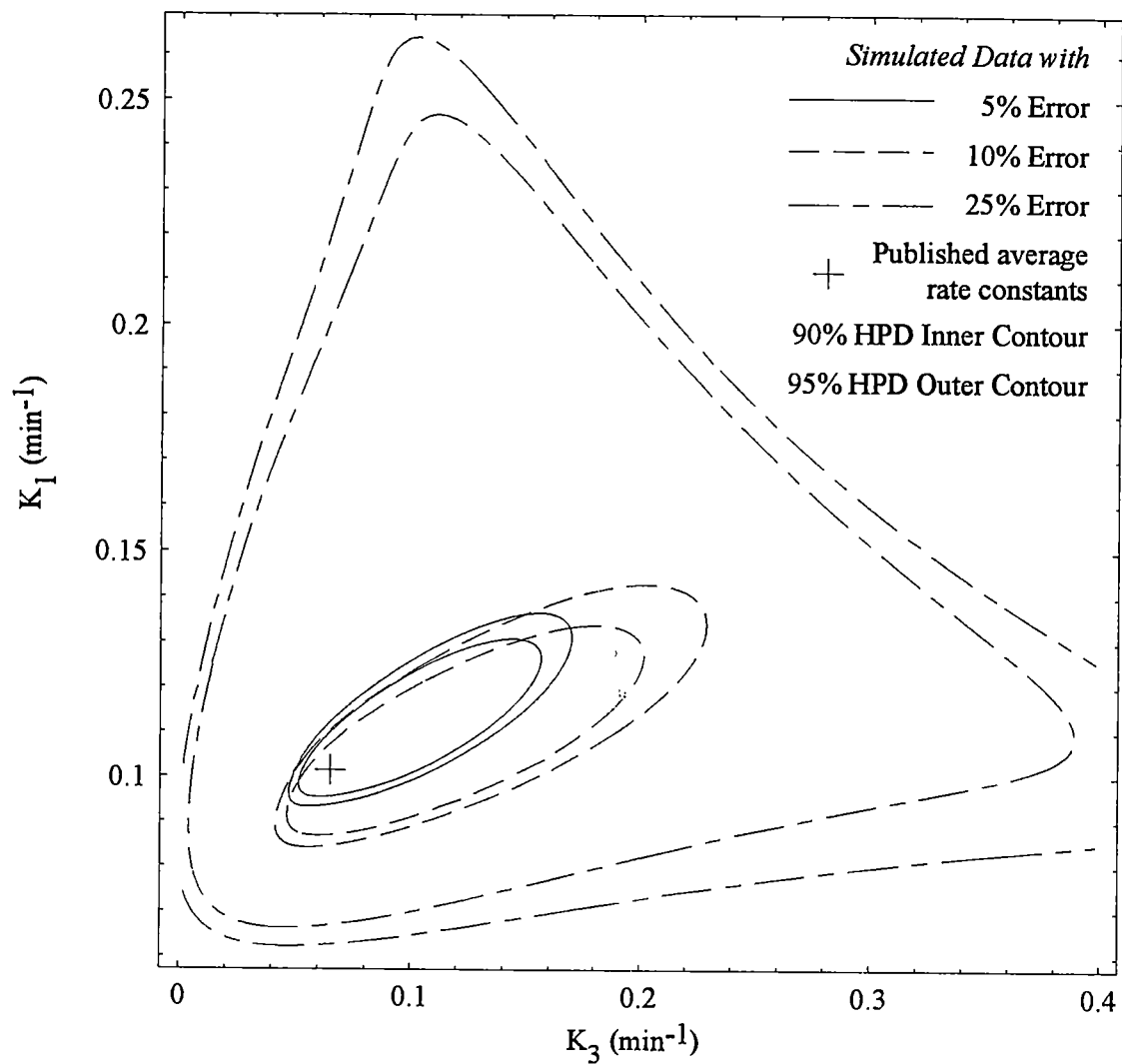


Figure 4.25. Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_3 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.

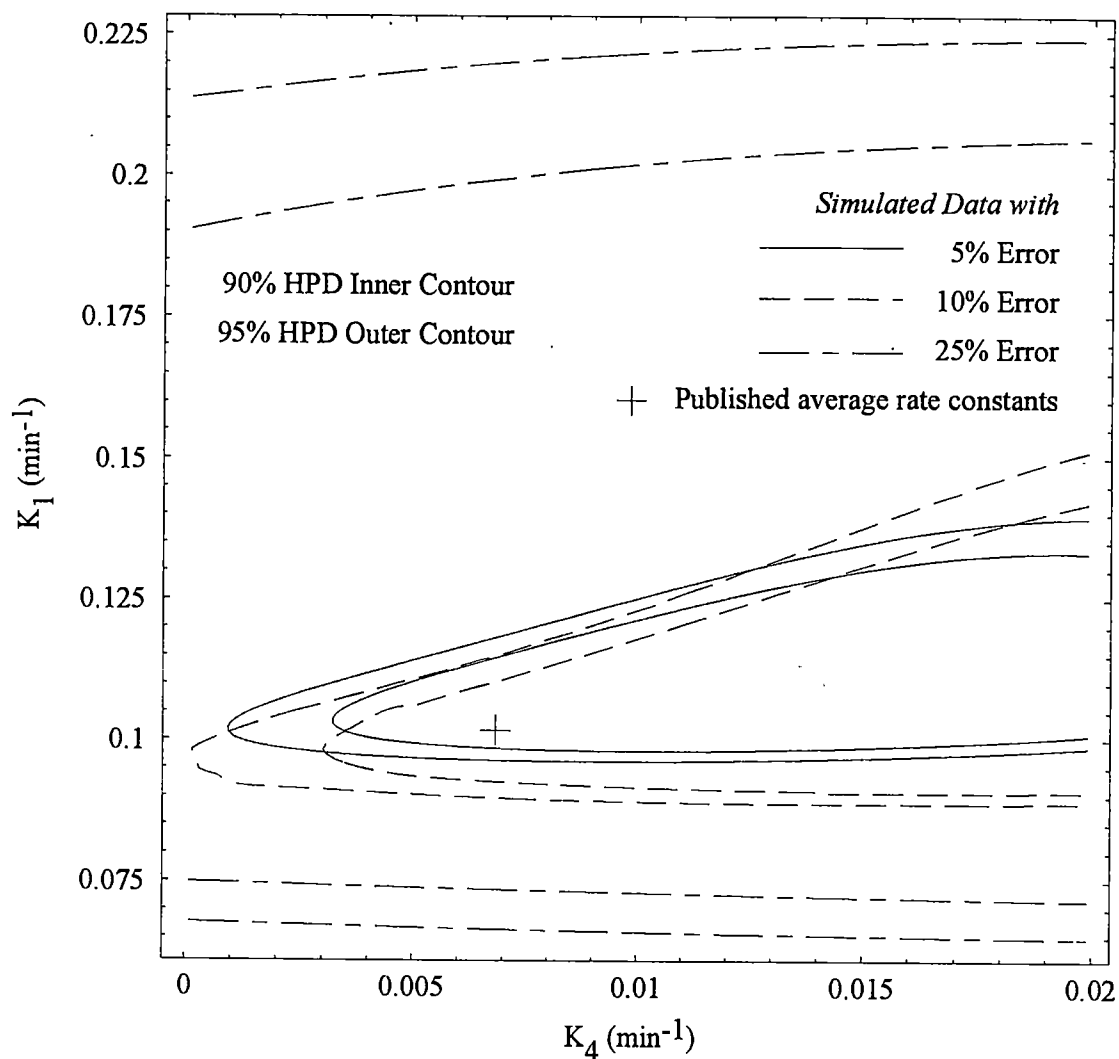


Figure 4.26. Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_1 and K_4 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.

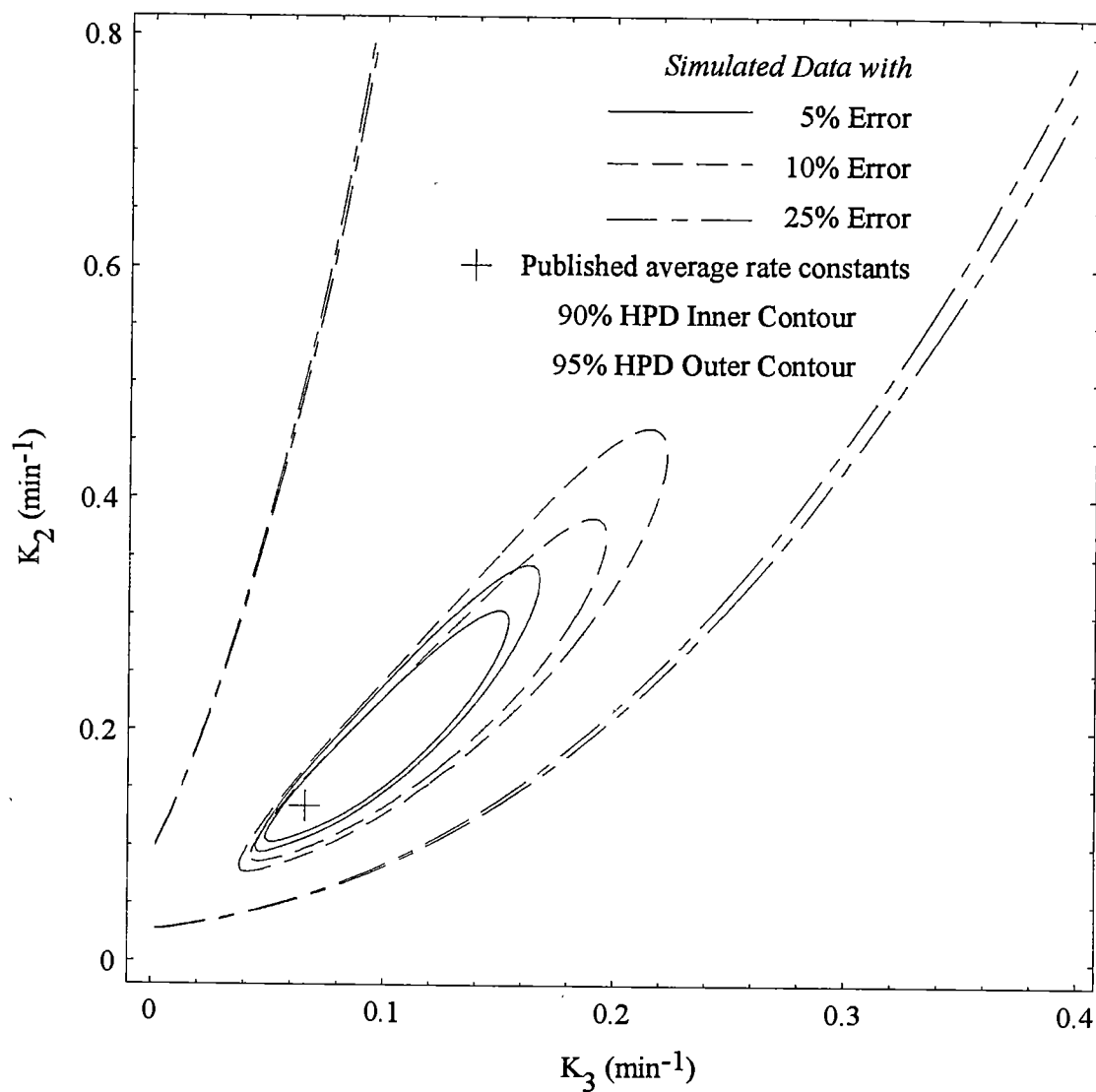


Figure 4.27. Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_2 and K_3 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.

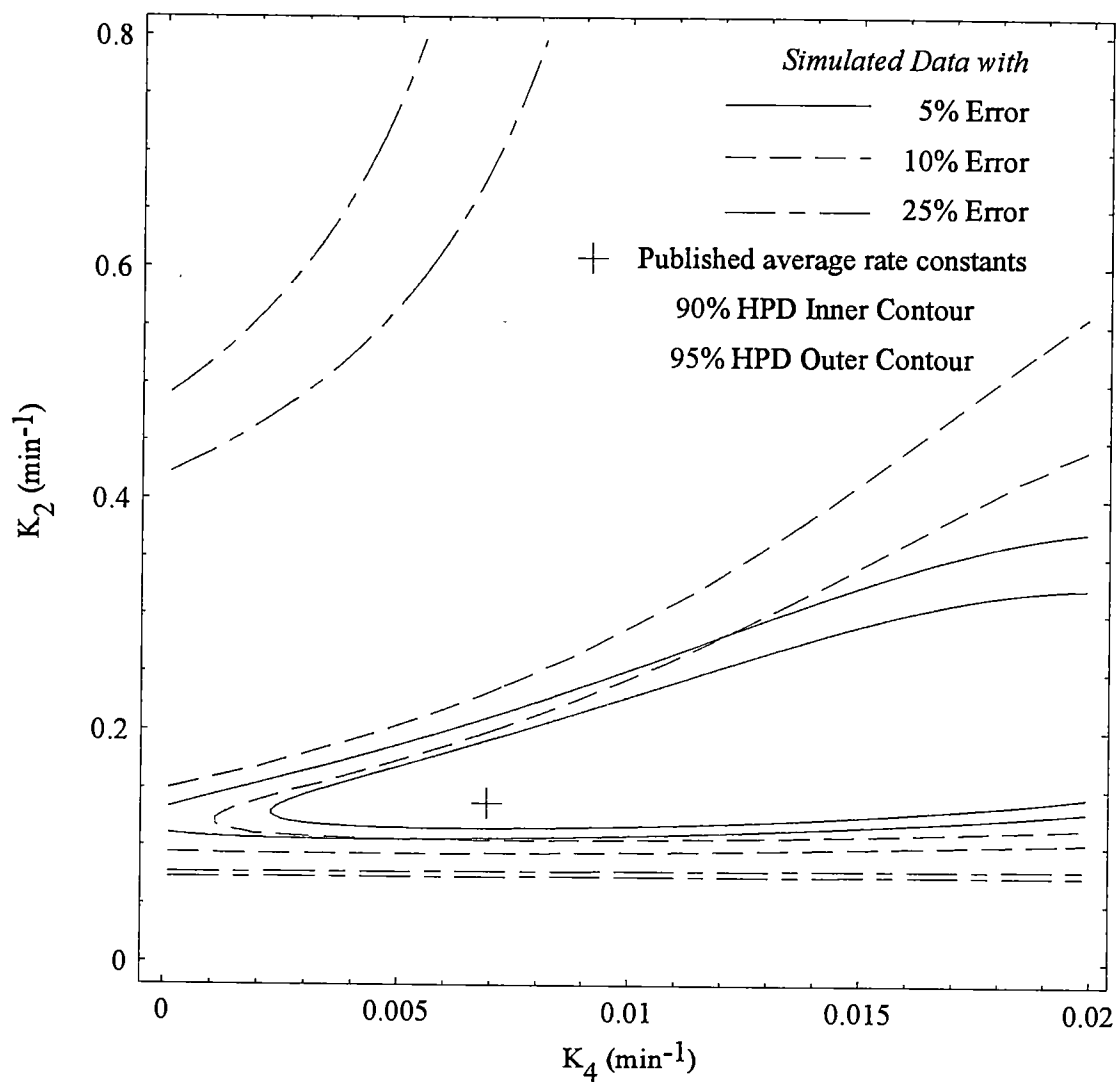


Figure 4.28. Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_2 and K_4 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.

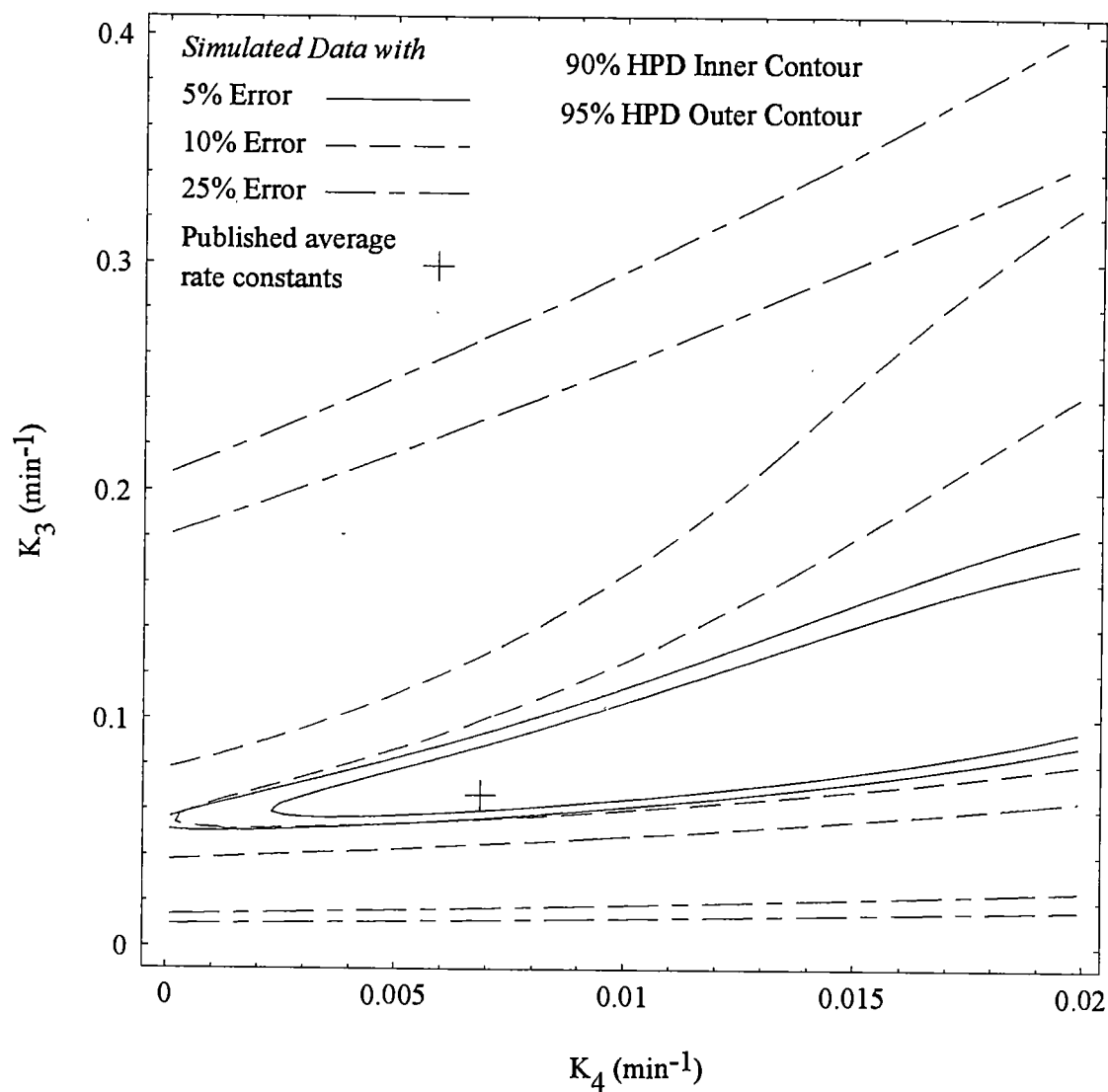


Figure 4.29. Ninety and ninety-five percent HPD contours for the human cerebral gray matter glucose metabolism rates K_3 and K_4 calculated with uniform priors and simulated FDG PET data sets with 5, 10 and 25% noise.

Table 4.7. Ninety and ninety-five percent HPD contour z values for various combinations of the human cerebral gray matter glucose metabolism rates calculated with uniform priors and simulated FDG PET data sets 5, 10 and 25% noise.

Parameter	z values (90% HPD, 95% HPD)		
Combinations	5% Noise	10% Noise	25% Noise
K_1 and K_2	(26, 85)	(11, 33)	(2.5, 4.4)
K_1 and K_3	(40, 99)	(16, 42)	(4.3, 7.3)
K_1 and K_4	(268, 547)	(200, 393)	(6.7, 123)
K_2 and K_2	(11, 28)	(3.9, 11)	(1.15, 1.89)
K_2 and K_3	(47, 108)	(29, 68)	(40, 46)
K_3 and K_4	(146, 296)	(19, 138)	(41, 65)

CHAPTER 5

EXCHANGE OF HUMAN SERUM ALBUMIN

The last biokinetic model examined is the exchange of ^{131}I labeled human serum albumin (iodoalbumin) injected into the ascitic fluid of the peritoneal or abdominal cavity. Albumin is the most abundant plasma protein and performs many functions such as buffer, clotting factor, and bind with other plasma constituents (Vander et. al., 1990). Discussions about the mathematical model and the data are found in sections 5.1 and 5.2. This is followed by the analyses using different compartmental observations: all compartments, ascitic fluid only, plasma only, and both ascitic fluid and plasma. Finally, the results of the analyses are presented in section 5.3 and reviewed in section 5.4.

5.1 Mathematical Model

The kinetics of iodoalbumin administered intraperitoneally can be described by a three-compartment catenary system similar to the one used to model cerebral glucose metabolism in Chapter 4 (Berson and Yalow, 1953). Shown in Fig. 5.1, the three-compartment catenary system is composed of the ascitic fluid, the blood plasma and the extravascular spaces other than the peritoneal cavity. The movements of the serum albumin from the plasma to the ascitic fluid and to the extravascular spaces are denoted by parameters K_2 and K_3 , respectively. The return flows to the plasma are denoted by parameters K_1 and K_4 .

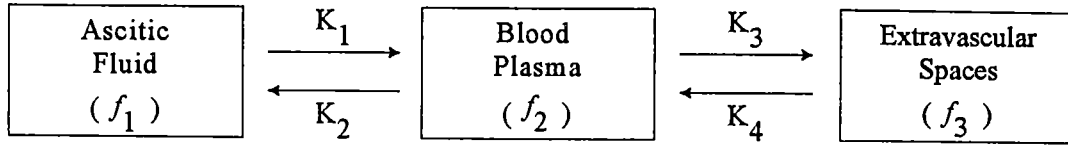


Figure 5.1. Three-compartment catenary system describing the exchange of ^{131}I labeled human serum albumin administered intraperitoneally.

Since both the albumin and glucose models are described by a three-compartment catenary system, the differential equations describing them are the same (see Eqn. (4.1)). Assuming an initial ascitic fluid iodoalbumin concentration of x_o and zero for the other compartments, the solution of the differential equations for the albumin model is:

$$\begin{aligned}
 f_1(\bar{K}, t) &= \frac{K_2 K_4 x_o}{m_2} + \frac{K_1 (K_1 + K_2 + \lambda_3) x_o}{\lambda_2 m_3} e^{\lambda_2 t} - \frac{K_1 (K_2 K_4 + K_1 \lambda_3) x_o}{\lambda_3 m_3 (K_1 + \lambda_3)} e^{\lambda_3 t} \\
 f_2(\bar{K}, t) &= \frac{K_1 K_4 x_o}{m_2} + \frac{K_1 (K_4 + \lambda_2) x_o}{\lambda_2 m_3} e^{\lambda_2 t} - \frac{K_1 (K_4 + \lambda_3) x_o}{\lambda_3 m_3} e^{\lambda_3 t} \\
 f_3(\bar{K}, t) &= \frac{K_1 K_3 x_o}{m_2} + \frac{K_1 K_3 \lambda_3 x_o}{m_2 m_3} e^{\lambda_2 t} - \frac{K_1 K_3 x_o}{\lambda_3 m_3} e^{\lambda_3 t}
 \end{aligned} \quad , \quad (5.1)$$

where $\bar{K} = K_1, K_2, K_3, K_4$, and parameters m_1, m_2, m_3, λ_2 and λ_3 were defined earlier in Eqn. (4.2).

5.2 Iodoalbumin Biokinetic Data

The biokinetic data used came from the plot of relative specific activities of iodoalbumin as a function of time shown in Fig. 5.2. To make the analyses slightly easier, the biokinetic data used were taken every two days and are listed in Table 5.1.

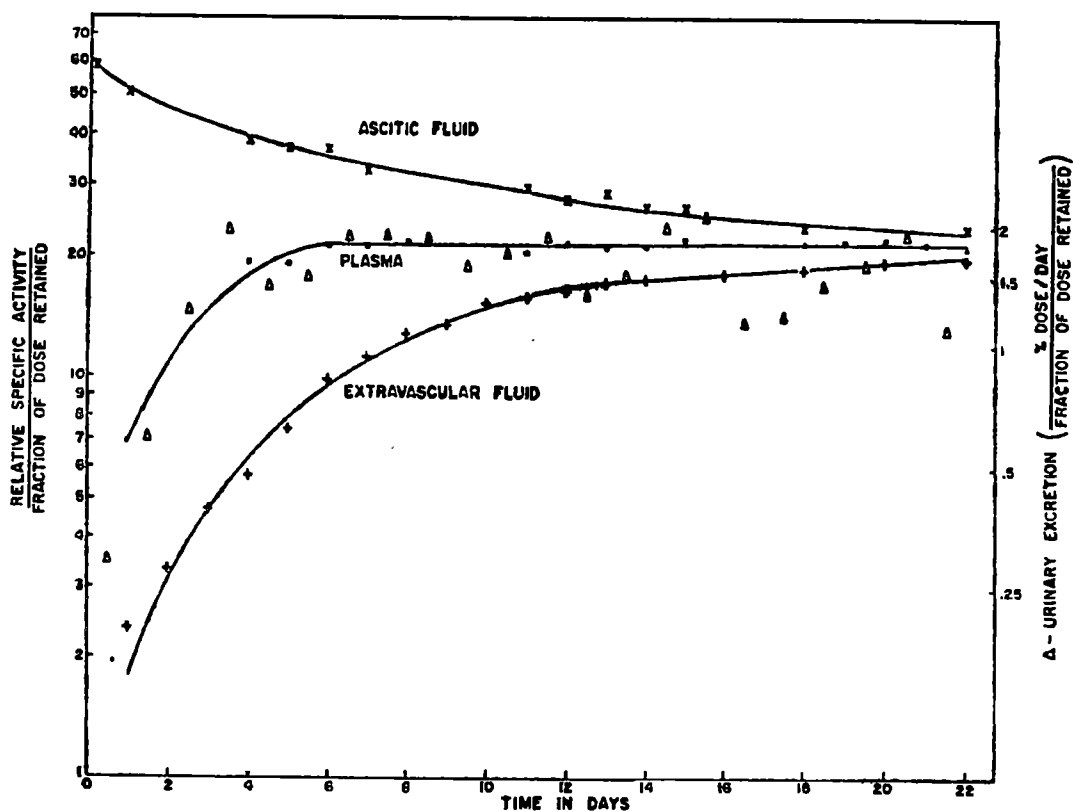


Figure 5.2. Relative specific activities of ^{131}I albumin in ascitic fluid, plasma and extravascular fluid and urinary excretion of radioactivity as a function of time following intraperitoneal injection of ^{131}I albumin. Source: Berson, S. A.; Yalow, R. S. "The Distribution of I^{131} Labeled Human Serum Albumin Introduced into Ascitic Fluid: Analysis of the Kinetics of a Three Compartment Catenary Transfer System in Man and Speculations on Possible Sites of Degradation." *Journal of Clinical Investigation* 33: 377-387, 1954.

Table 5.1. Activities of ^{131}I labeled human serum albumin in the ascitic fluid, the plasma and the extravascular spaces administered intraperitoneally.^a

Time (Days)	Ascitic Fluid (Relative Specific Activity / Fraction of Dose Retained)	Plasma	Extravascular Space ^b
0	60	0	0
2	45	10.2	3.2
4	40	18	6
6	30	21	10
8	32	22	13
10	30	21	15
12	28	21	16
14	26	21	18
16	24	22	19
18	23	23	19.5
20	22	22	20

^a Source: Berson, S. A.; Yalow, R. S. "The Distribution of I^{131} Labeled Human Serum Albumin Introduced into Ascitic Fluid: Analysis of the Kinetics of a Three Compartment Catenary Transfer System in Man and Speculations on Possible Sites of Degradation." *Journal of Clinical Investigation* 33: 377-387, 1954.

^b Exclusive of the peritoneal cavity.

5.3 Bayesian Analysis

As stated earlier, estimation precision is sensitive to the data. Since both the ascitic fluid and the plasma iodoalbumin concentrations can be easily assayed, the analysis is divided into four cases: using data for all three compartments, for ascitic fluid only, for plasma only, and for both ascitic fluid and plasma. Because no prior information about the exchange of iodoalbumin was available, uniform priors were assumed.

5.3.1 All data are used

The first analysis deals with the use of data from all three compartments. The posterior distribution for the parameters with uniform priors can be written as:

$$p(K_1, K_2, K_3, K_4 | data) \propto \begin{vmatrix} S_{11}(\theta) & S_{12}(\theta) & S_{13}(\theta) \\ S_{21}(\theta) & S_{22}(\theta) & S_{23}(\theta) \\ S_{31}(\theta) & S_{32}(\theta) & S_{33}(\theta) \end{vmatrix}^{-5}, \quad (5.2)$$

where

$$S_{11}(\theta) = \sum_{u=1}^{10} [\gamma_{u1} - f_1(K_1, K_2, K_3, K_4, t_u)]^2$$

$$S_{22}(\theta) = \sum_{u=1}^{10} [\gamma_{u2} - f_2(K_1, K_2, K_3, K_4, t_u)]^2$$

$$S_{33}(\theta) = \sum_{u=1}^{10} [\gamma_{u3} - f_3(K_1, K_2, K_3, K_4, t_u)]^2$$

$$S_{12}(\theta) = S_{21}(\theta) = \sum_{u=1}^{10} [\gamma_{u1} - f_1(K_1, K_2, K_3, K_4, t_u)] \cdot [\gamma_{u2} - f_2(K_1, K_2, K_3, K_4, t_u)]$$

$$S_{13}(\theta) = S_{31}(\theta) = \sum_{u=1}^{10} [\gamma_{u1} - f_1(K_1, K_2, K_3, K_4, t_u)] \cdot [\gamma_{u3} - f_3(K_1, K_2, K_3, K_4, t_u)]$$

$$S_{23}(\theta) = S_{32}(\theta) = \sum_{u=1}^{10} [\gamma_{u2} - f_2(K_1, K_2, K_3, K_4, t_u)] \cdot [\gamma_{u3} - f_3(K_1, K_2, K_3, K_4, t_u)]$$

After some algebra, Eqn. (5.2) is simplified to:

$$p(K_1, K_2, K_3, K_4 | data) = \left(2 \cdot S_{12}S_{13}S_{23} + S_{11}S_{22}S_{33} - S_{13}^2S_{22} - S_{11}S_{23}^2 - S_{12}^2S_{33} \right)^{-5} \quad (5.3)$$

Based on the published rate constants listed in Table 5.2 (Berson and Yalow, 1954), integration limits of zero to one were chosen. The normalized marginal density for the parameters are plotted in Fig. 5.3 with the Bayesian estimates listed in Table 5.2. Although no bimodality was found, small “shoulders” were observed in the marginal posterior densities of K_1 and K_3 . The differences between the Bayesian and the Berson – Yalow estimates are likely due to the differences in the parameter estimation techniques.

Next, the solution of the differential equations was fitted to the iodoalbumin data using both the Bayesian and the Berson – Yalow parameter estimates. Plots of the fits are shown in Figs. 5.4 through 5.6. Interestingly, the fits using the Berson – Yalow estimates were poor. As for the ascitic fluid and the extravascular space data, all three parameter estimates provided adequate fits with the posterior means being the best.

Finally, the 90 and 95 percent HPD contours are plotted in Figs. 5.7 through 5.12 with the corresponding contour z values listed in Table 5.3. Aside from the open contours for the parameter combinations (K_1, K_4) and (K_2, K_4) , no awkward contour feature was observed. We will now examine the effects of using only data from one versus two compartments.

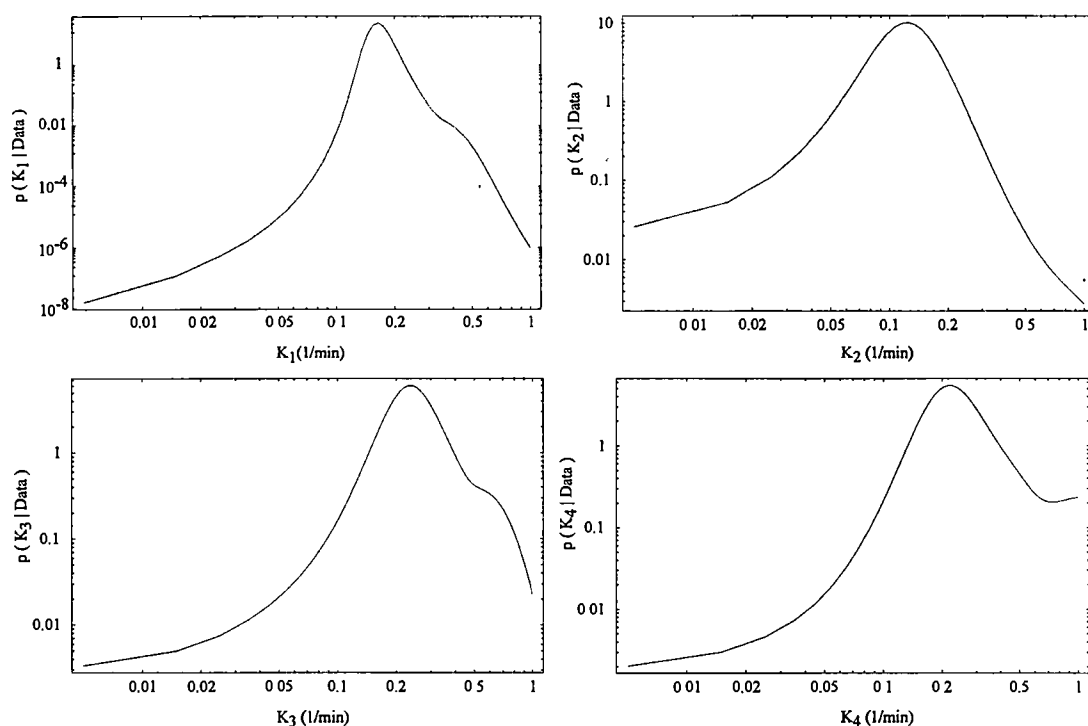


Figure. 5.3. Normalized marginal posterior densities for the human serum albumin exchange rates calculated with all iodoalbumin data and uniform priors. The means are (day^{-1}): $K_1 = 0.1705 \pm 0.0229$, $K_2 = 0.1428 \pm 0.0606$, $K_3 = 0.2908 \pm 0.13$, $K_4 = 0.3061 \pm 0.176$.

Table 5.2. Posterior modes, means and standard deviations for the human serum albumin exchange rates calculated with all iodoalbumin data and uniform priors.

Parameter	Berson and Yalow	Posterior Mean (1/day)	Posterior Mode
K_1	0.102	0.1705 ± 0.0229	0.165
K_2	0.178	0.1428 ± 0.0606	0.124
K_3	0.236	0.2908 ± 0.13	0.242
K_4	0.175	0.3061 ± 0.176	0.218

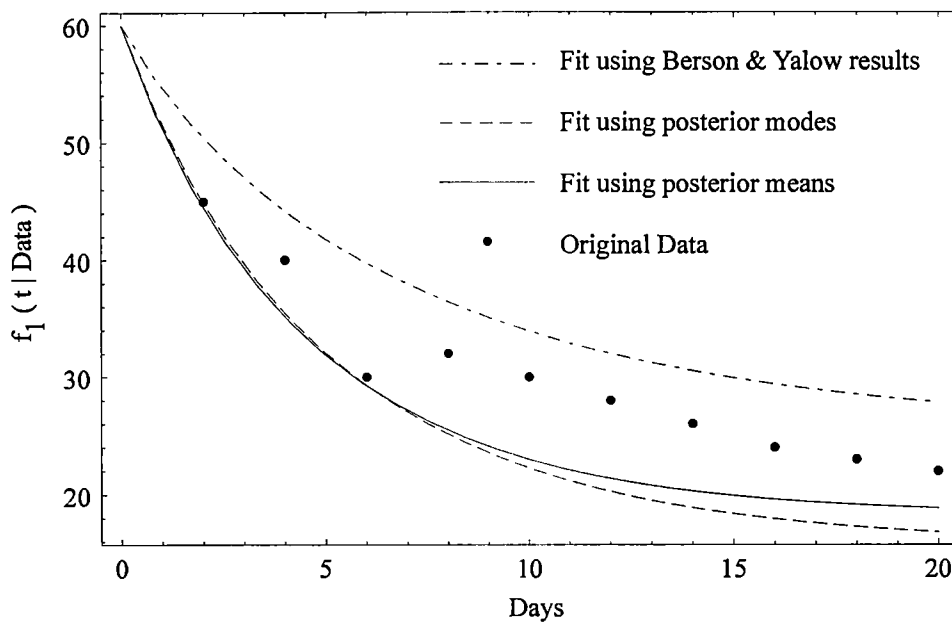


Figure 5.4. Solution of the differential equations for the parameter estimates calculated from all iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human ascitic fluid iodoalbumin data.

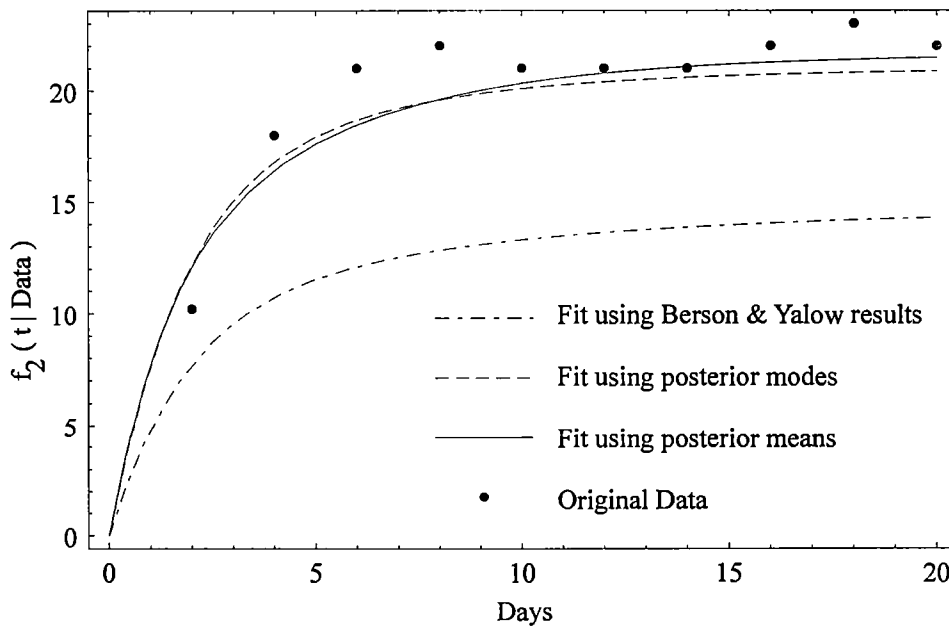


Figure 5.5. Solution of the differential equations for the parameter estimates calculated from all iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human plasma iodoalbumin data.

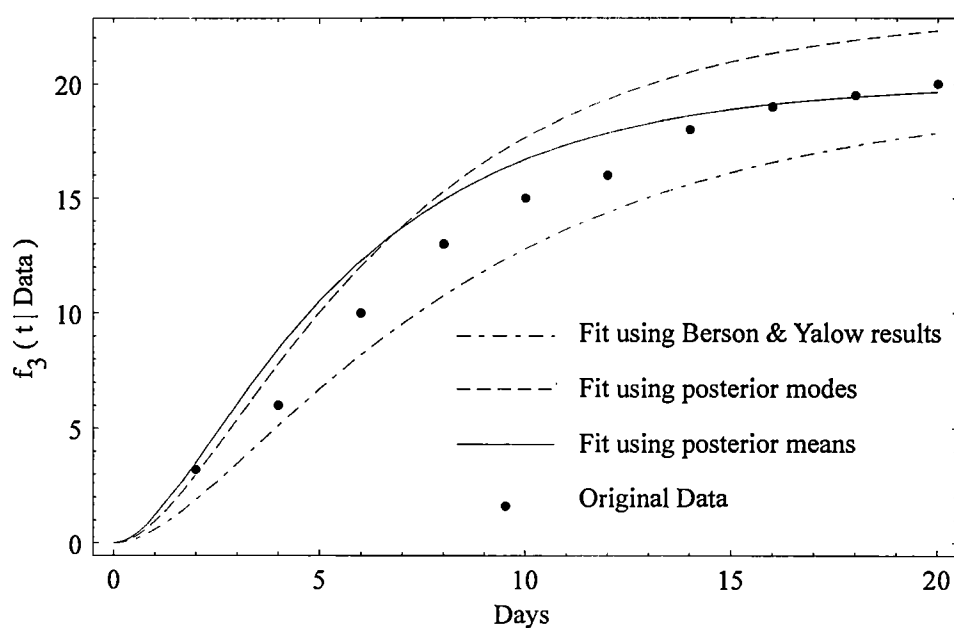


Figure 5.6. Solution of the differential equations for the parameter estimates calculated from all iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human extravascular spaces iodoalbumin data

Table 5.3. Ninety and ninety-five percent HPD contour z values for various combinations of the human serum albumin exchange rates calculated with all iodoalbumin data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
K_1 and K_2	15	6
K_1 and K_3	3.9	1.7
K_1 and K_4	3.2	1.8
K_2 and K_3	1.5	0.67
K_2 and K_4	1.2	0.7
K_3 and K_4	0.74	0.44

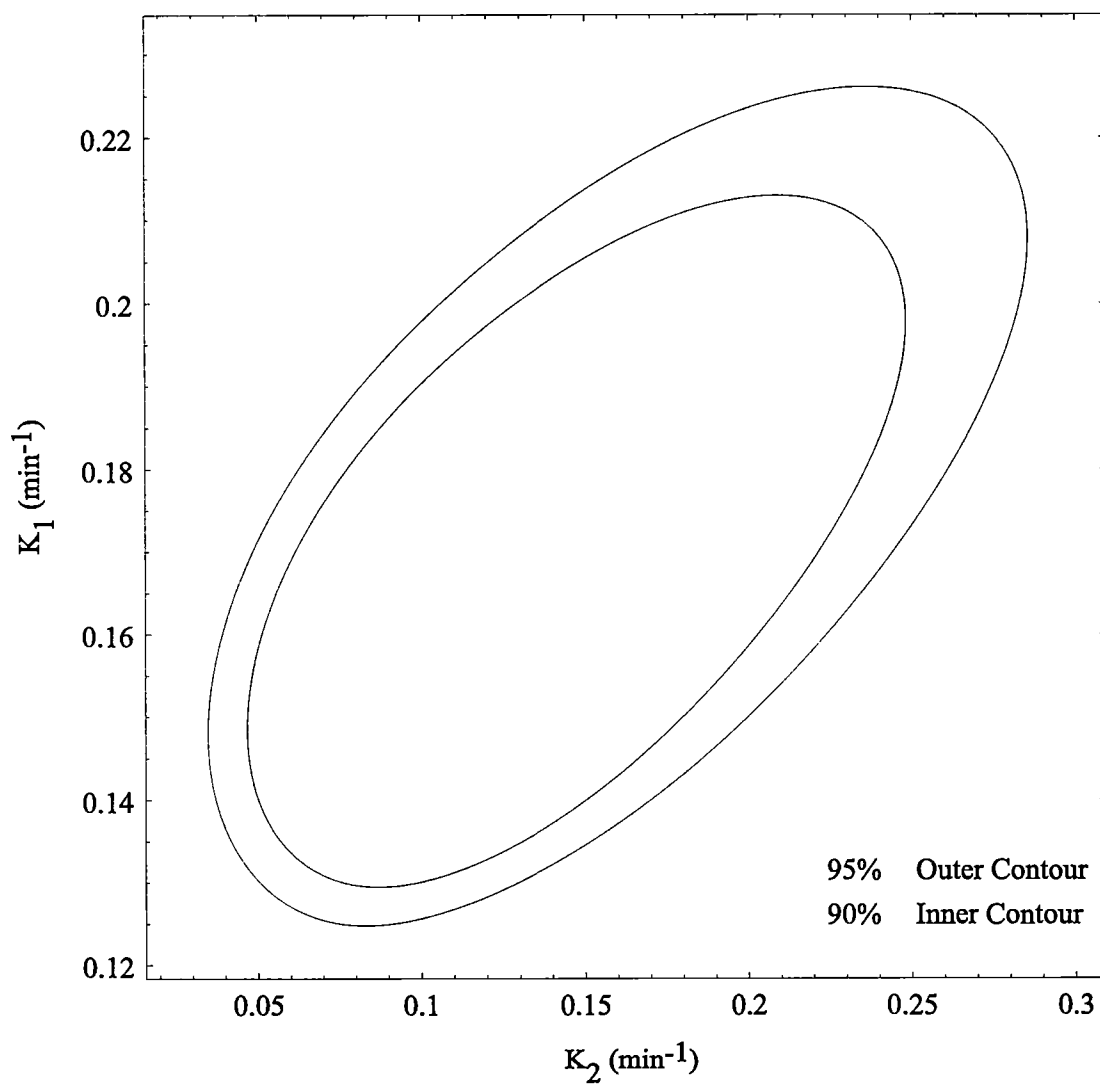


Figure 5.7. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with all iodoalbumin data and uniform priors.

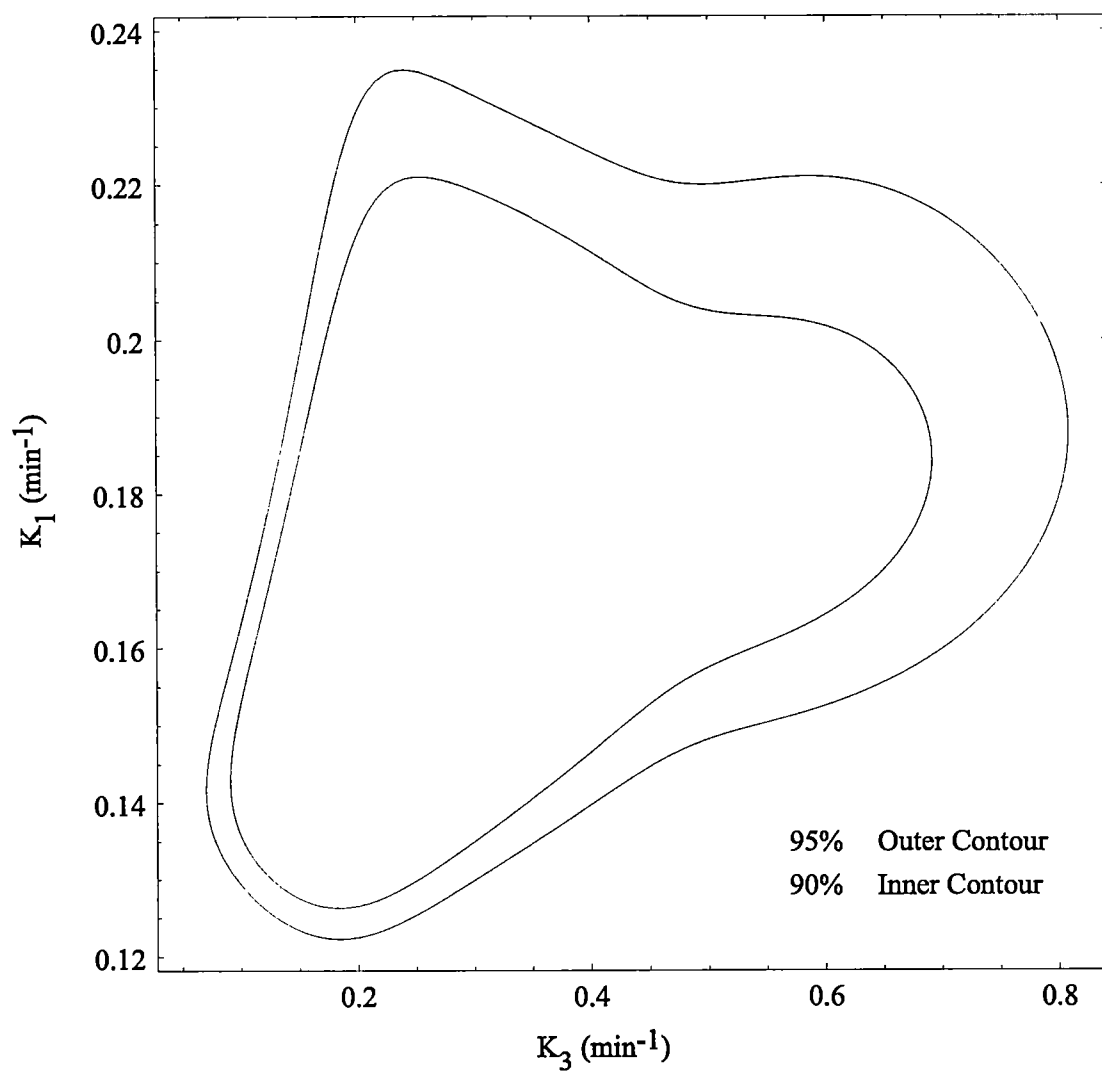


Figure 5.8. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with all iodoalbumin data and uniform priors.

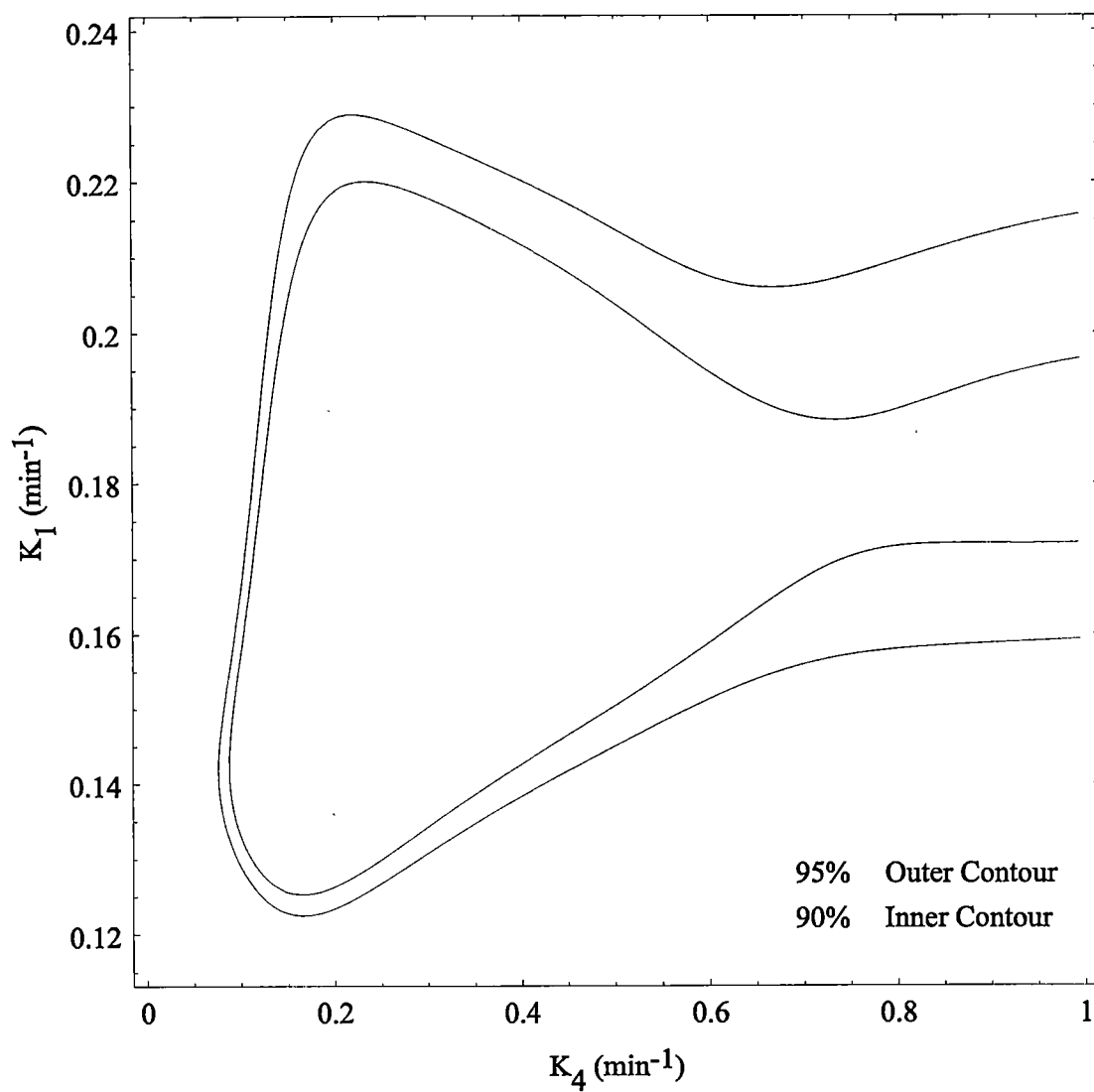


Figure 5.9. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with all iodoalbumin data and uniform priors.

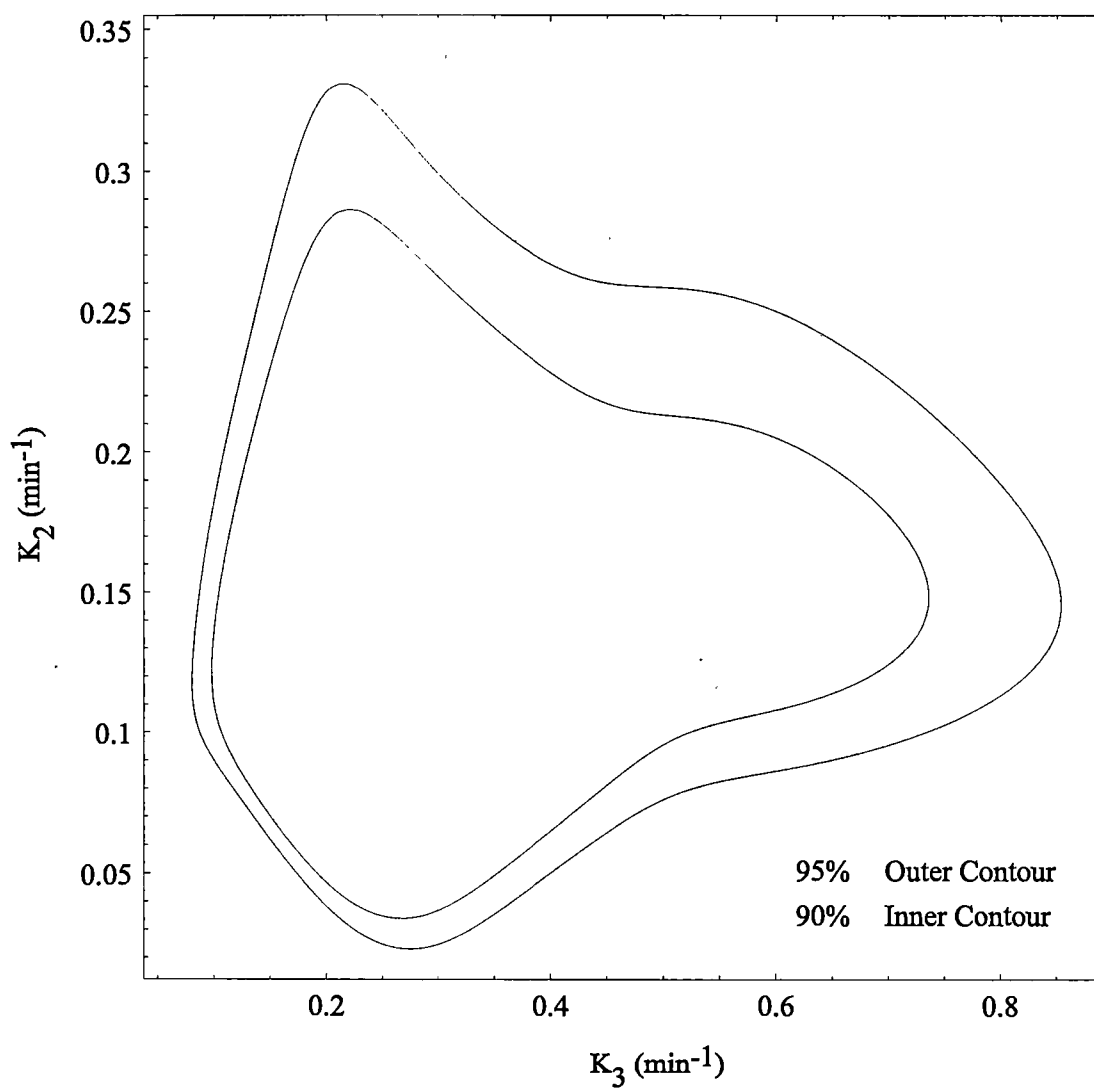


Figure 5.10. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with all iodoalbumin data and uniform priors.

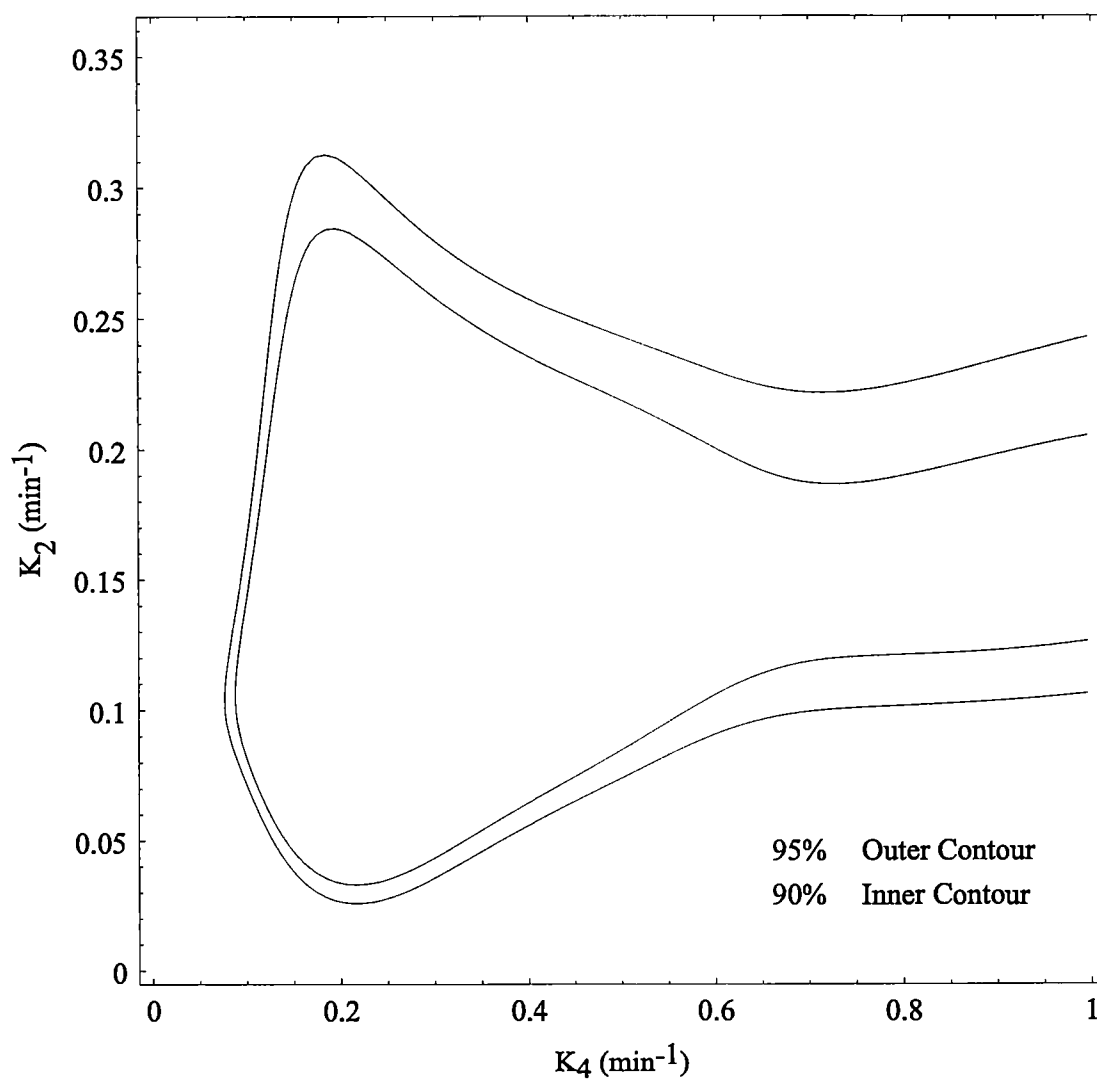


Figure 5.11. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with all iodoalbumin data and uniform priors.

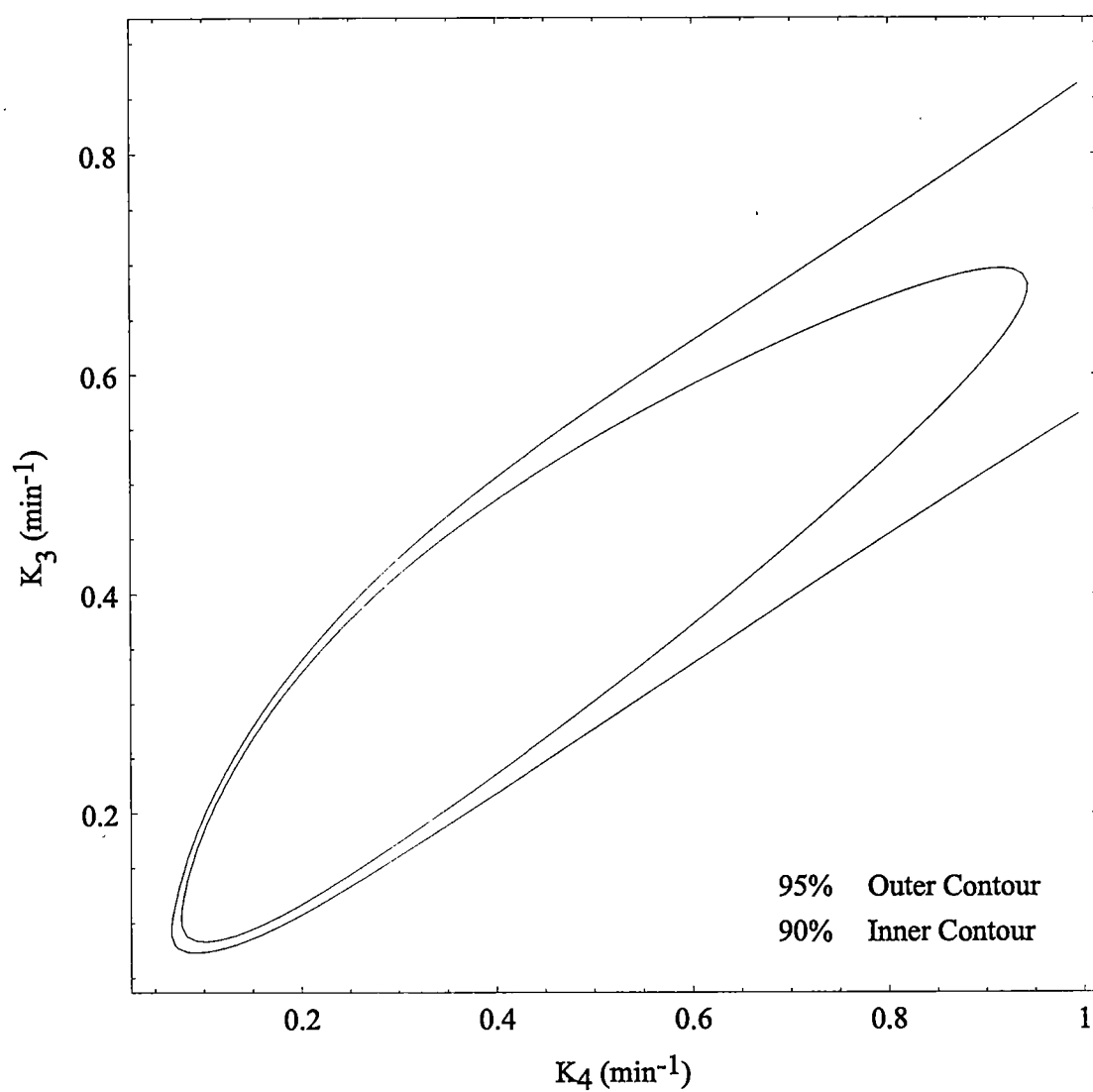


Figure 5.12. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with all iodoalbumin data and uniform priors.

5.3.2 Only the ascitic fluid data are used

This section examines the estimation results when only the ascitic fluid data are used. The resulting joint posterior density with uniform priors is:

$$p(K_1, K_2, K_3, K_4 | data) \propto S_{11}(\theta)^{-5}, \quad (5.4)$$

where $S_{11}(\theta)$ was defined earlier for Eqn. (5.2). Using the same integration limits as before, the normalized marginal posterior densities for the parameters are plotted in Fig. 5.13 with the Bayesian estimates listed in Table 5.4.

The resulting marginal posterior density plots were very interesting. A closer examination of parameter K_3 's "inverted bell curve" revealed that the marginal density is decreasing after reaching its local mode around $K_3 = 0.9$. The large probability density values at $K_2 = K_4 = 1$ could be reduced by increase the upper integration limit. However, it will widen the densities and increase the posterior means to unrealistic values.

Next, the solution of the differential equations was fitted to the data using the parameter estimates. Shown in Figs. 5.14 through 5.16, none of the estimates provided reasonable fits to the data for all three compartments. The Berson – Yalow estimates were judged to offer the best fits for the ascitic fluid and the extravascular spaces data. Finally, the 90 and 95 percent HPD contours z values for various parameter combinations are listed in Table 5.5. The corresponding HPD contour are plotted in Figs. 5.17 through 5.22. The results were poor. All of the contours are open and are significantly larger than the contours calculated using all iodoalbumin data

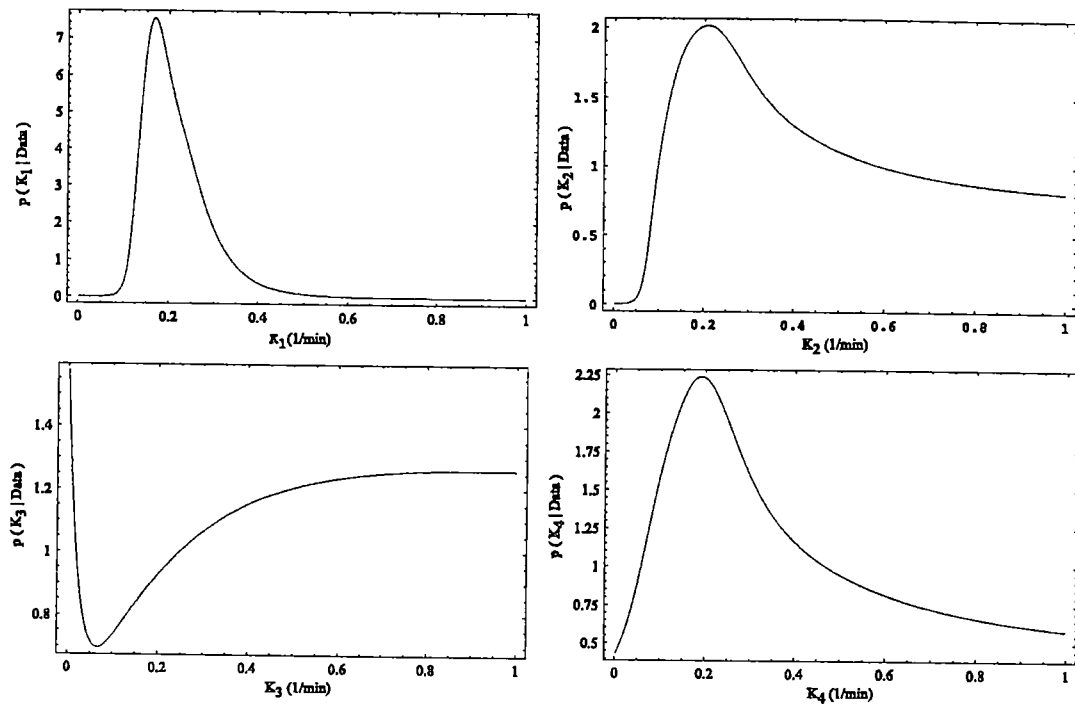


Figure 5.13. Normalized marginal posterior density for the human serum albumin exchange rates calculated with the ascitic fluid iodoalbumin data and uniform priors. The means are (day^{-1}): $K_1 = 0.2146 \pm 0.0724$, $K_2 = 0.4587 \pm 0.272$, $K_3 = 0.5359 \pm 0.297$, $K_4 = 0.3918 \pm 0.271$.

Table 5.4. Posterior modes, means and standard deviations for the human serum albumin exchange rates calculated with the ascitic fluid iodoalbumin data and uniform priors.

Parameters	Posterior Mean	Posterior Mode
	(1/day)	
K_1	0.2146 ± 0.0724	0.168
K_2	0.4587 ± 0.272	0.208
K_3	0.5359 ± 0.297	0.898
K_4	0.3918 ± 0.271	0.188

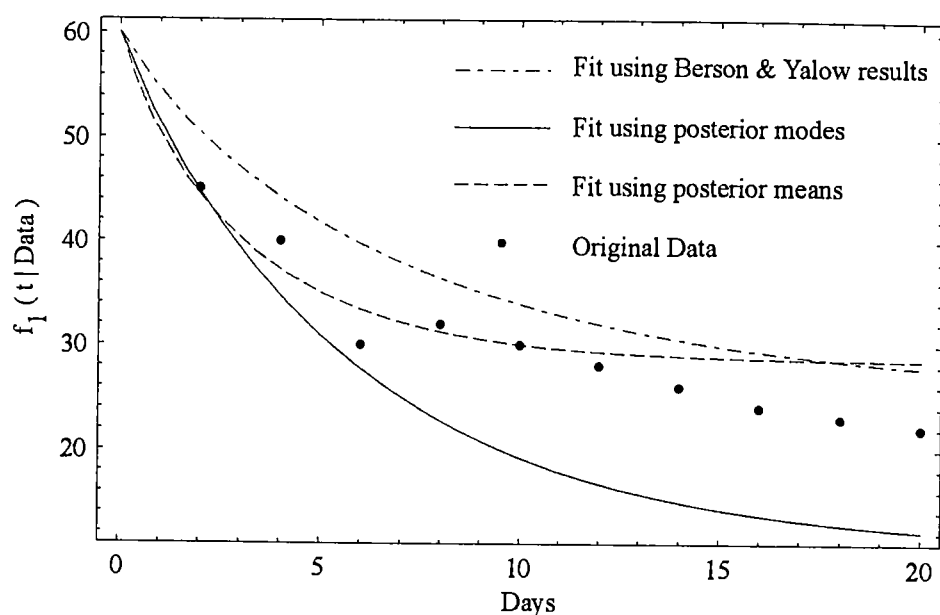


Figure 5.14. Solution of the differential equations for the parameter estimates calculated from the ascitic fluid iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human ascitic fluid iodoalbumin data.

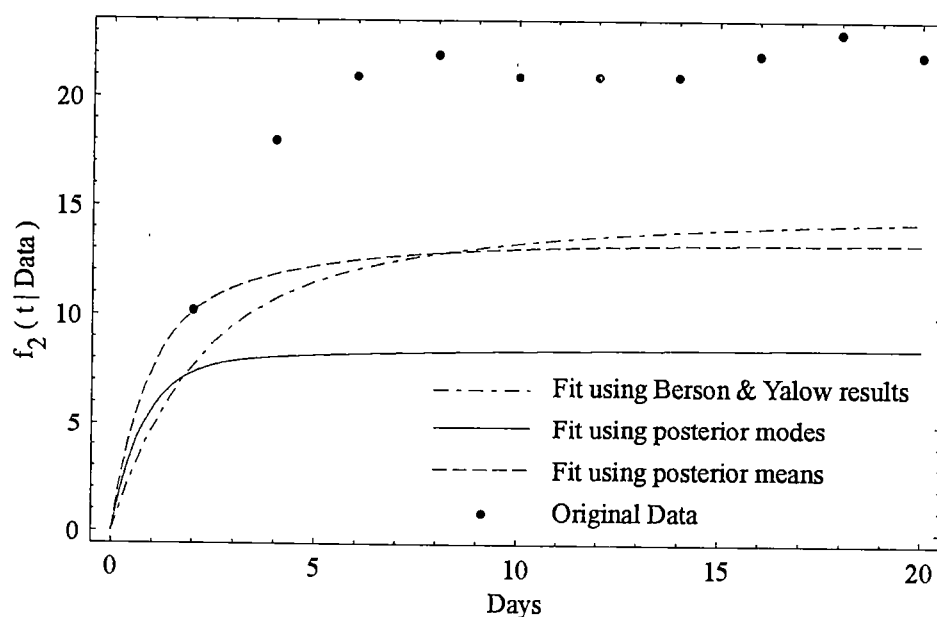


Figure 5.15. Solution of the differential equations for the parameter estimates calculated from the ascitic fluid iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human plasma iodoalbumin data.

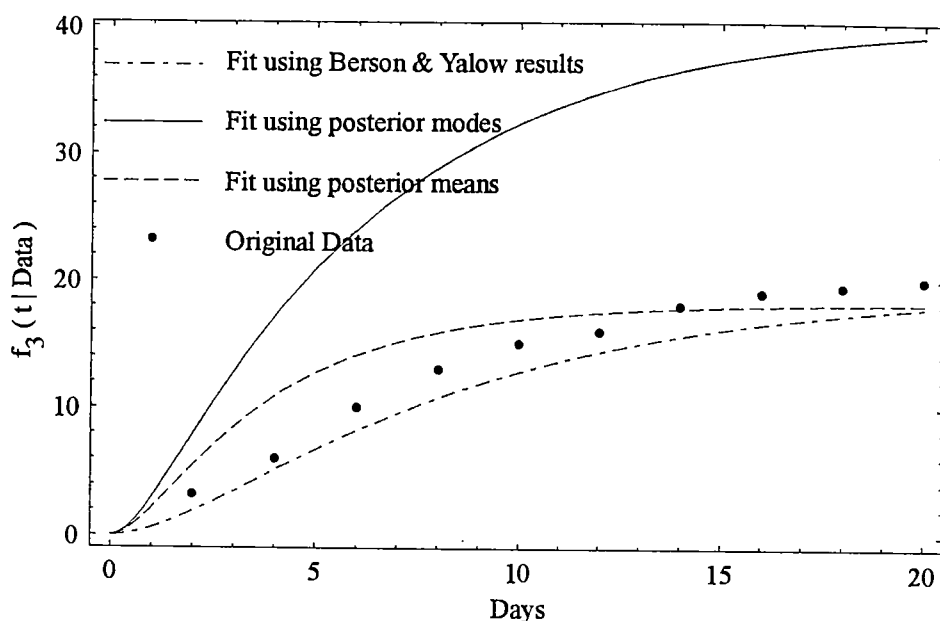


Figure 5.16. Solution of the differential equations for the parameter estimates calculated from the ascitic fluid iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human extravascular space iodoalbumin data.

Table 5.5. Ninety and ninety-five percent HPD contour z values for various combinations of the human serum albumin exchange rates calculated with the ascitic fluid iodoalbumin data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
K_1 and K_2	1.9	0.9
K_1 and K_3	1.5	0.7
K_1 and K_4	1.4	0.6
K_2 and K_3	0.9	0.6
K_2 and K_4	0.8	0.4
K_3 and K_4	0.62	0.51

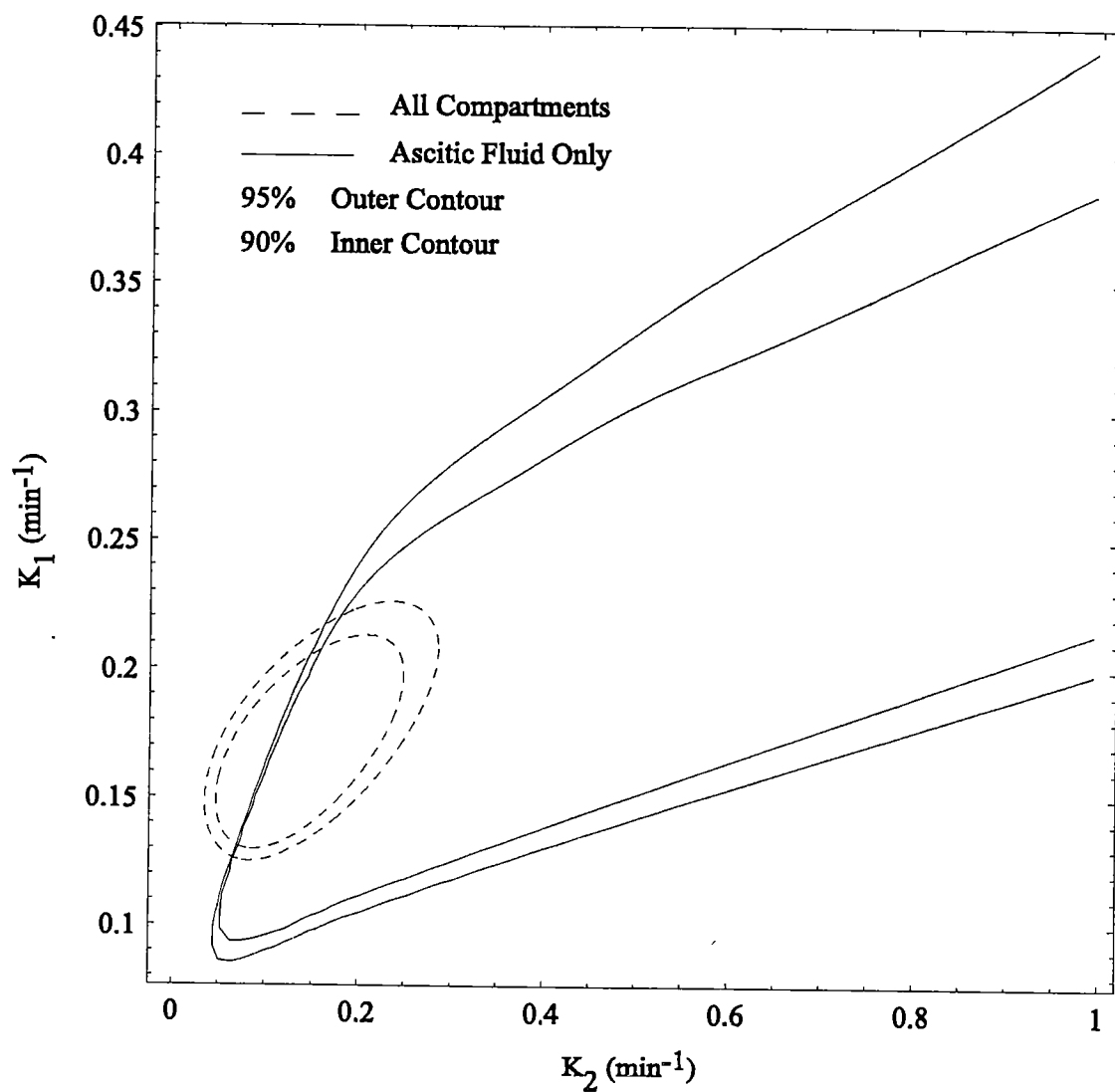


Figure 5.17. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with the ascitic fluid iodoalbumin data and uniform priors.

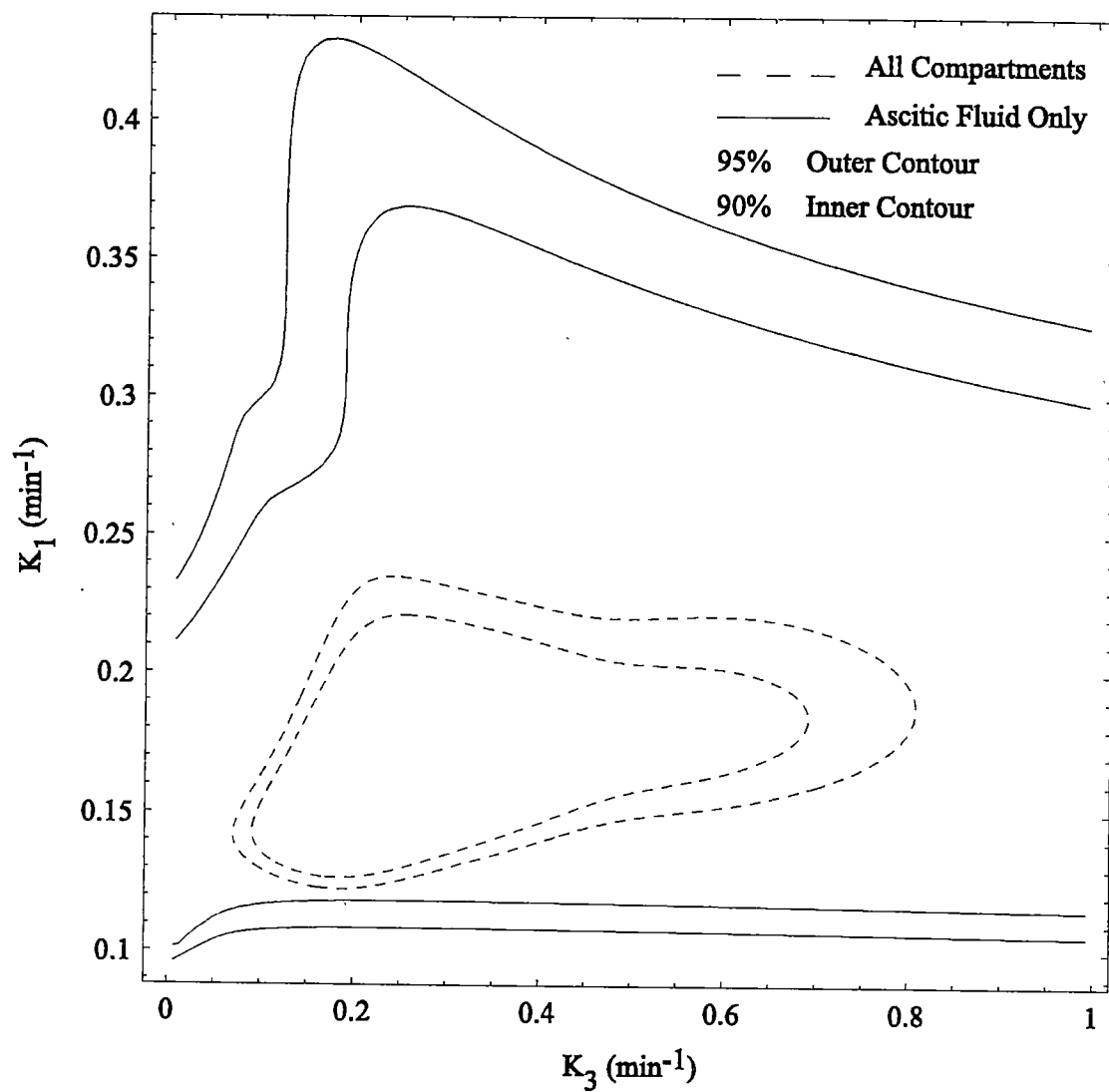


Figure 5.18. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with the ascitic fluid iodoalbumin data and uniform priors.

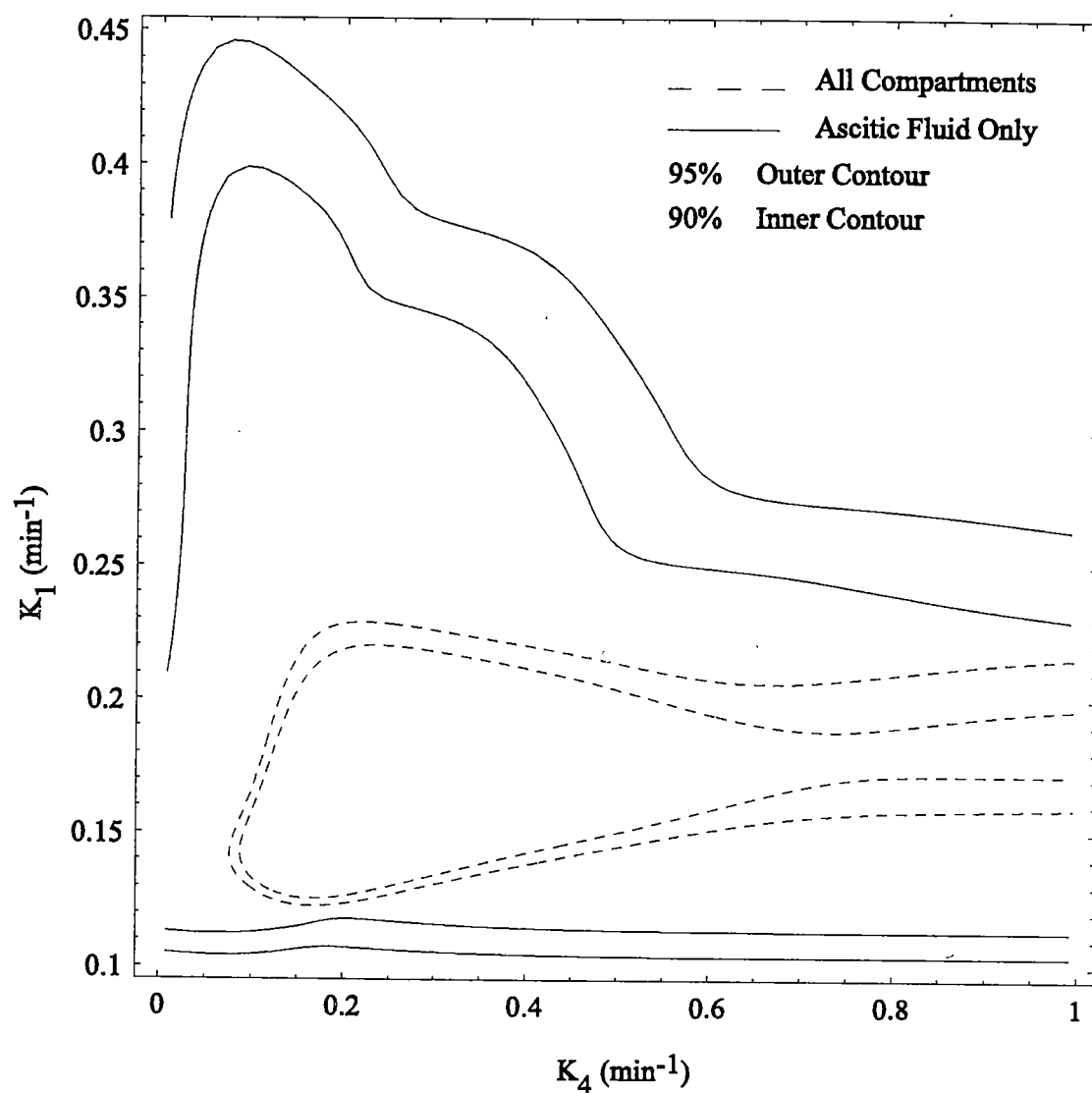


Figure 5.19. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with the ascitic fluid iodoalbumin data and uniform priors.

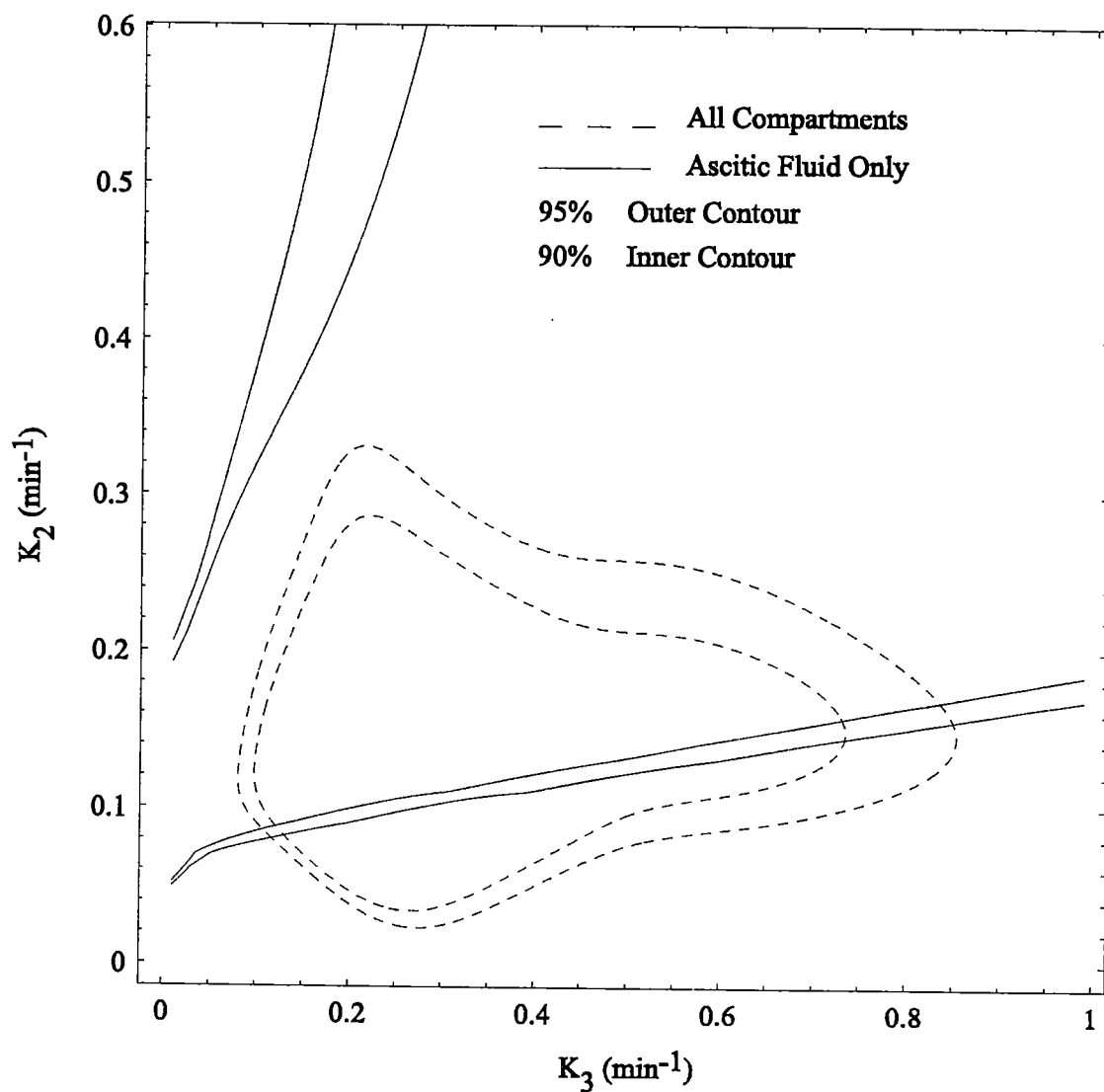


Figure 5.20. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with the ascitic fluid iodoalbumin data and uniform priors.

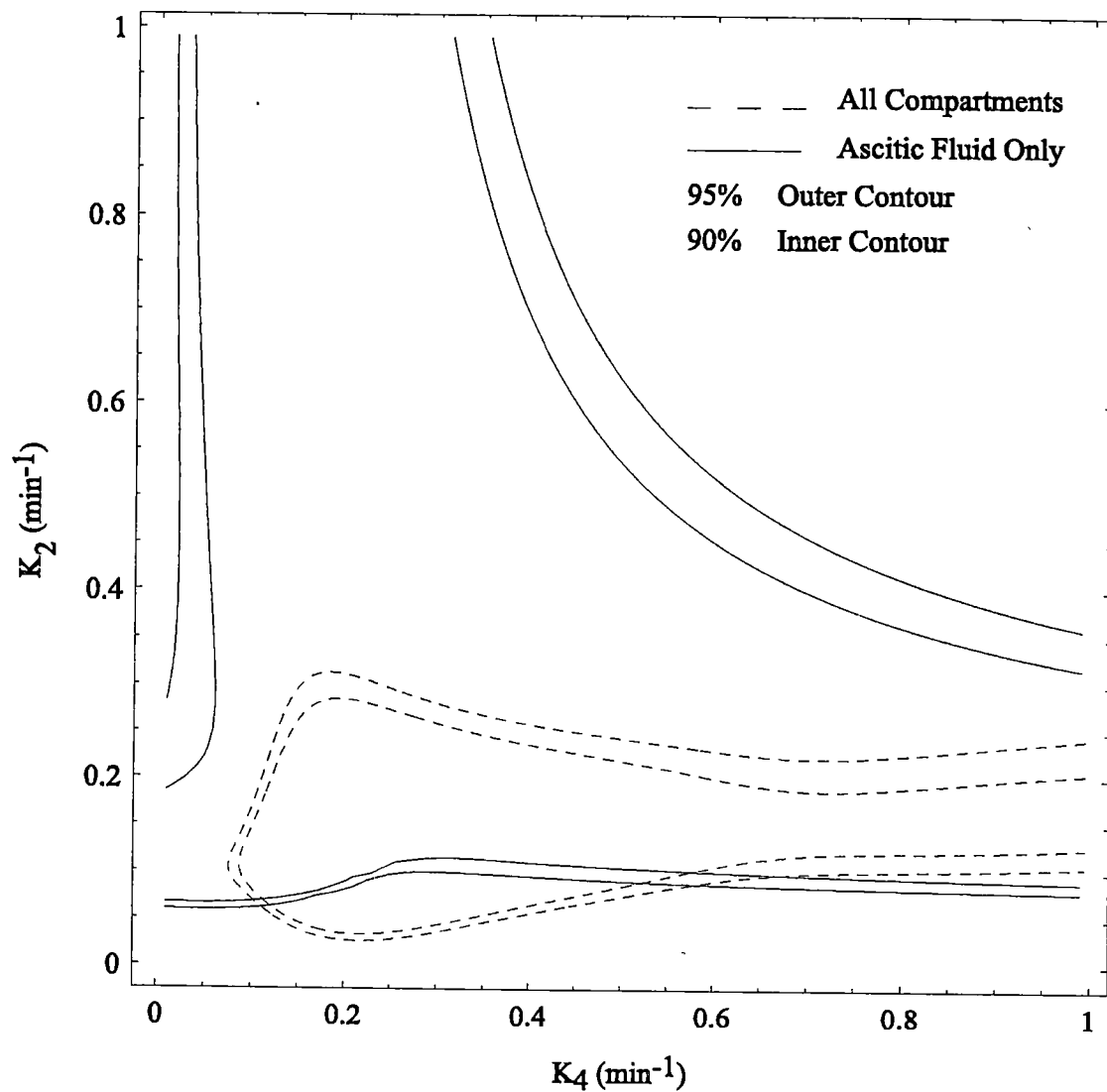


Figure 5.21. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with the ascitic fluid iodoalbumin data and uniform priors.

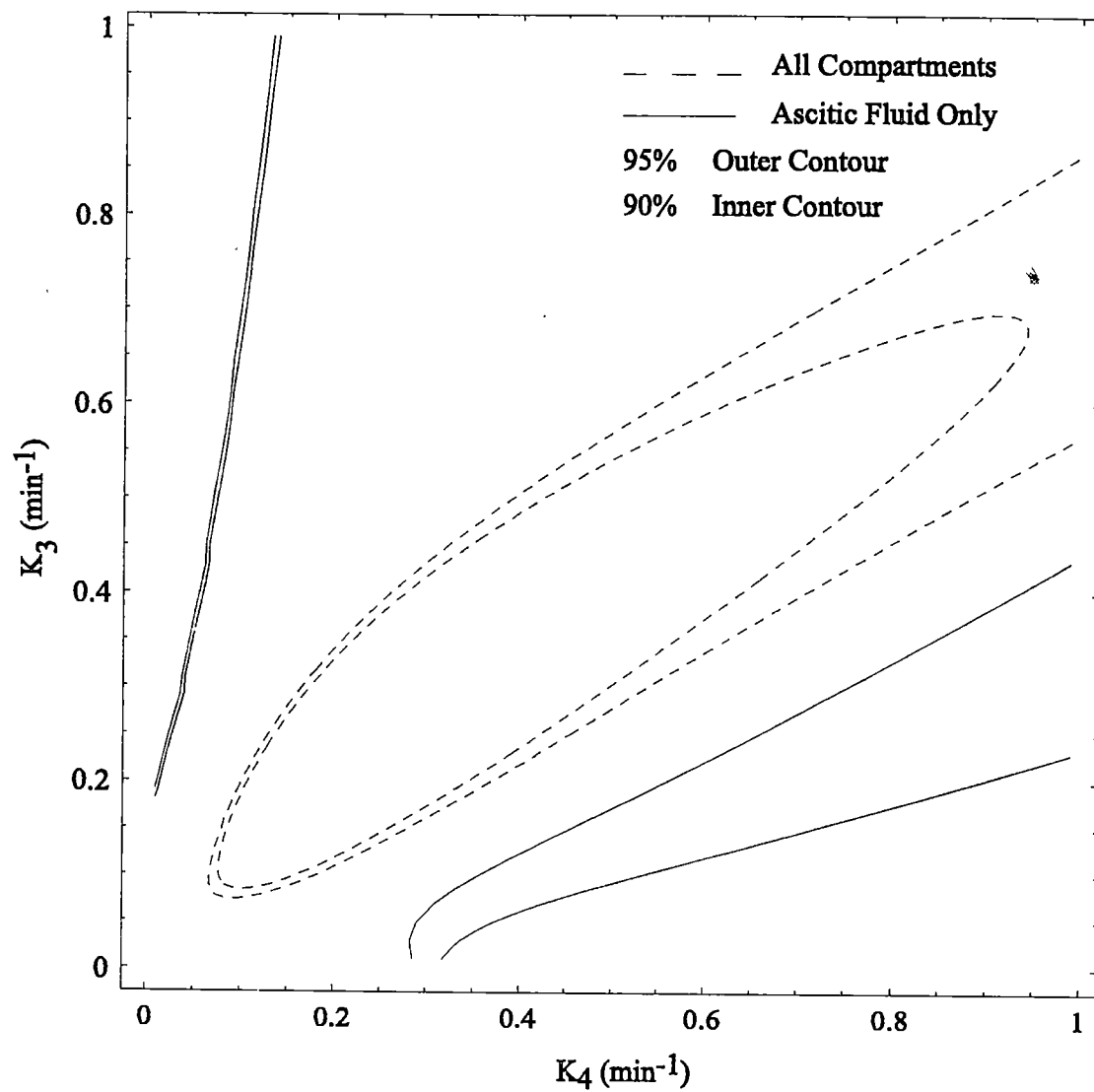


Figure 5.22. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with the ascitic fluid iodoalbumin data and uniform priors.

5.3.3 Only the plasma data are used

If only the plasma iodoalbumin data are used, then the joint posterior density for the parameters with uniform priors can be written as:

$$p(K_1, K_2, K_3, K_4 | \text{data}) \propto S_{22}(\theta)^{-5}, \quad (5.5)$$

where $S_{22}(\theta)$ was defined earlier for Eqn. (5.2). The normalized marginal posterior density for the parameters are plotted in Fig. 5.23 with the Bayesian estimates listed in Table 5.6. The parameter K_4 's "divergent" behavior is striking, and the divergence could be reduced or eliminated by using different data sets and/or proper priors.

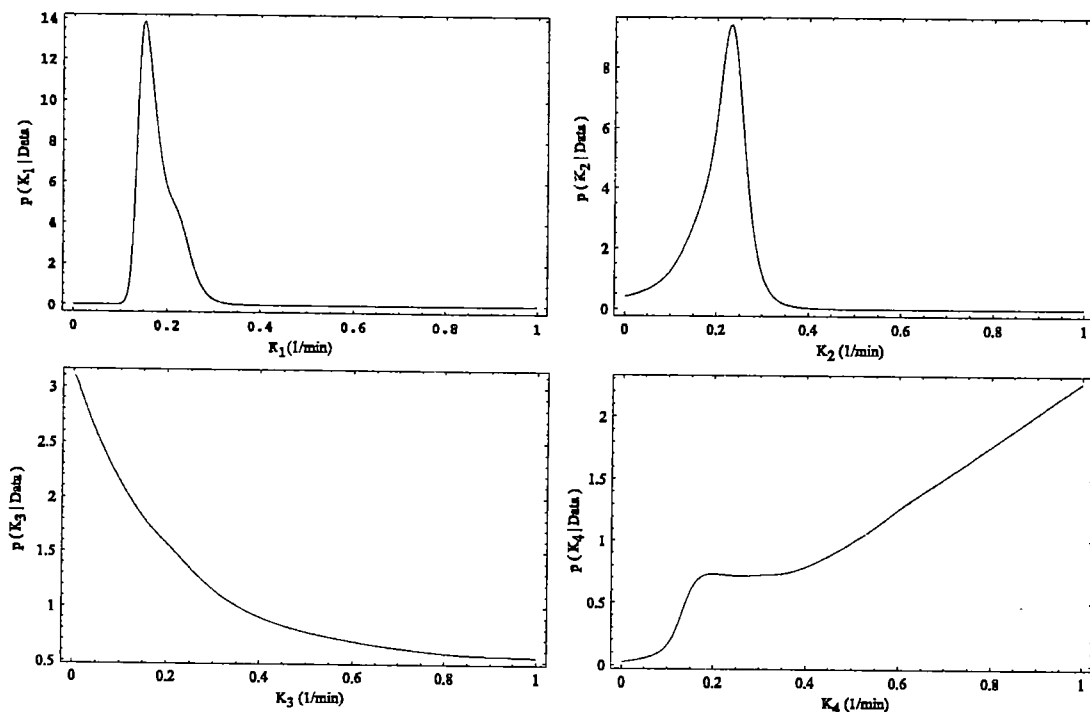


Figure 5.23. Normalized marginal posterior density for the human serum albumin exchange rates calculated with the plasma iodoalbumin data and uniform priors. The means are (day^{-1}): $K_1 = 0.1798 \pm 0.0401$, $K_2 = 0.2057 \pm 0.0626$, $K_3 = 0.3329 \pm 0.289$, $K_4 = 0.6714 \pm 0.256$.

Table 5.6. Posterior modes, means and standard deviations for the human serum albumin exchange rates calculated with the plasma iodoalbumin data and uniform priors.

Parameters	Posterior Mean (1/day)	Posterior Mode
K ₁	0.1798 ± 0.0401	0.152
K ₂	0.2057 ± 0.0626	0.232
K ₃	0.3329 ± 0.289	None
K ₄	0.6714 ± 0.256	None

Next, the solution of the differential equations was fitted to the data using both the Bayesian and the Berson – Yalow parameter estimates. Since posterior modes do not exist for parameters K₃ and K₄ they were not used in the fittings. As Figs. 5.24 through 5.26 show, none of the estimates provided satisfactory fits to the data from all three compartments. For this scenario, the best fits to the ascitic fluid and the plasma data were the posterior means, and the Berson – Yalow estimates for the extravascular spaces data.

Finally, the 90 and 95 percent HPD contours z values for various parameter combinations are listed in Table 5.7, with the corresponding HPD contours plotted in Figs. 5.27 through 5.32. The resulting HPD contours were rather interesting. Typical of all parameter estimation techniques, the less information one has the greater the variance of the estimates. In this example, the contours were frequently open and irregularly shaped. This is similar to the findings presented in Chapter 4. One good example are the HPD contours for parameters (K₃, K₄). Since the majority of the (K₃, K₄) contours are open, it is difficult to comprehend and interpret the results without the use of additional visual aides such as a surface density plot or more contour levels.

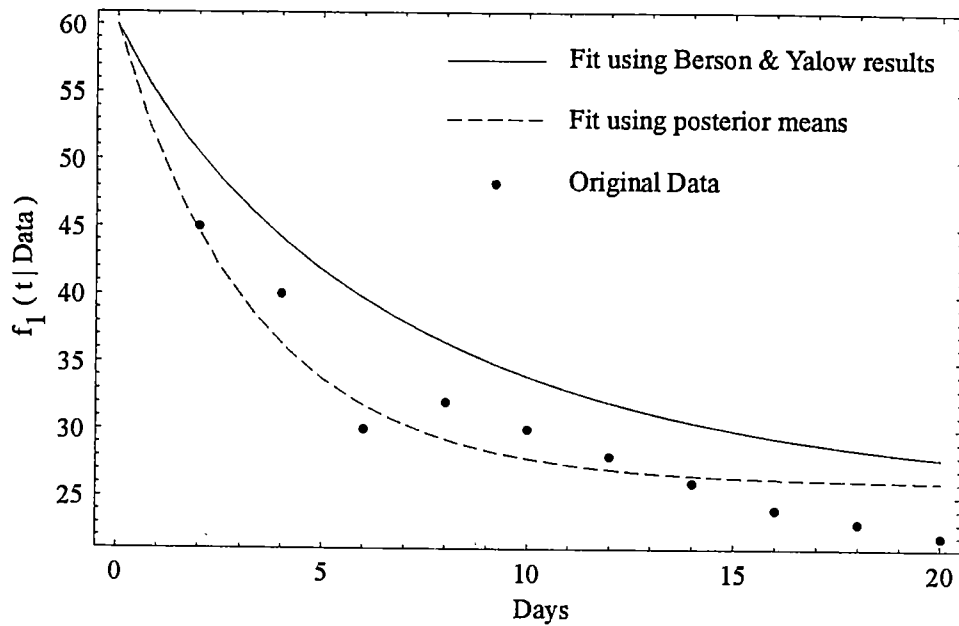


Figure 5.24. Solution of the differential equations for the parameter estimates calculated from the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human ascitic fluid iodoalbumin data.

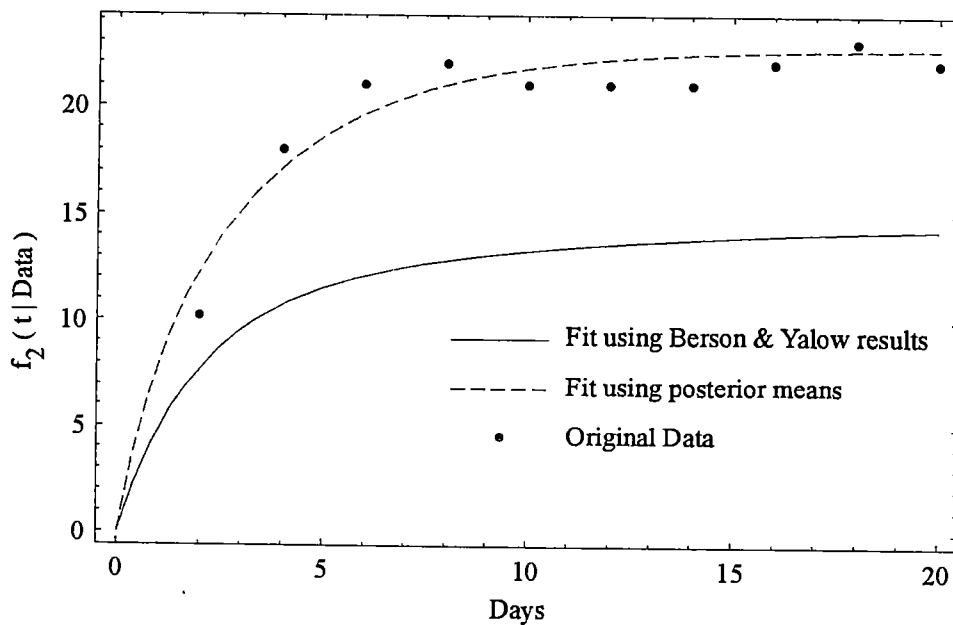


Figure 5.25. Solution of the differential equations for the parameter estimates calculated from the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human plasma iodoalbumin data.

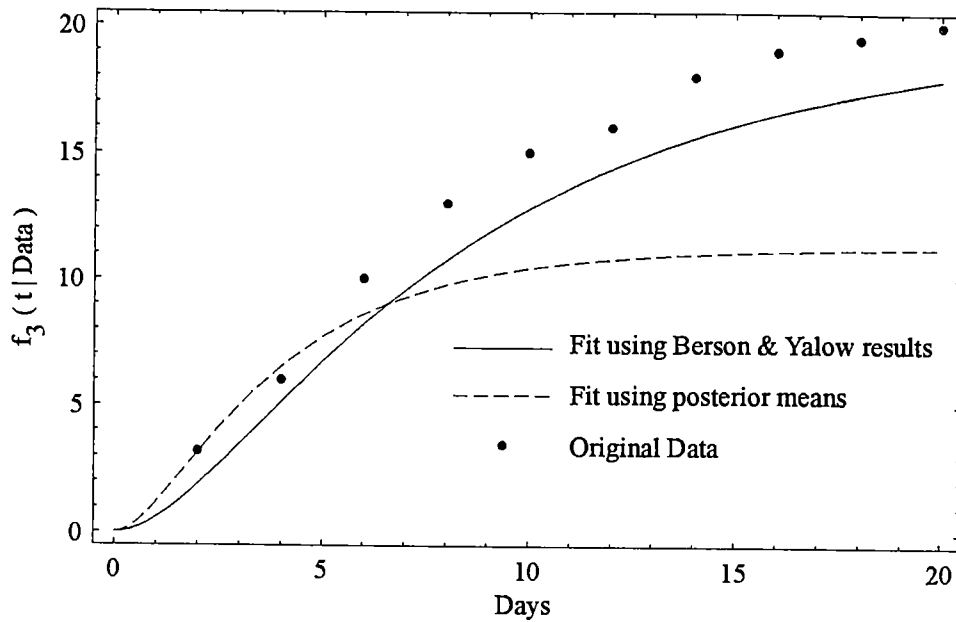


Figure 5.26. Solution of the differential equations for the parameter estimates calculated from the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human extravascular space iodoalbumin data.

Table 5.7. Ninety and ninety-five percent HPD contour z values for various combinations of the human serum albumin exchange rates calculated with the plasma iodoalbumin data and uniform priors.

Parameter Combinations	z values	
	90% HPD	95% HPD
K_1 and K_2	6.6	3.7
K_1 and K_3	3.6	1.8
K_1 and K_4	3.8	2.1
K_2 and K_3	1.4	0.8
K_2 and K_4	1.6	1.1
K_3 and K_4	0.9	0.7

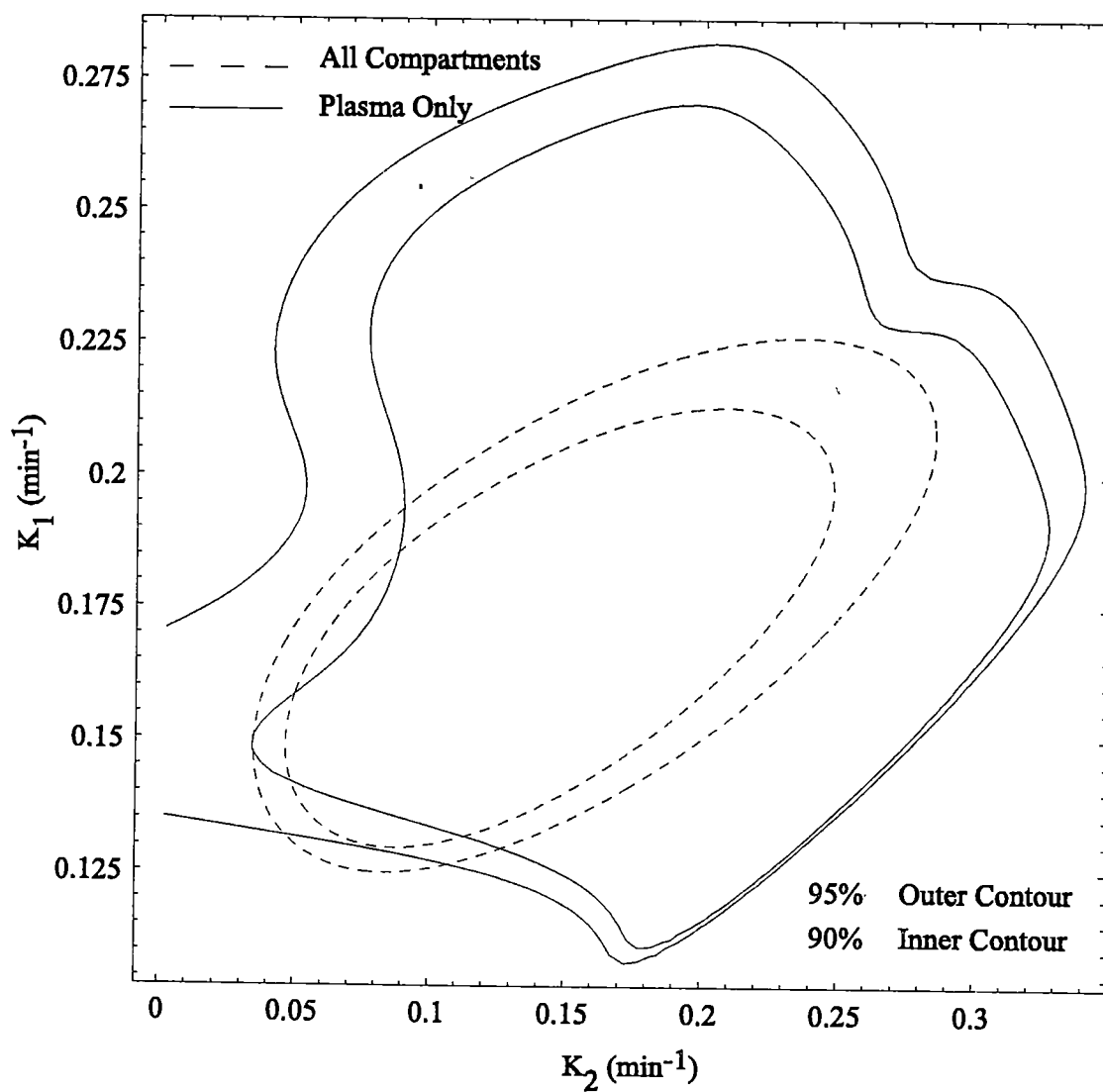


Figure 5.27. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with the plasma iodoalbumin data and uniform priors.

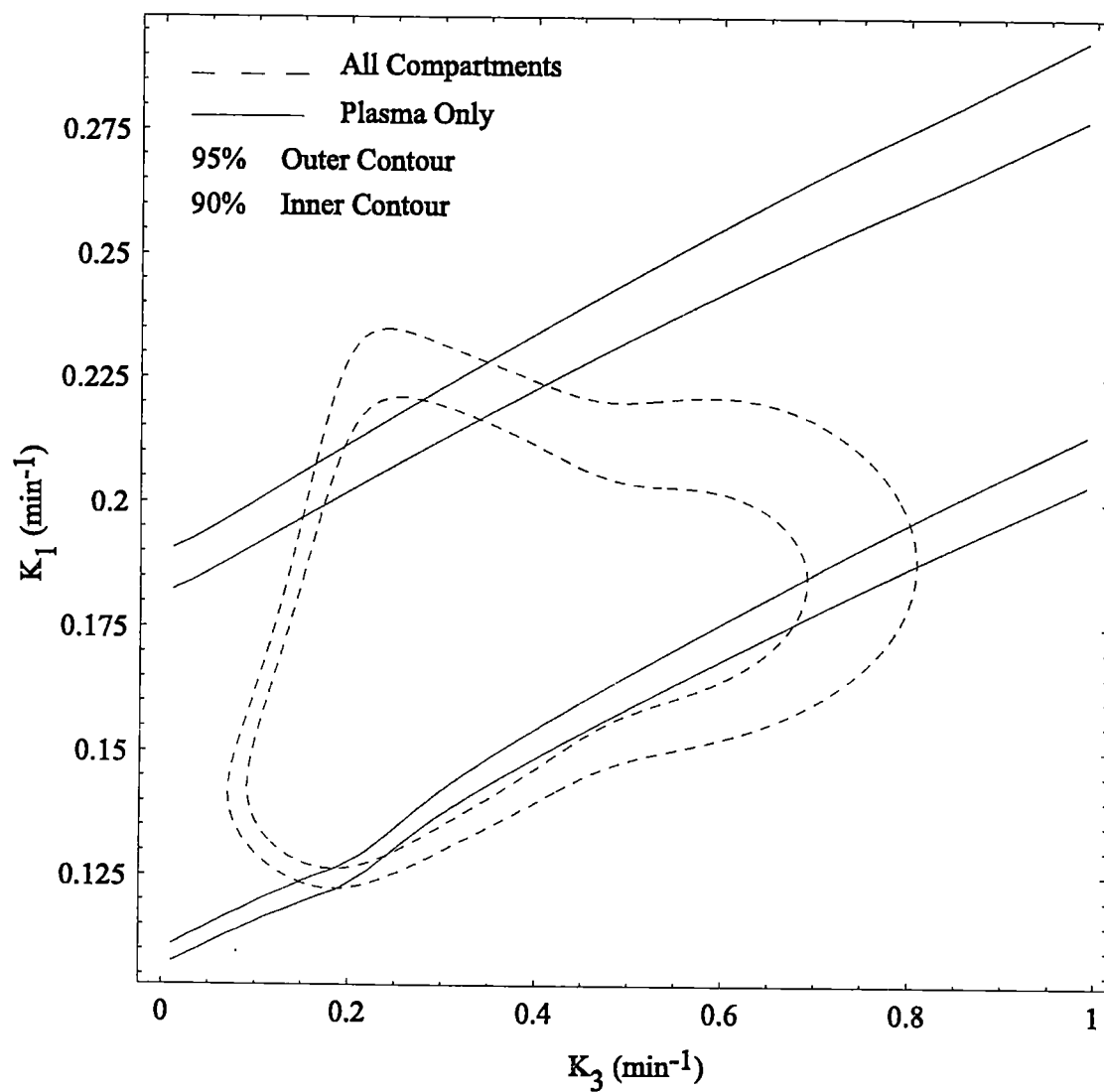


Figure 5.28. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with the plasma iodoalbumin data and uniform priors.

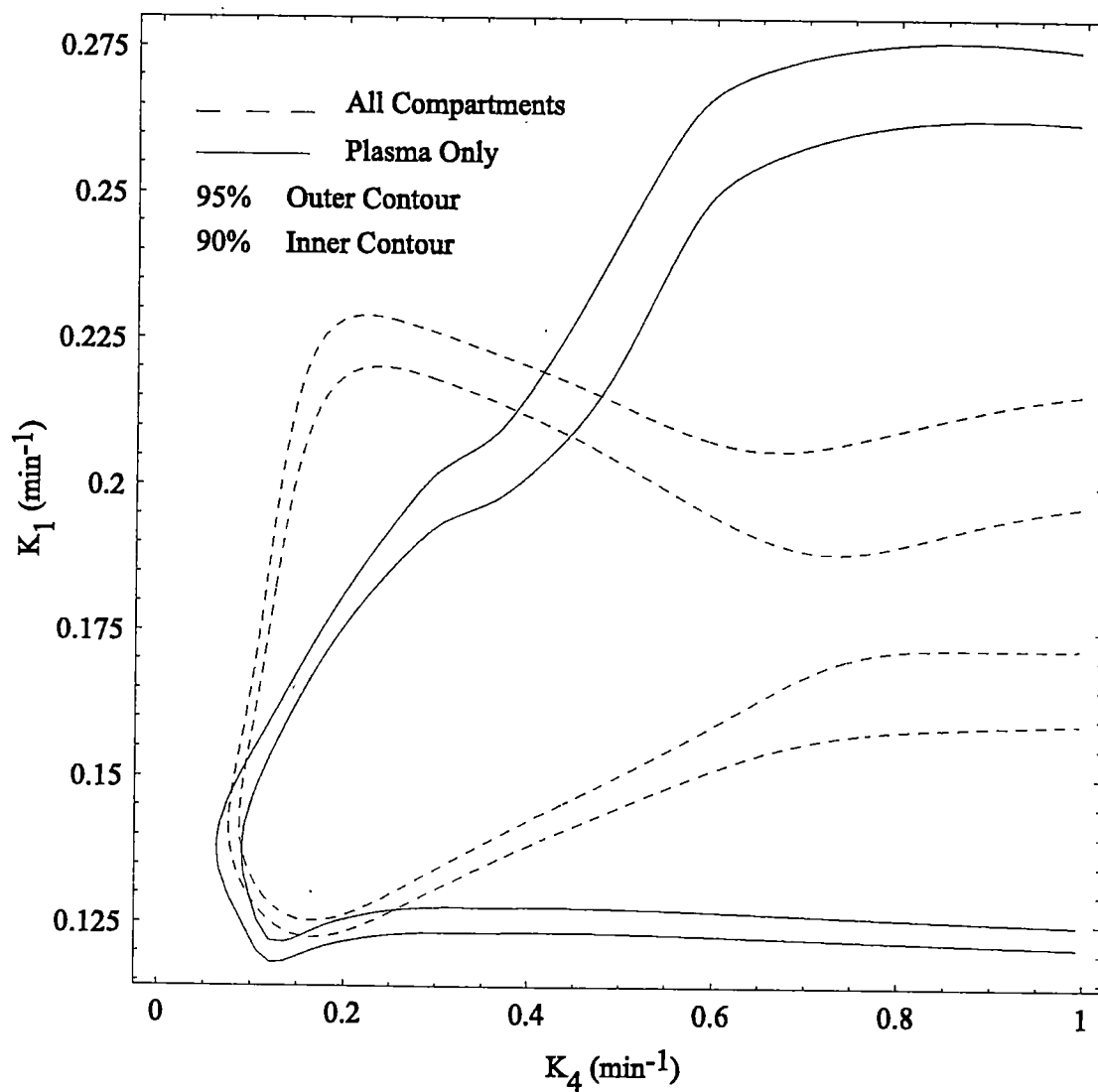


Figure 5.29. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with the plasma iodoalbumin data and uniform priors.

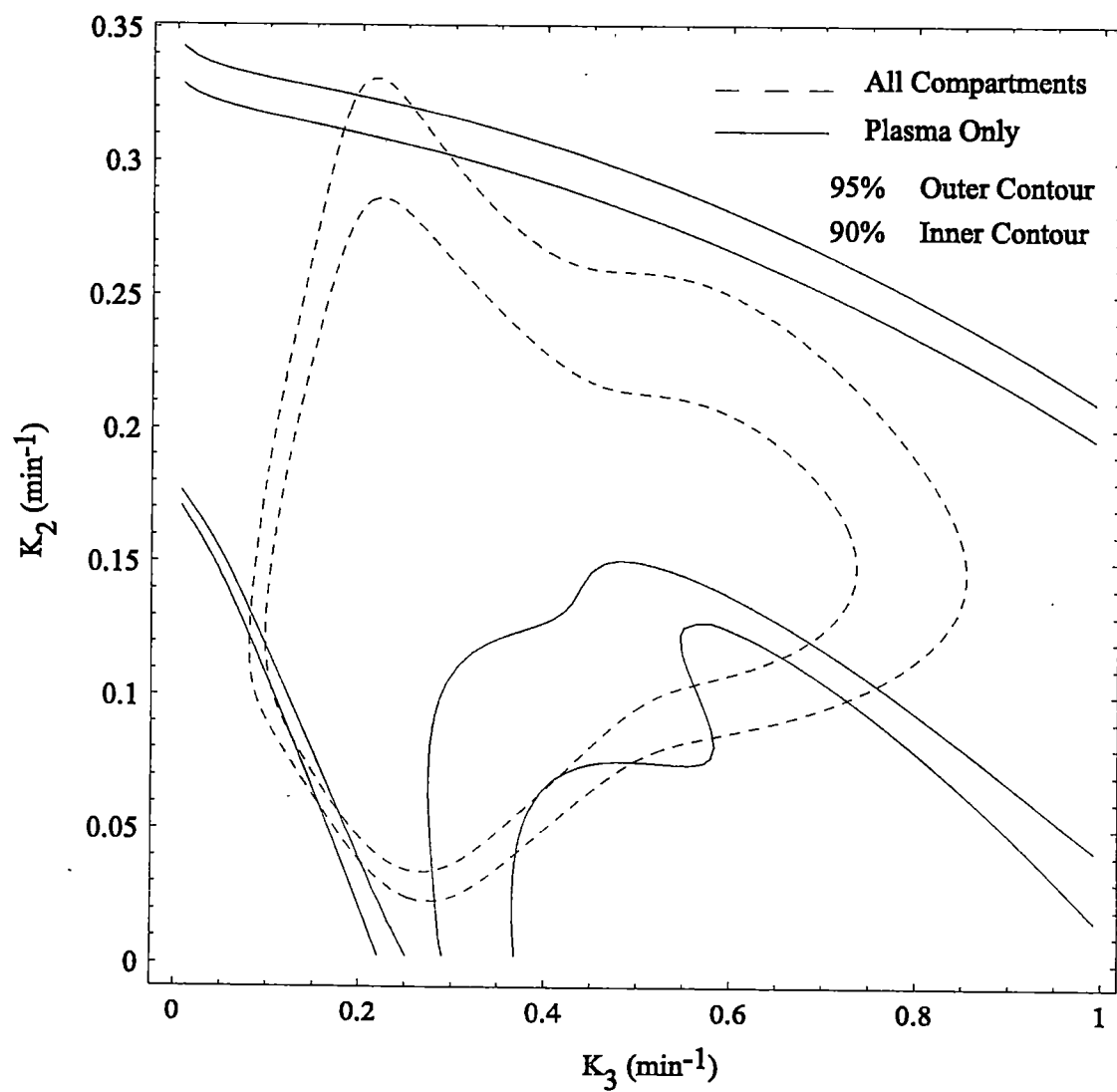


Figure 5.30. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with the plasma iodoalbumin data and uniform priors.

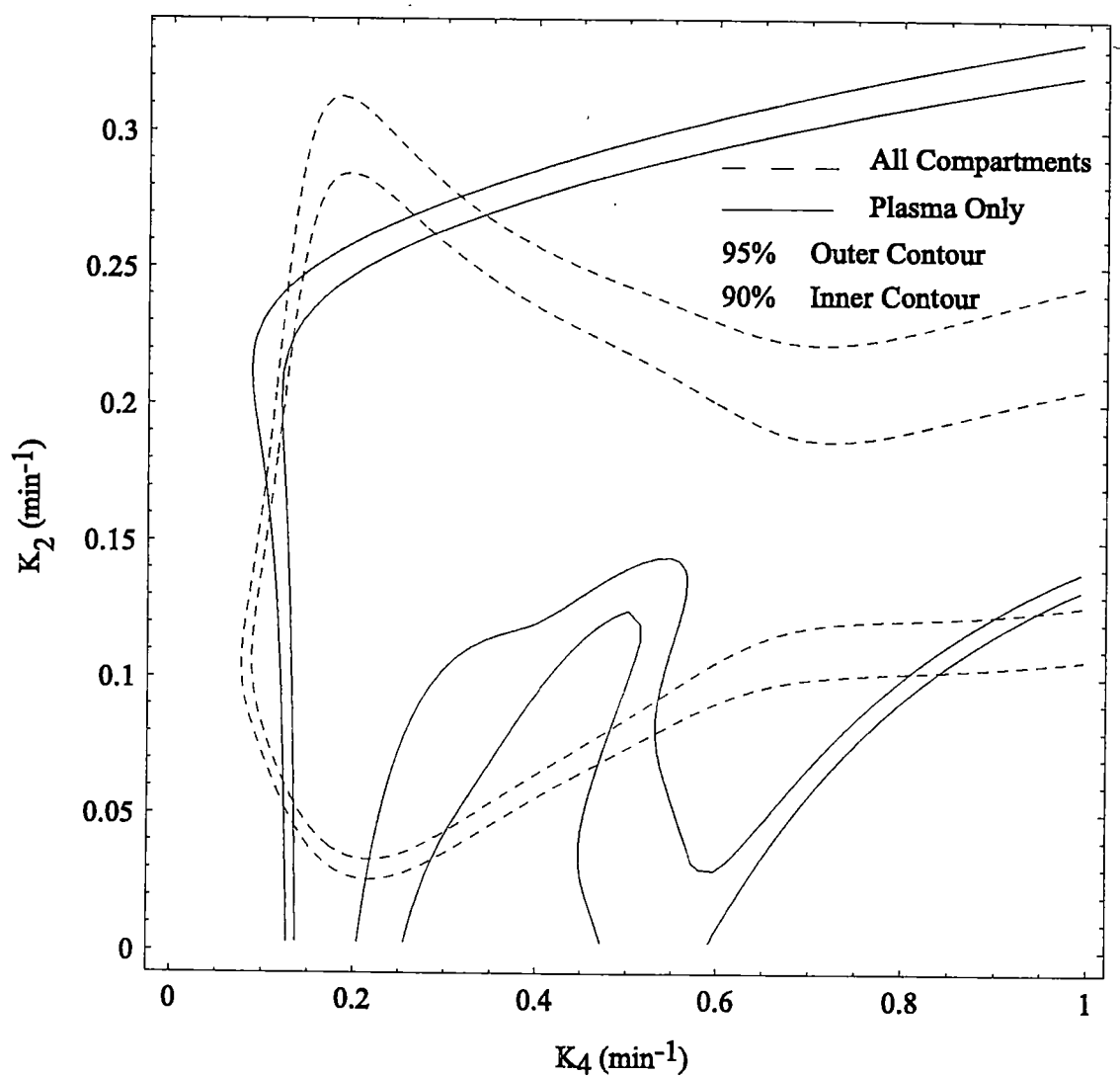


Figure 5.31. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with the plasma iodoalbumin data and uniform priors.

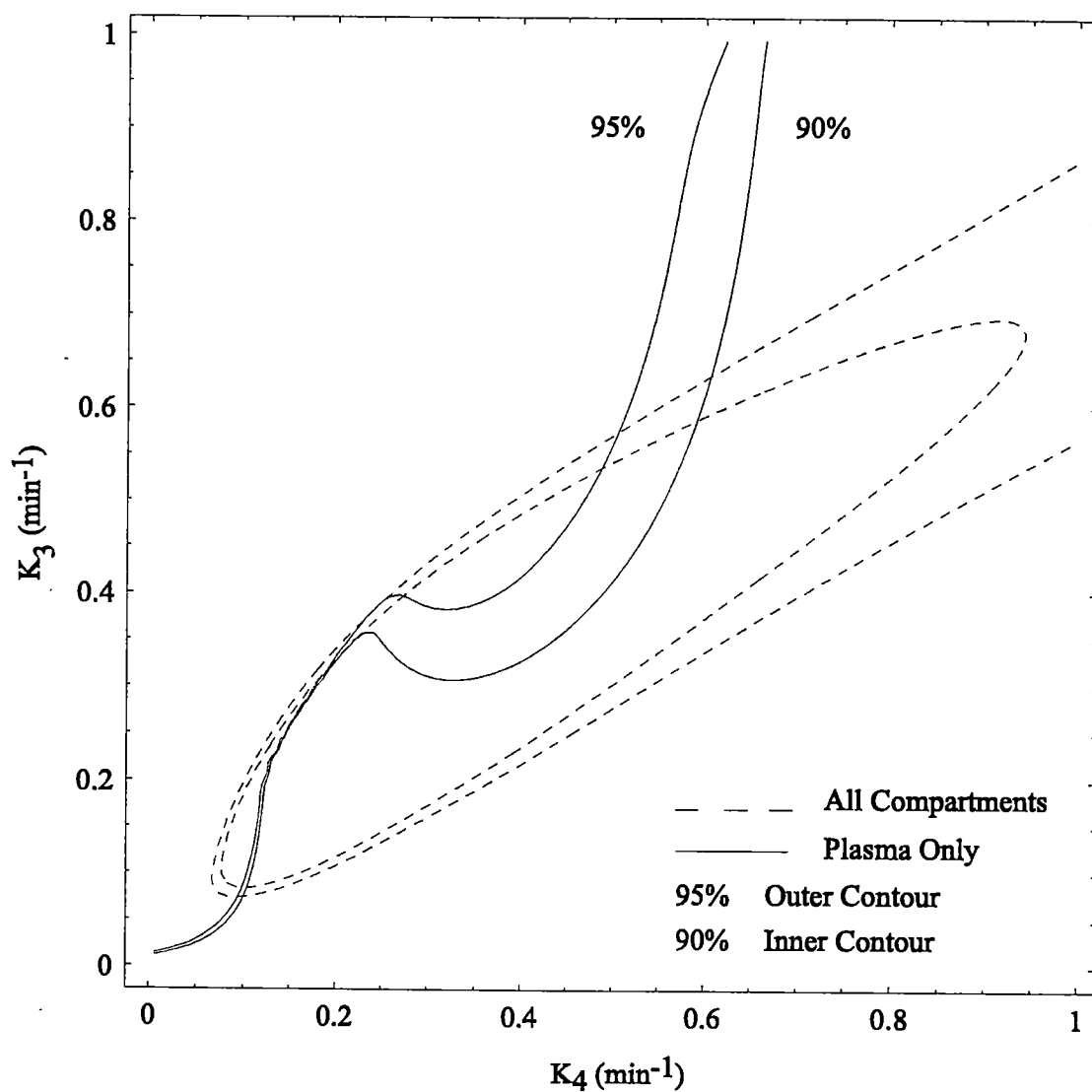


Figure 5.32. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with the plasma iodoalbumin data and uniform priors.

5.3.4 Both the ascitic fluid and the plasma data are used

In the last scenario, data from both the ascitic fluid and the plasma compartments are used. The resulting joint posterior density of the parameters with uniform priors is:

$$p(K_1, K_2, K_3, K_4 | data) \propto [S_{11}(\theta) \cdot S_{22}(\theta) - S_{12}(\theta)^2]^{-5}, \quad (5.6)$$

where $S_{11}(\theta)$, $S_{12}(\theta)$ and $S_{22}(\theta)$ were defined earlier for Eqn. (5.2). The normalized posterior densities for the parameters with uniform priors are plotted in Fig. 5.33, with the corresponding Bayesian estimates listed in Table 5.8.

Although data from two compartments were used, there was no significant improvement in the precision of the estimates as compared with the single compartment analyses. Bimodalities were observed in parameters K_3 and K_4 , and the peaks were large enough to be seen on linear-linear plots. Interestingly, K_3 's bimodality is located in the same neighborhood as the small "shoulder" found in K_3 's marginal density plot calculated with all data (see Fig. 5.3).

Next, the solution of the differential equations was fitted to the data using both the Bayesian and the Berson – Yalow parameter estimates in Figs. 5.34 through 5.36. Again, none of the estimates provided satisfactory fits to all three compartmental data. The best fits resulted from using the posterior means. They offered the best fits to the ascitic fluid and the plasma data, and followed by the Berson – Yalow estimates for the extravascular spaces data.

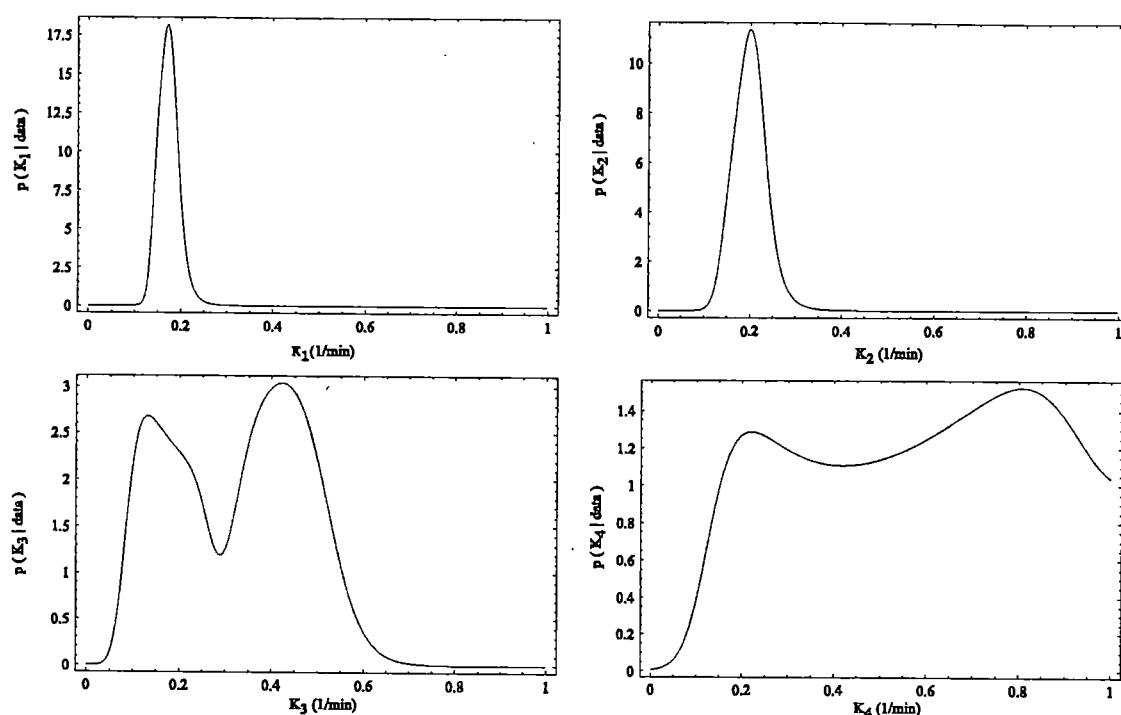


Figure 5.33. Normalized marginal posterior density for the human serum albumin exchange rates calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data. The means are (day^{-1}): $K_1 = 0.173 \pm 0.0235$, $K_2 = 0.2004 \pm 0.0381$, $K_3 = 0.3004 \pm 0.134$, $K_4 = 0.5714 \pm 0.271$.

Table 5.8. Posterior modes, means and standard deviations for the human serum albumin exchange rates calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.

Parameters	Posterior Mean	Posterior Mode
		(1/day)
K_1	0.173 ± 0.0235	0.171
K_2	0.2004 ± 0.0381	0.202
K_3	0.3004 ± 0.134	0.422
K_4	0.5714 ± 0.271	0.808

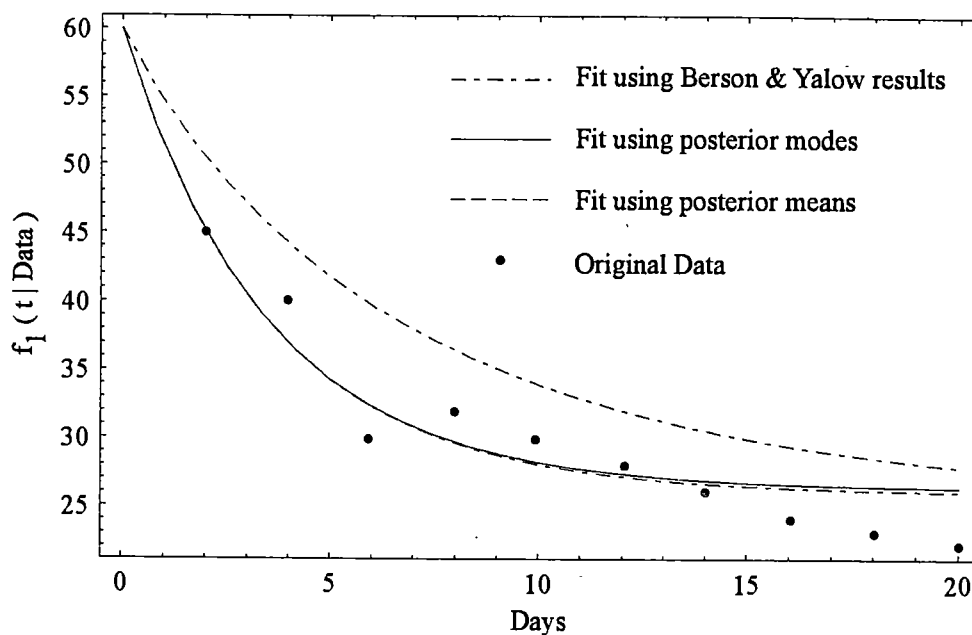


Figure 5.34. Solution of the differential equations for the parameter estimates calculated from both the ascitic fluid and the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human ascitic fluid iodoalbumin data.

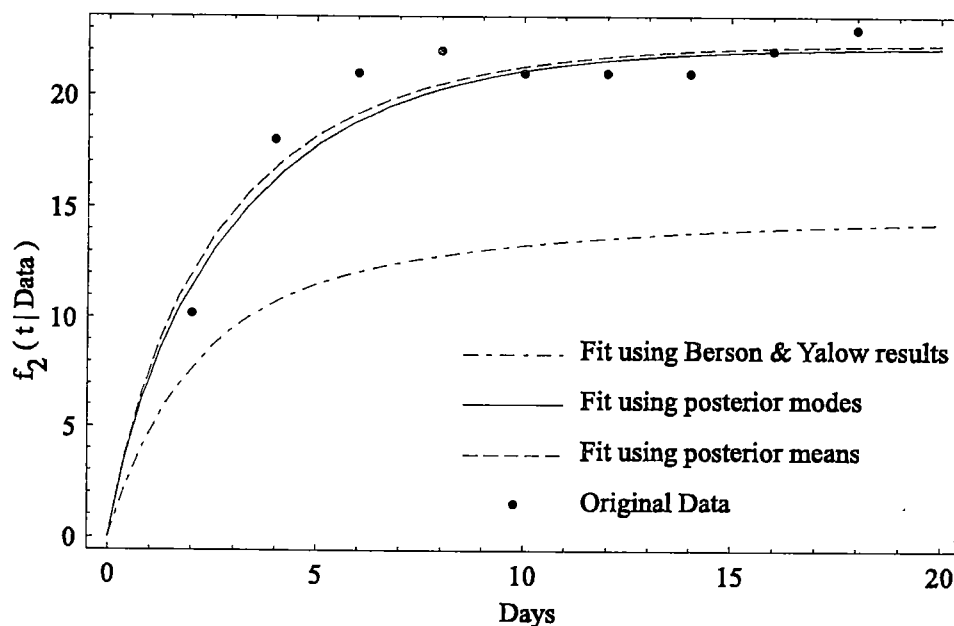


Figure 5.35. Solution of the differential equations for the estimates calculated from both the ascitic fluid and the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human plasma iodoalbumin data.

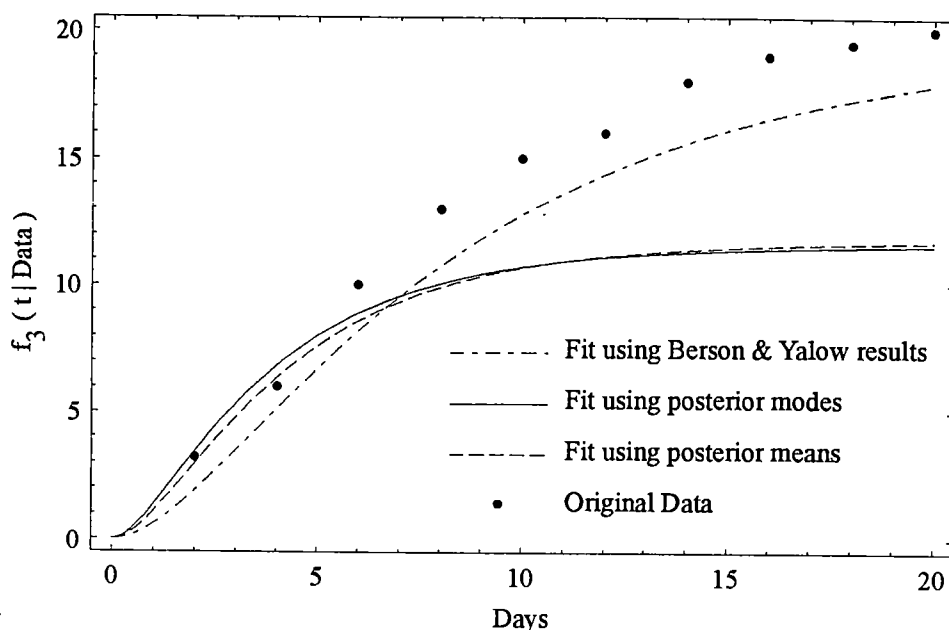


Figure 5.36. Solution of the differential equations for the parameter estimates calculated from both the ascitic fluid and the plasma iodoalbumin data with uniform priors, and those found by Berson – Yalow fitted to the human extravascular iodoalbumin data.

Lastly, the 90 and 95 percent HPD contours for various parameter combinations calculated using the ascitic fluid and the plasma data are plotted in Figs. 5.37 through 5.42. The corresponding contour z values are listed in Table 5.9. Generally speaking, the HPD contours expand when less information is used. However, in this example, the HPD contours for parameter combinations (K_1, K_2) and (K_2, K_3) actually got smaller when the data used were reduced from three compartments down to two. The most likely explanation is that the extravascular spaces data used are flawed. Either this due to how the data points were selected from the log plot (see Fig. 5.2), or that the data itself were imprecise since extravascular space concentrations can not be assayed but estimated (Berson and Yalow, 1954).

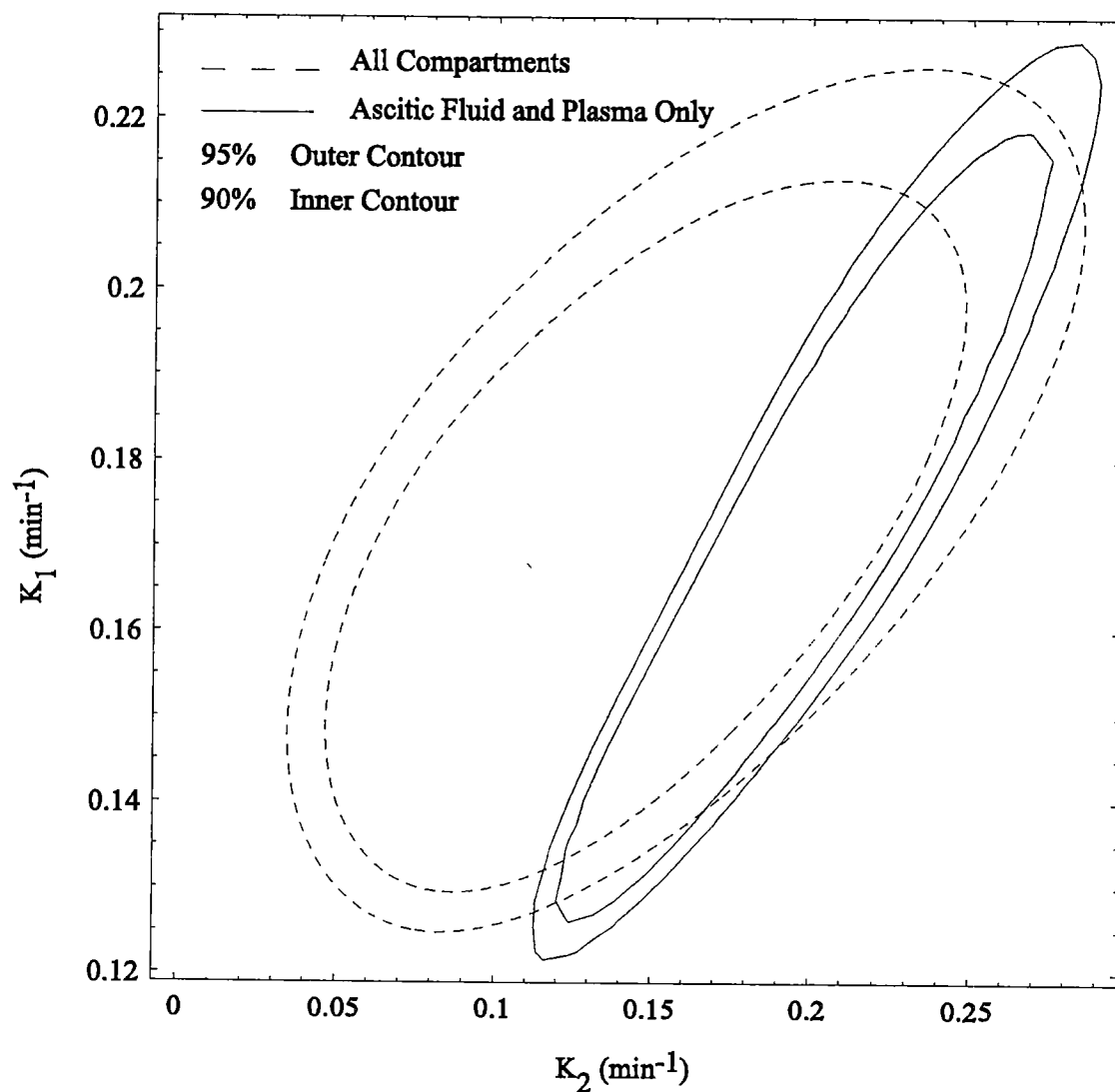


Figure 5.37. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_2 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.

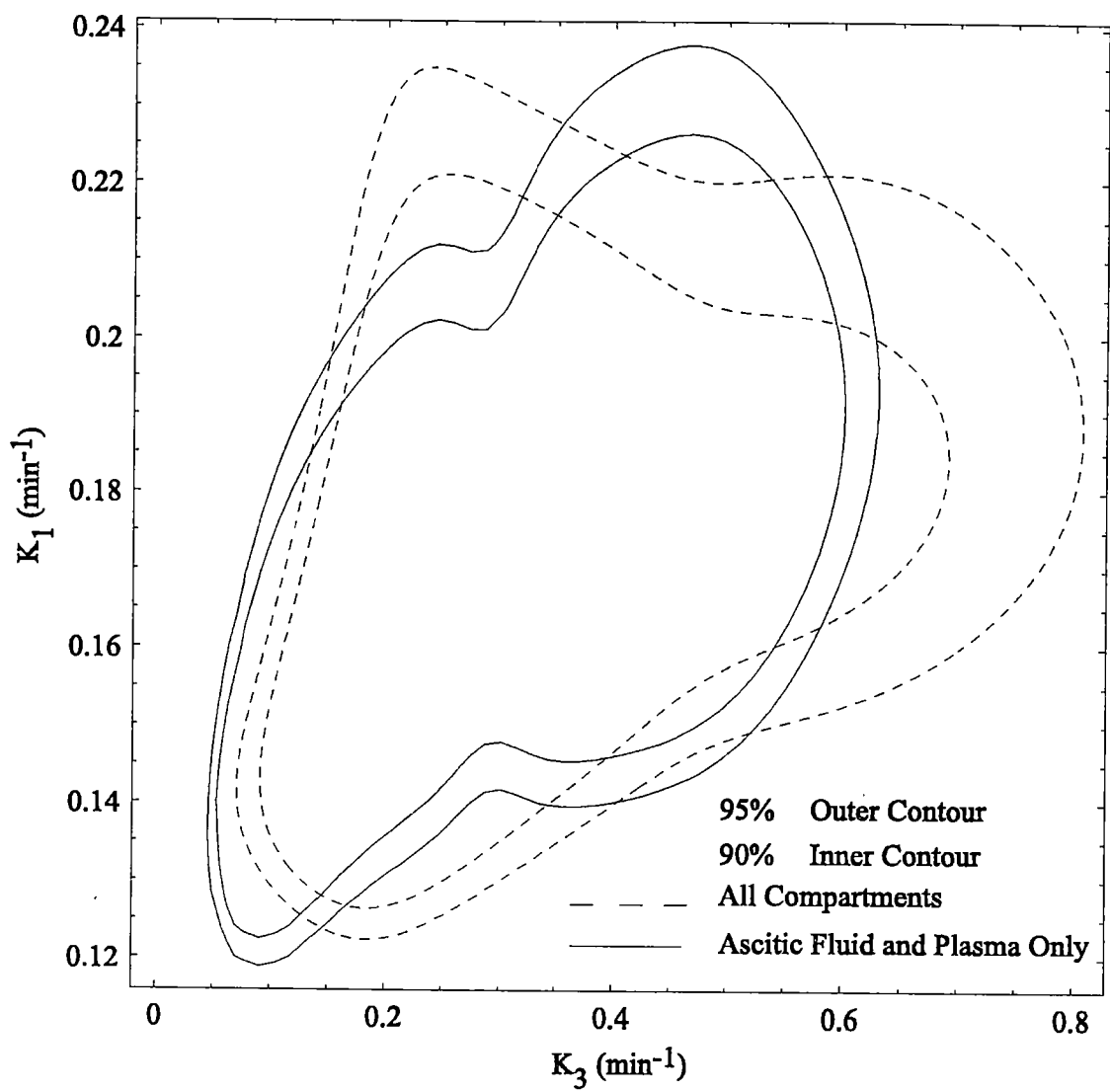


Figure 5.38. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.

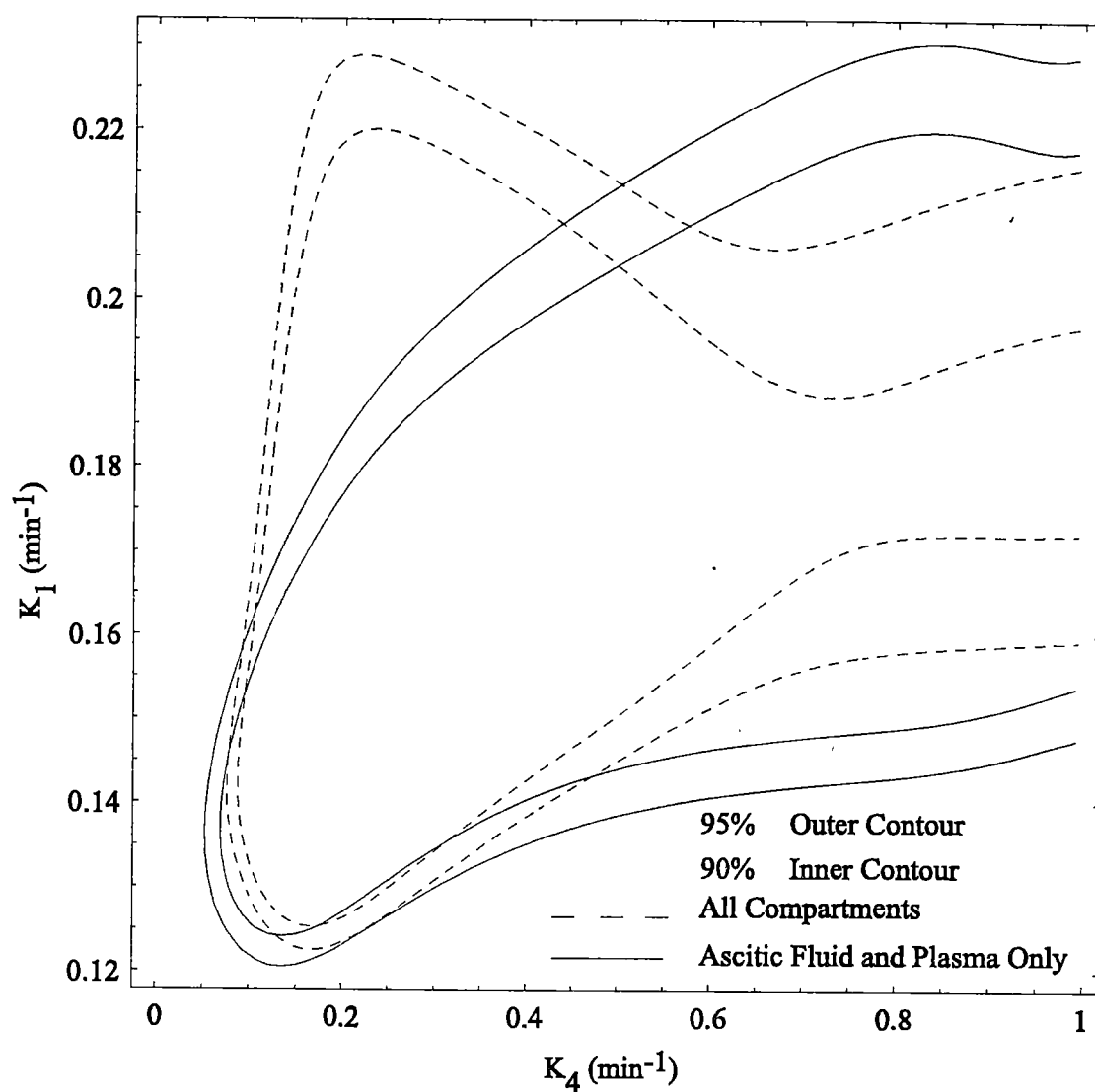


Figure 5.39. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.

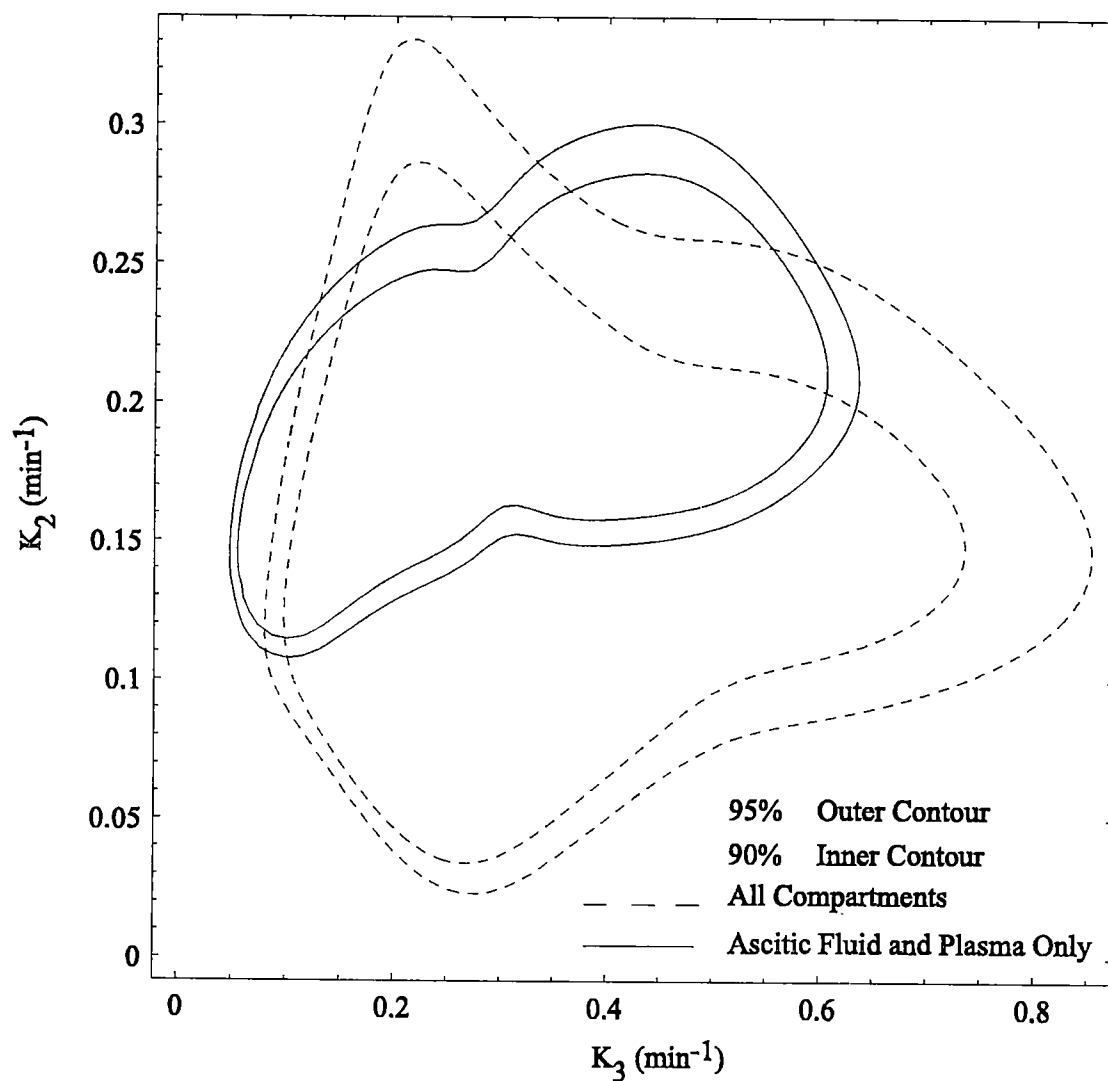


Figure 5.40. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.

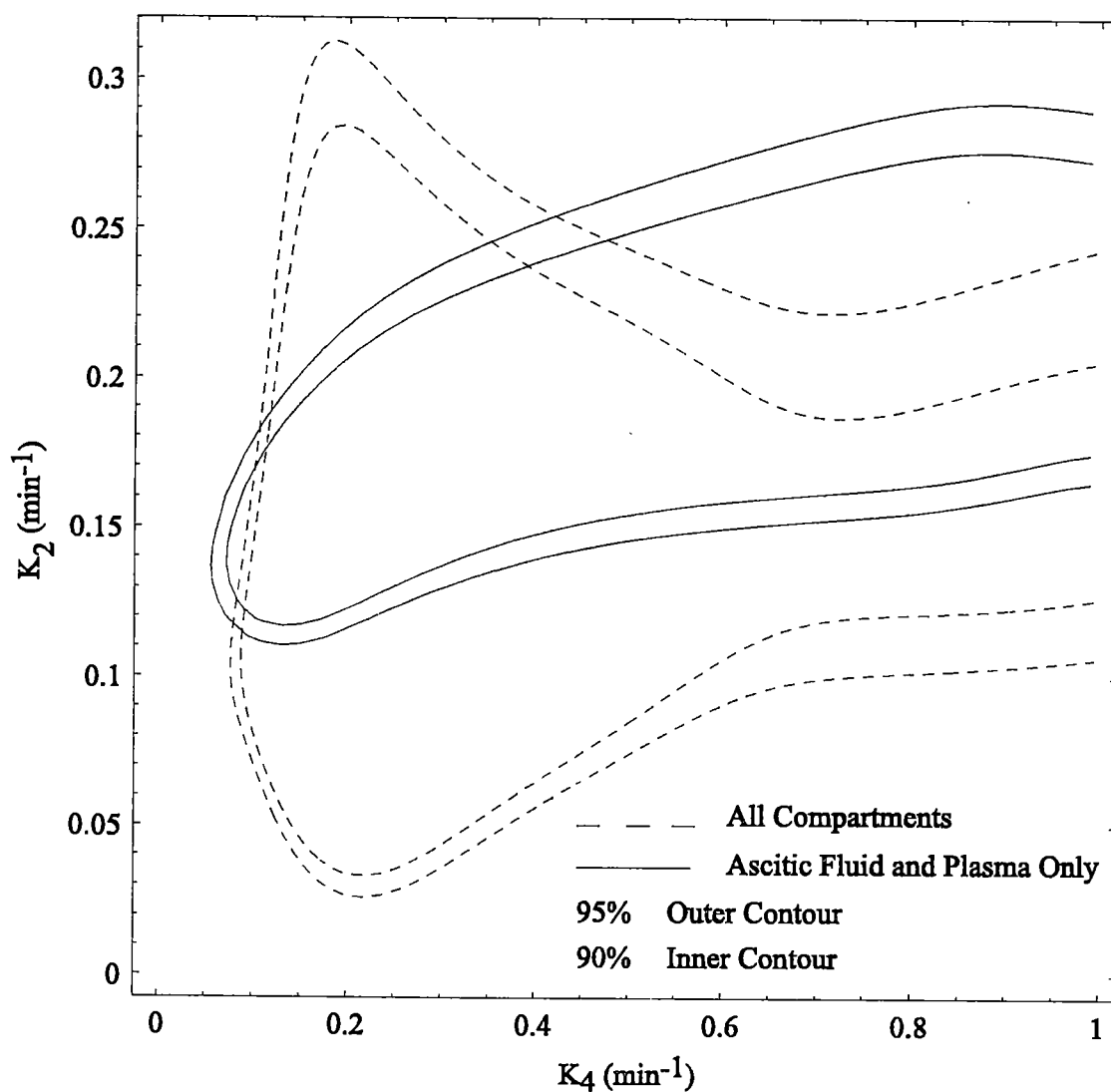


Figure 5.41. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.

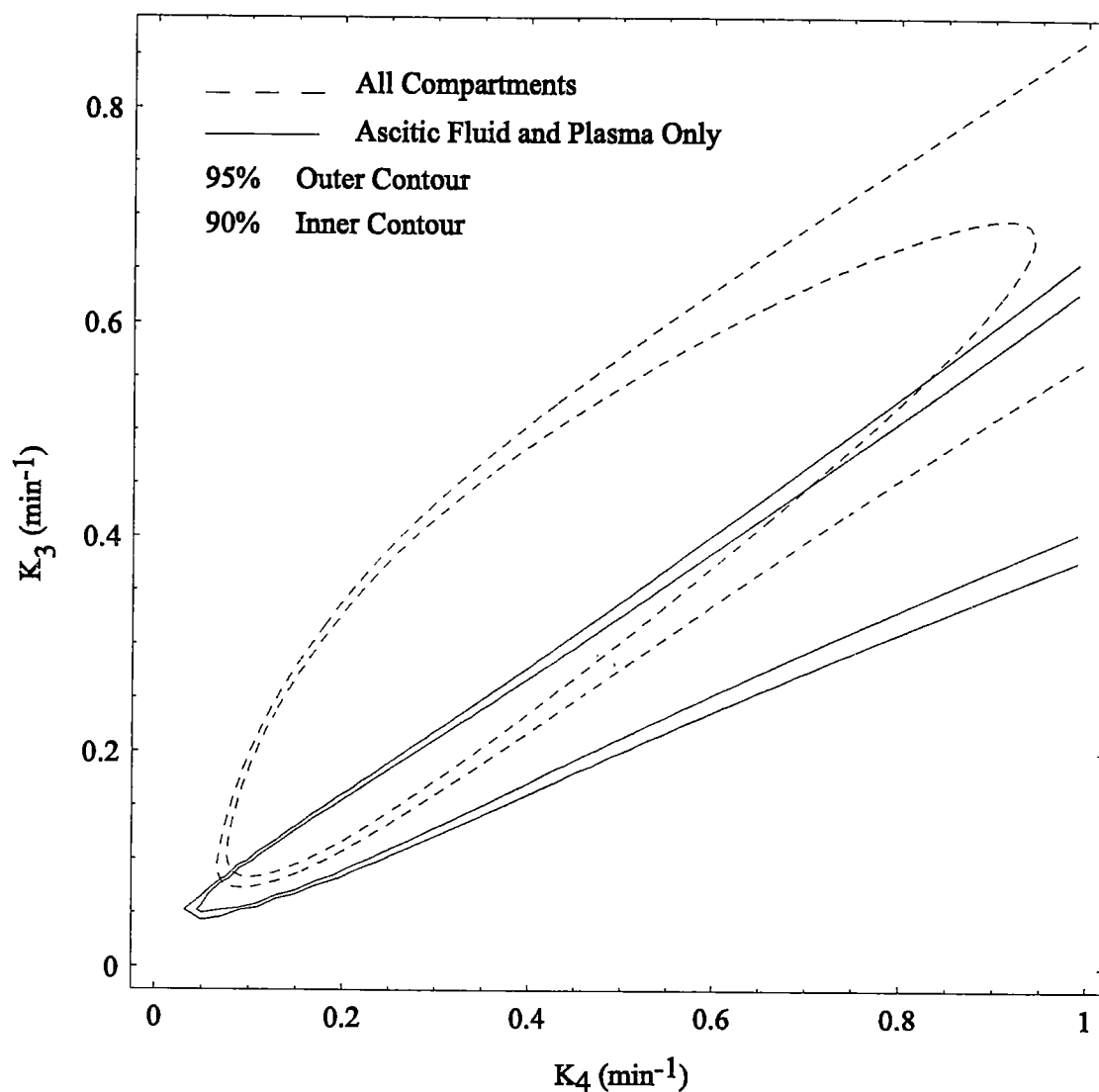


Figure 5.42. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.

Table 5.9. Ninety and ninety-five percent HPD contour z values for various combinations of the human serum albumin exchange rates calculated with uniform priors and both the ascitic fluid and the plasma iodoalbumin data.

Parameter Combinations	z values	
	90% HPD	95% HPD
K_1 and K_2	20	46
K_1 and K_3	3.3	7.1
K_1 and K_4	2.5	5.1
K_2 and K_3	2.1	4.5
K_2 and K_4	1.6	3.2
K_3 and K_4	1.3	2.6

5.3.5 Review of the results for the iodoalbumin analyses

Overall, the results of the iodoalbumin analyses were good. Typically, less information usually implies diminished precision. But for this model, increased precision was observed for some of the parameters when extravascular space data were omitted. This could be related to the accuracy of the extravascular space data and further analyses are needed. In this section, the results of the iodoalbumin analyses are reviewed. The combined normalized marginal posterior density plots for various data sets are shown in Figs. 5.43 through 5.46, with the corresponding numerical estimates listed in Table 5.10. The combined 90 and 95 percent HPD contour plots for each parameter pairs with various data sets are shown in Figs. 5.47 through 5.52.

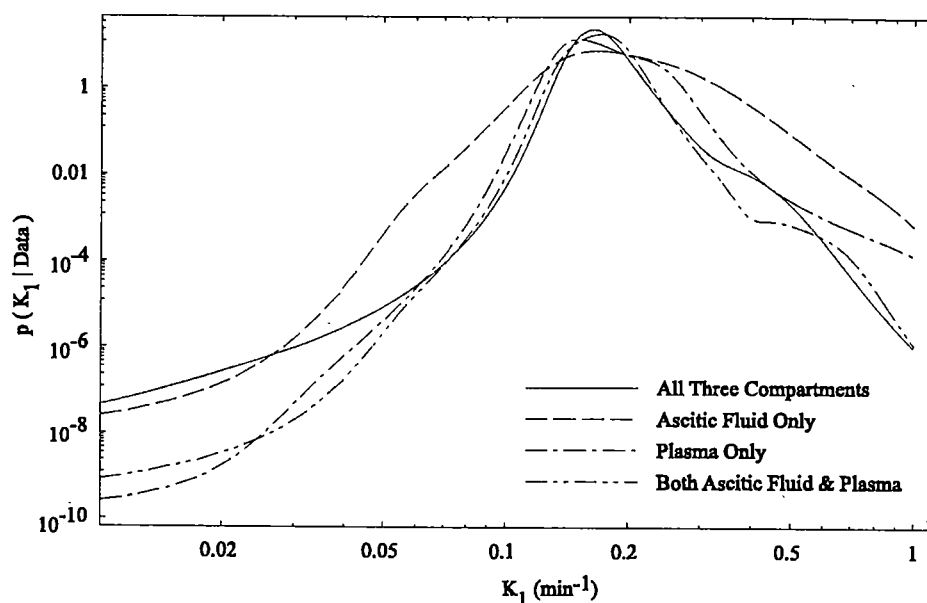


Figure 5.43. Normalized marginal posterior density for the human serum albumin exchange rate K_1 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

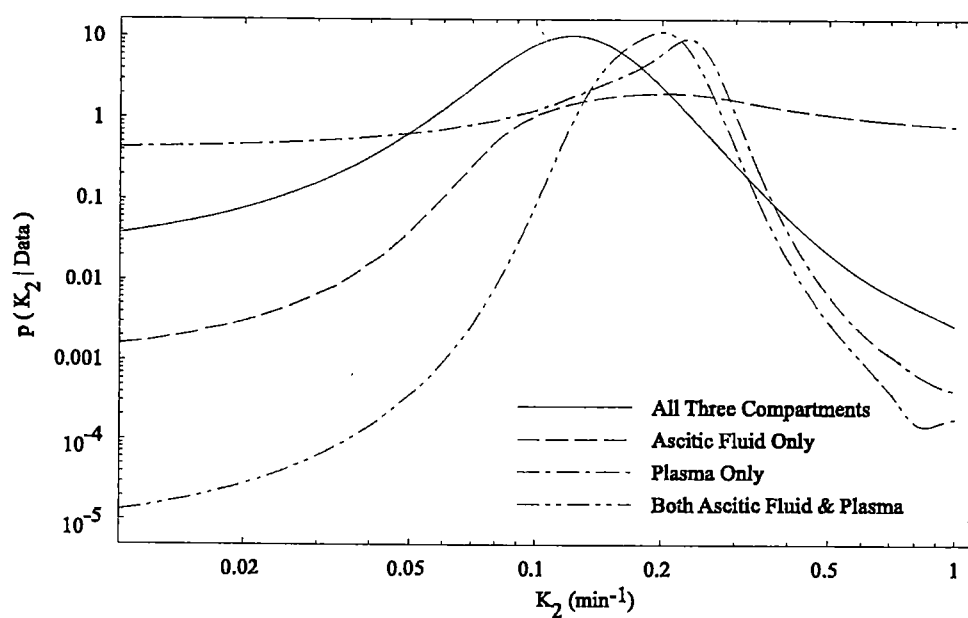


Figure 5.44. Normalized marginal posterior density for the human serum albumin exchange rate K_2 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

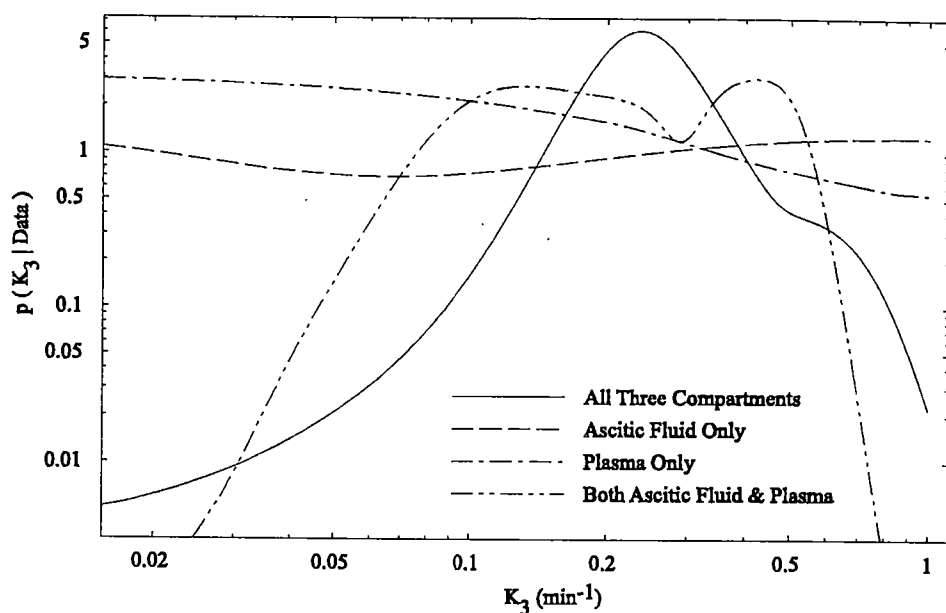


Figure 5.45. Normalized marginal posterior density for the human serum albumin exchange rate K_3 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

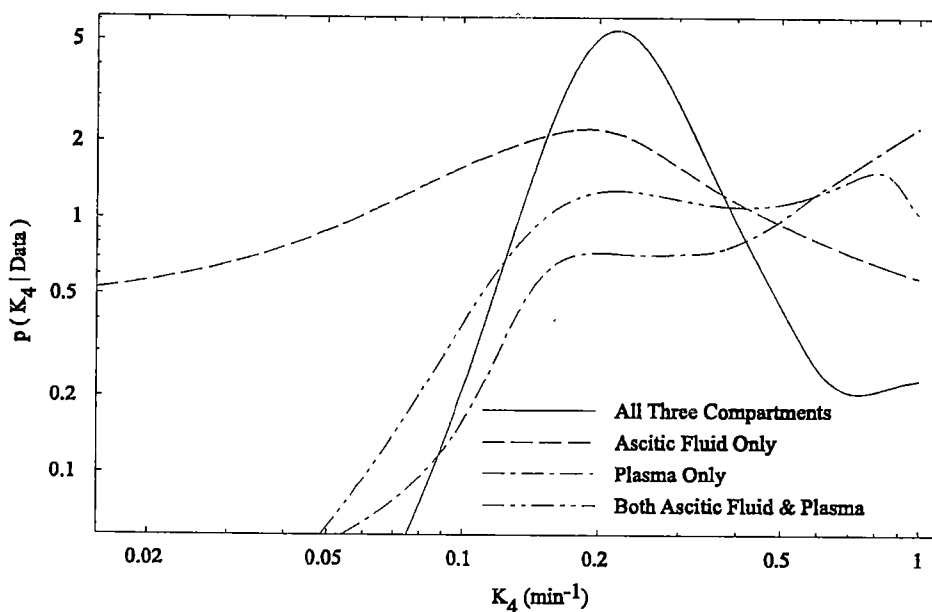


Figure 5.46. Normalized marginal posterior density for the human serum albumin exchange rate K_4 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

Table 5.10. Bayesian parameter estimates for the human serum albumin exchange rates calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

		Data From			
		Ascitic Fluid	Plasma	Ascitic Fluid and Plasma	All
Posterior Mean (1/day)	K ₁	0.2146 ± 0.0724	0.1798 ± 0.0401	0.173 ± 0.0235	0.1705 ± 0.0229
	K ₂	0.4587 ± 0.272	0.2057 ± 0.0626	0.2004 ± 0.0381	0.1428 ± 0.0606
	K ₃	0.5359 ± 0.297	0.3329 ± 0.289	0.3004 ± 0.134	0.2908 ± 0.13
	K ₄	0.3918 ± 0.271	0.6714 ± 0.256	0.5714 ± 0.271	0.3061 ± 0.176
Posterior Mode (1/day)	K ₁	0.168	0.152	0.171	0.165
	K ₂	0.208	0.232	0.202	0.124
	K ₃	0.898	None	0.422	0.242
	K ₄	0.188	None	0.808	0.218

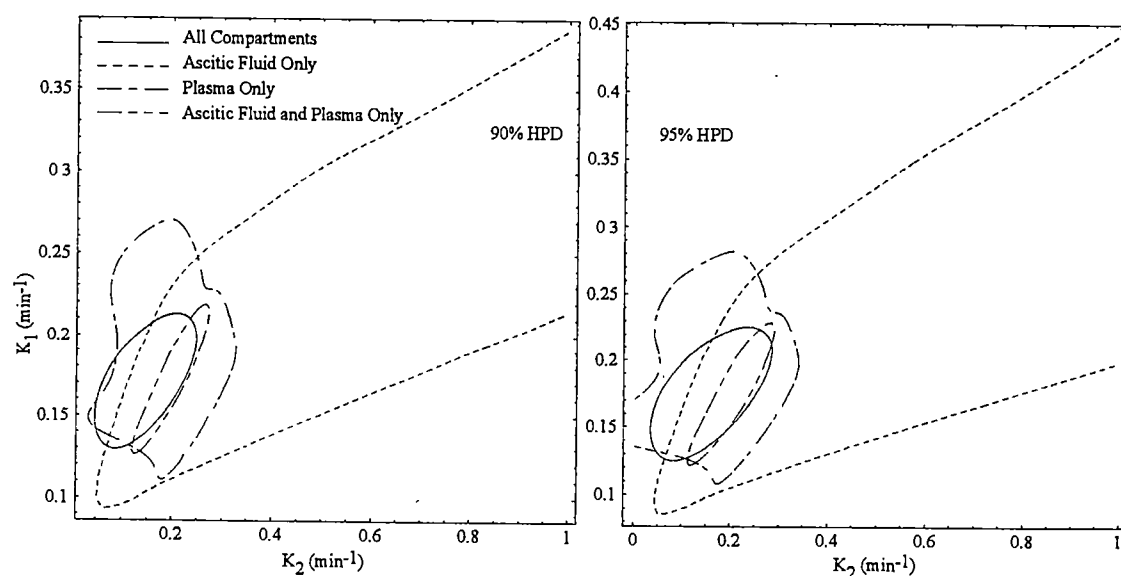


Figure 5.47. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K₁ and K₂ calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

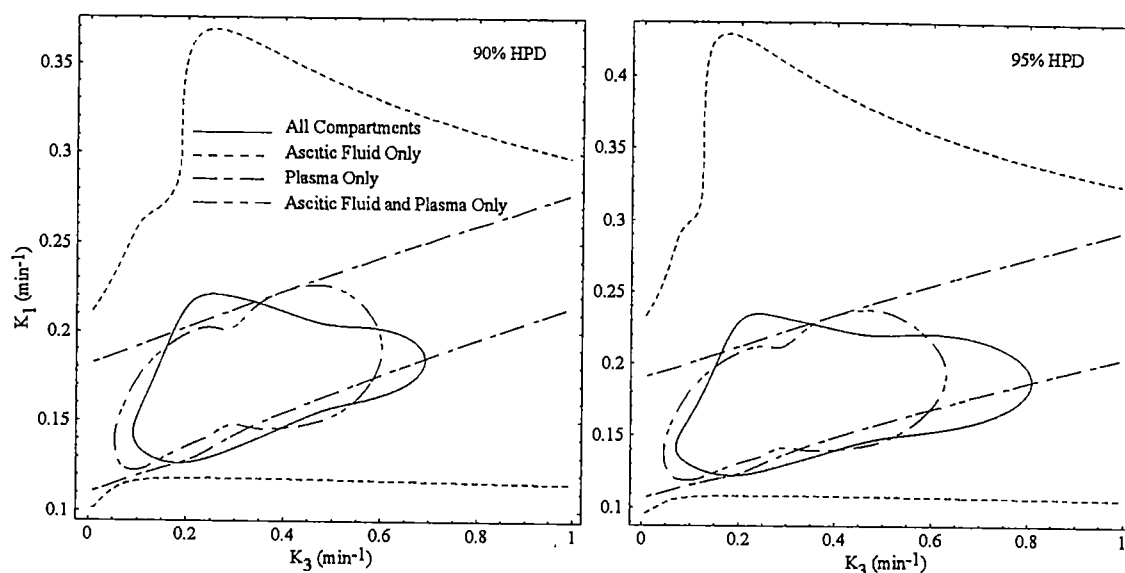


Figure 5.48. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_3 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

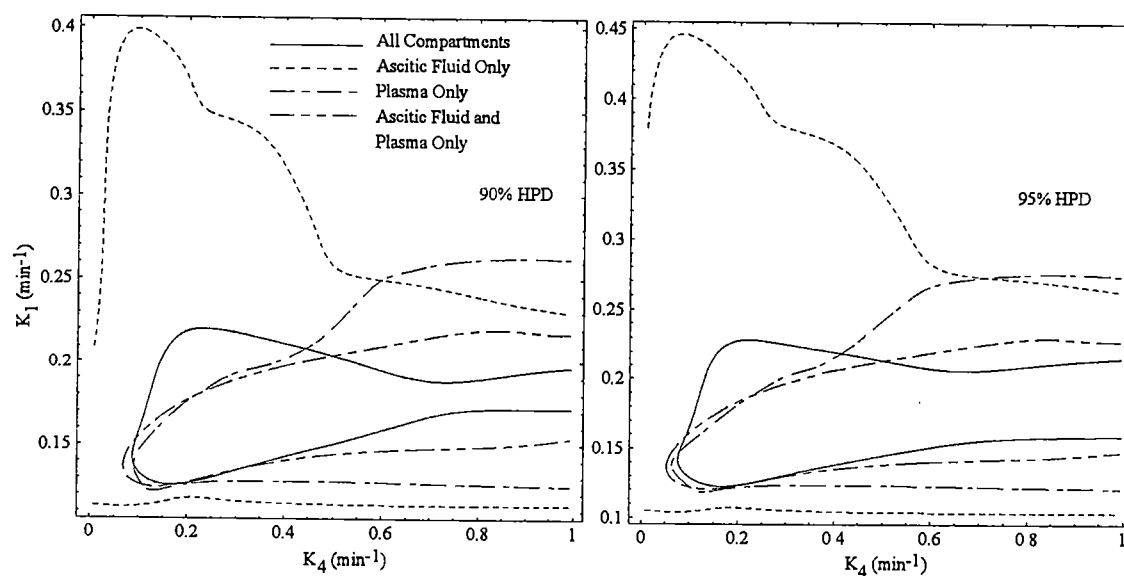


Figure 5.49. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_1 and K_4 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

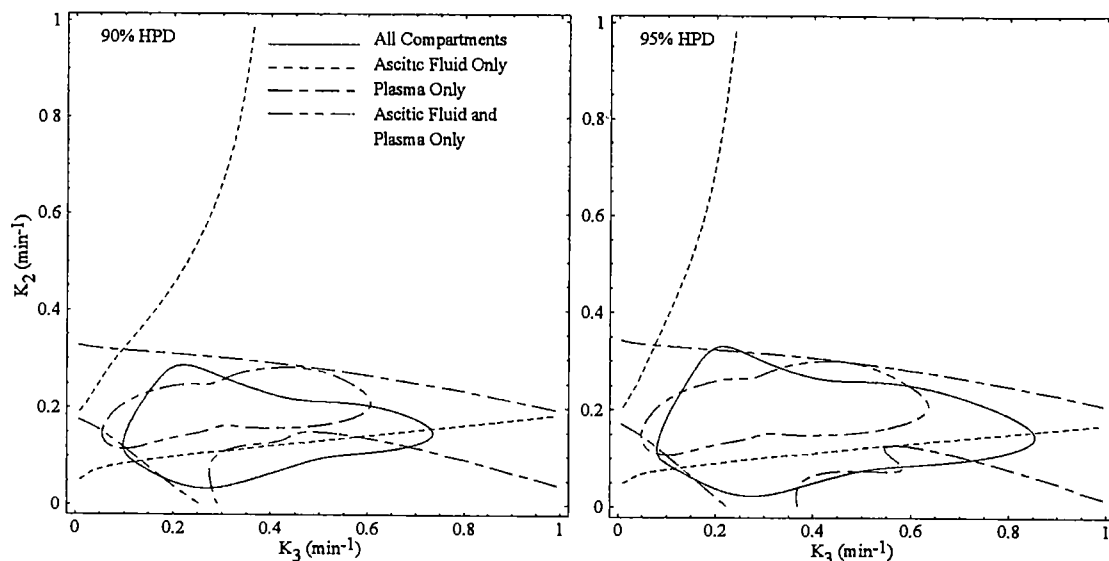


Figure 5.50. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_3 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

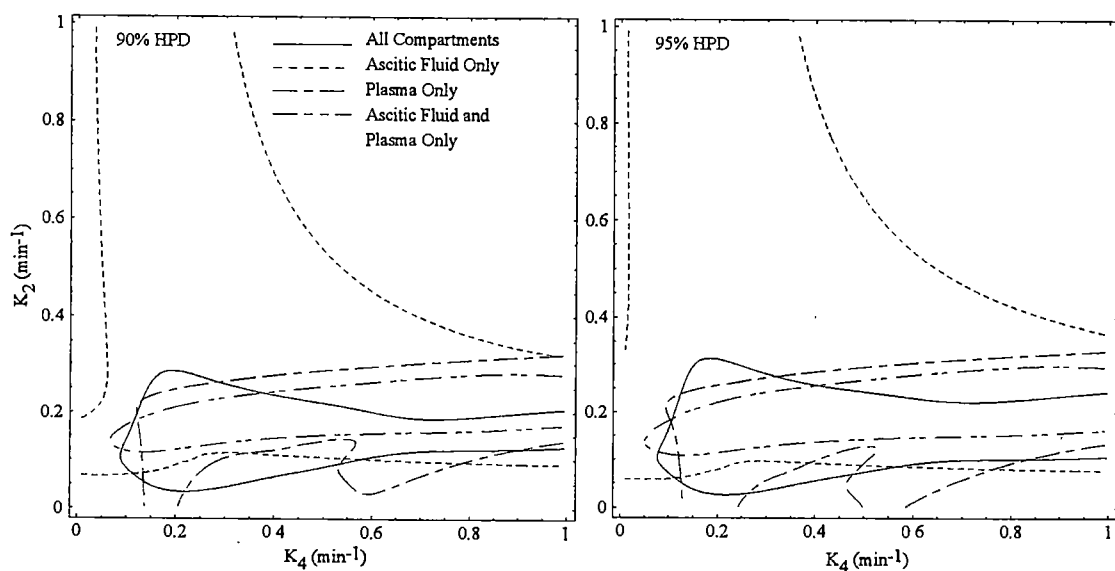


Figure 5.51. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_2 and K_4 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

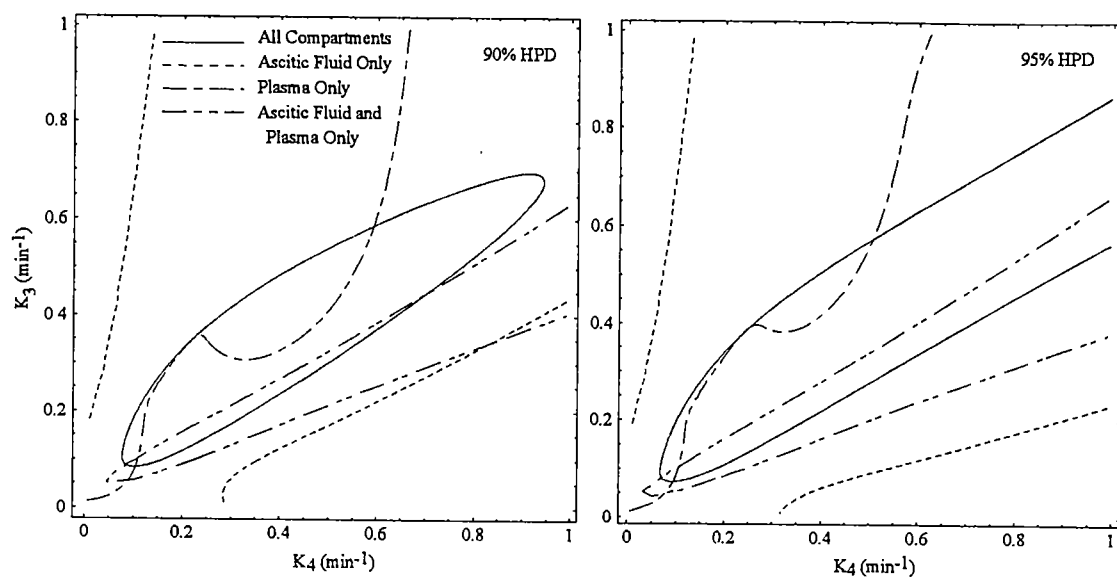


Figure 5.52. Ninety and ninety-five percent HPD contours for the human serum albumin exchange rates K_3 and K_4 calculated with uniform priors and iodoalbumin data from ascitic fluid, plasma, both ascitic fluid and plasma, or all three compartments.

CHAPTER 6

ESTIMATION OF THE HALF-LIVES OF ^{226}Rn , ^{222}Rn AND ^{218}Po

Although compartmental modeling is predominantly used to describe biological systems, other processes can also benefit from the marriage of compartmental modeling and Bayesian parameter estimation technique. One such process is the estimation of half-lives. Because radioactive decay is a random process, Bayes' Theorem can be used to describe the uncertainty of the estimated half-life. This is particularly helpful when the half-life to be estimated is significantly larger than the counting period and substantial estimation error due to random decay can occur. With this in mind, the following decay schemes were chosen:

- ^{226}Ra ($T_{1/2} \approx 1602$ years) $\rightarrow$ ^{222}Rn ($T_{1/2} \approx 3.8235$ days)
- ^{222}Rn ($T_{1/2} \approx 3.8235$ days) $\rightarrow$ ^{218}Po ($T_{1/2} \approx 3.05$ minutes)

where $T_{1/2}$ are the published half-life values. Discussions about the mathematical model and the simulated decay data are presented in sections 6.1 and 6.2, with the results of the analyses presented in sections 6.3 and 6.4.

6.1 *Mathematical Model*

The above mentioned parent – daughter decay scheme can be described by a two-compartment two-parameter system shown in Fig. 6.1. The number of parent atoms decreases with decay constant $\lambda_1 = \ln 2 / \text{parent half-life}$. The number of daughter atoms

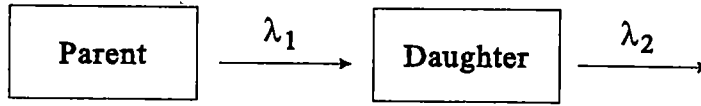


Figure 6.1. Parent – daughter decay scheme, where λ_i are the decay constants.

changes due to the buildup caused by the decay of the parent less than its own decay with decay constant $\lambda_2 = \ln 2 / \text{daughter half-life}$.

With constant decay rates, the differential equations describing the average number of parent (N_1) and daughter (N_2) atoms present are:

$$\begin{aligned}\frac{dN_1}{dt} &= -\lambda_1 N_1 \\ \frac{dN_2}{dt} &= \lambda_1 N_1 - \lambda_2 N_2\end{aligned}\tag{6.1}$$

If only N_{10} parent atoms are initially present, then the average number of parent and daughter atoms present can be expressed as:

$$\begin{aligned}N_1(\lambda_1, \lambda_2, t) &= N_{10} e^{-\lambda_1 t} \\ N_2(\lambda_1, \lambda_2, t) &= \frac{\lambda_1 N_{10}}{\lambda_2 - \lambda_1} \left(e^{-\lambda_1 t} - e^{-\lambda_2 t} \right)\end{aligned}\tag{6.2}$$

6.2 Simulated Decay Data

The two parent-daughter decay schemes examined here, see Fig. 6.2, are part of the larger uranium decay series. They were analyzed separately to show the effects of short counting intervals on the precision of the long half-life estimation.

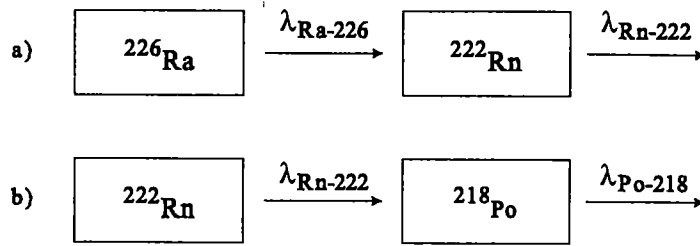


Figure 6.2. Parent – daughter decay schemes for (a) $^{226}\text{Ra} - ^{222}\text{Rn}$ and (b) $^{222}\text{Rn} - ^{218}\text{Po}$.

There are several methods to simulate decay data. The easiest way is to use the solutions of the differential equations, 100% counting efficiency, and the published half-lives to calculate the average number of parent and daughter atoms present. Since decay is a random process, Normal noise was added to simulate the statistical fluctuations. Let the mean of the Normal distribution be the number of atoms calculated from Eqn. (6.2), the next step is to determine its standard deviation.

Since in this example the parent half-life is longer than the daughter, the process for the build-up and decay of daughter atoms can be characterized approximately as a stochastic “immigration-death” process. For this model, the daughter atom is formed by the random decay of the parent at constant rate α , the parent’s decay rate. At the same time, each daughter nucleus present decays randomly at a constant rate μ , daughter’s decay rate. If $N(t)$ is the number of daughter atoms present at time t and $p_i(t)$ denotes the $\text{Prob}\{N(t) = i\}$, then the immigration-death differential-difference equation is (Cox and Miller, 1965):

$$p'_i(t) = -(\alpha + i\mu)p_i(t) + \mu(i+1)p_{i+1}(t) + \alpha p_{i-1}(t), \quad i = 0, 1, \dots \quad (6.3)$$

with the initial condition $p_0(t=0) = 1$. To solve Eqn. (6.3), we first transform it into the partial differential equation (p.d.e) describing the number of daughter atoms present:

$$\frac{\partial G(x,t)}{\partial t} = \alpha(x-1)G - \lambda(x-1)\frac{\partial G(x,t)}{\partial x}. \quad (6.4)$$

Since no daughter atom is initially present, the solution to the above p.d.e is:

$$G(x,t) = \exp\left[\frac{\alpha}{\lambda}(x-1)(1-e^{-\lambda t})\right]. \quad (6.5)$$

Finally, the MacLaurin series expansion is applied to Eqn. (6.5), and the probability of m daughter atom present at time t is (Lo, 1996):

$$p_m(t) = \frac{\left[\frac{\alpha}{\lambda}(1-e^{-\lambda t})\right]^m \exp\left[-\frac{\alpha}{\lambda}(1-e^{-\lambda t})\right]}{m!}. \quad (6.6)$$

The solution is a Poisson distribution where the variance equal the mean. Therefore, the standard deviation for the number of atoms present is equal to the square root of the mean.

Given the initial parent activity, the number of parent atoms initially present is:

$$N_{10} = \text{activity} \times \text{half-life} / \ln 2. \quad (6.7)$$

Assuming an initial activity of 10 pCi, the initial numbers of parent atoms for the two decay series are:

$$\begin{aligned} {}^{226}\text{Ra}: N_{10} &\approx 10 \text{ pCi} \times \frac{0.037 \text{ dps}}{\text{pCi}} \times \frac{31,536,000 \text{ sec}}{\text{year}} \times \frac{1602 \text{ years}}{\ln 2} \\ &\approx 2.697 \times 10^{10} \quad {}^{226}\text{Ra atoms} \end{aligned}$$

$$\begin{aligned} {}^{222}\text{Rn}: N_{10} &\approx 10 \text{ pCi} \times \frac{0.037 \text{ dps}}{\text{pCi}} \times \frac{86,400 \text{ sec}}{\text{day}} \times \frac{3.8235 \text{ days}}{\ln 2} \\ &\approx 176,340 \quad {}^{222}\text{Rn atoms} \end{aligned}$$

To make the Bayesian analysis easier, equal observation time intervals were used. For 24 data points, the number of parent and daughter atoms present subject to Normal random errors can be simulated using the following *Mathematica*[®] (Wolfram, 1998) commands:

```
<<Statistics`ContinuousDistributions`
ObservationTime=
  {1,2,3,4,5;6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24};
lambda1=Log[2]/parent_half-life;
lambda2=Log[2]/daughter_half-life;
N10=Initial_number_of_parent_atoms;
f1[t_]=N10*Exp[-lambda1*t];
f2[t_]=lambda1*N10*(Exp[-lambda1*t]-Exp[-lambda2*t])/(lambda2-lambda1);
mean1=f1[ObservationTime];
mean2=f2[ObservationTime];
sd1=Sqrt[mean1];
sd2=Sqrt[mean2];
ListParent=IntegerPart[Table[Random[
  NormalDistribution[mean1[[j]],sd1[[j]]]],{j,1,24}]];
ListDaughter=IntegerPart[Table[Random[
  NormalDistribution[mean2[[j]],sd2[[j]]]],{j,1,24}]]];
```

The command `<<Statistics`ContinuousDistributions`` loads the continuous statistical distributions library that contains the definition for a Normal density, and `IntegerPart[]` is used to keep the integer portion of the results to represent the number of atoms present. Most importantly, the half-lives and the observation times must have the same units. For example, the data are observed daily for the decay of ²²⁶Ra – ²²²Rn and hourly for ²²²Rn – ²¹⁸Po. Therefore, the half-lives used are in days and hours, respectively. Substituting the appropriate initial number of parent atoms and the published half-lives, examples of the simulated decay data sets are listed in Tables 6.1.

Table 6.1. Simulated radioactive decay data based on an initial parent activity of 10pCi and Normal random error. Observation times are in days for $^{226}\text{Ra} - ^{222}\text{Rn}$ and in hours for $^{222}\text{Rn} - ^{218}\text{Po}$.

Time	$^{226}\text{Ra} - ^{222}\text{Rn}$: Number of atoms		$^{222}\text{Rn} - ^{218}\text{Po}$: Number of atoms	
	^{226}Ra	^{222}Rn	^{222}Rn	^{218}Po
0	26,934,123,839	0	176,340	0
1	26,934,242,493	29,368	175,165	104
2	26,934,285,561	53,903	174,019	115
3	26,934,288,634	74,198	171,540	113
4	26,934,157,529	90,755	171,281	102
5	26,934,109,447	105,268	170,131	94
6	26,933,963,429	117,655	168,537	100
7	26,933,930,675	126,735	166,867	103
8	26,933,704,934	134,602	165,908	103
9	26,933,959,160	141,549	164,849	100
10	26,933,973,982	147,832	163,961	100
11	26,933,922,878	151,763	162,958	92
12	26,933,350,907	155,811	161,186	76
13	26,933,815,292	159,411	160,626	93
14	26,933,545,612	162,285	159,329	71
15	26,933,812,418	163,935	156,608	92
16	26,933,329,557	166,362	156,506	76
17	26,933,678,861	168,222	155,140	76
18	26,933,480,669	169,279	154,087	65
19	26,933,450,436	171,038	152,679	71
20	26,933,207,425	171,781	151,451	77

6.3 Analysis of Simulated Data

Radioactive decay is random and requires repeated samplings to obtain an acceptable half-life value. Therefore, it is convenient to represent the results of the analyses, the estimated half-lives, by a frequency distribution function or histogram. In this analysis, 500 data sets were simulated for each of the two decay series using the methods described in section 6.2.

Since estimation precision depends on the amount of data used and all three nuclides decay by alpha emissions, two observation scenarios were examined: using the number of parent and daughter atoms separately or lumped together. This correspond to the availability and the use of alpha spectroscopy to the discriminate alpha energies. Samples of the data sets used are given in Appendix C.

Assuming uniform priors, the joint posterior density for the decay constants λ_1 and λ_2 with 24 data points observed independently is:

$$p(\lambda_1, \lambda_2 | data) \propto [S_{11}(\theta) S_{22}(\theta) - S_{12}(\theta)^2]^{-12} \quad (6.8)$$

where

$$S_{11}(\theta) = \sum_{u=1}^{24} [\gamma_{u1} - \mathcal{N}_1(\lambda_1, \lambda_2, t_u)]^2$$

$$S_{22}(\theta) = \sum_{u=1}^{24} [\gamma_{u2} - \mathcal{N}_2(\lambda_1, \lambda_2, t_u)]^2$$

$$S_{12}(\theta) = \sum_{u=1}^{24} [\gamma_{u1} - \mathcal{N}_1(\lambda_1, \lambda_2, t_u)] \cdot [\gamma_{u2} - \mathcal{N}_2(\lambda_1, \lambda_2, t_u)]$$

y_{u1} and y_{u2} are the number of parent and daughter atoms present at time t_u , respectively, and N_i are the solution of the differential equations, Eqn. (6.2). When lumped decay data are used, the joint posterior density is simplified to:

$$p(\lambda_1, \lambda_2 | data) \propto S(\theta)^{-12} \quad (6.9)$$

where

$$S(\theta) = \sum_{u=1}^{24} [y_{u1} + y_{u2} - N_1(\lambda_1, \lambda_2, t_u) - N_2(\lambda_1, \lambda_2, t_u)]^2.$$

As for the integration limits of λ_i , limits zero to ($5 \times$ published decay constant _{i}) were used. Furthermore, the limits were adjusted to have the same units as the observation times. That is, day⁻¹ for ²²⁶Ra – ²²²Rn and hour⁻¹ for ²²²Rn – ²¹⁸Po:

$$^{226}\text{Ra} - ^{222}\text{Rn}: ^{226}\text{Ra}: 5 \times \ln 2 / (1602 \text{ years} \times 365 \text{ day}) \approx 0.000006 \text{ day}^{-1}$$

$$^{222}\text{Rn}: 5 \times \ln 2 / (3.8235 \text{ day}) \approx 1.0 \text{ day}^{-1}$$

$$^{222}\text{Rn} - ^{218}\text{Po}: ^{222}\text{Rn}: 5 \times \ln 2 / (3.8235 \text{ day} \times 24 \text{ hour/day}) \approx 0.04 \text{ hour}^{-1}$$

$$^{218}\text{Po}: 5 \times \ln 2 / (3.05 \text{ minutes} \times \text{hour}/60 \text{ minutes}) \approx 70 \text{ hour}^{-1}$$

6.3.1 Decay of ²²⁶Ra to ²²²Rn

Using Eqn. (6.8), the posterior means (PM) and standard deviations (SD) for each of the 500 simulated ²²⁶Ra – ²²²Rn data sets were calculated and partially listed in Appendix C. The frequency distribution of the posterior mean for the ²²⁶Ra and ²²²Rn half-lives, calculated using individual compartment data, are listed in Tables 6.2 and 6.3,

Table 6.2. Frequency table of the posterior mean for the ^{226}Ra half-lives in years for 500 simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data. They are given in the format of (bin midpoint, frequency). The average of the posterior mean of the half-life is 1599.86 ± 2.89 years.

(1585.63, 1)	(1586.26, 0)	(1586.89, 0)	(1587.52, 0)	(1588.15, 1)	(1588.78, 0)
(1589.41, 0)	(1590.04, 1)	(1590.67, 0)	(1591.30, 4)	(1591.93, 3)	(1592.56, 6)
(1593.19, 6)	(1593.81, 8)	(1594.44, 6)	(1595.07, 6)	(1595.70, 10)	(1596.33, 33)
(1596.96, 14)	(1597.59, 14)	(1598.22, 10)	(1598.85, 19)	(1599.48, 11)	(1600.11, 23)
(1600.74, 38)	(1601.37, 52)	(1602.00, 107)	(1602.63, 119)	(1603.26, 2)	(1603.89, 1)
(1604.52, 1)	(1605.15, 0)	(1605.78, 1)	(1606.41, 1)	(1607.04, 0)	(1607.67, 1)
(1608.30, 0)	(1608.93, 0)	(1609.56, 0)	(1610.18, 0)	(1610.81, 0)	(1611.44, 0)
(1612.07, 0)	(1612.70, 0)	(1613.33, 0)	(1613.96, 0)	(1614.59, 0)	(1615.22, 0)
(1615.85, 0)	(1616.48, 0)	(1617.11, 1)			

Table 6.3. Frequency table of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data. They are given in the format of (bin midpoint, frequency). The average of the posterior mean of the half-life is 3.8251 ± 0.0096 days.

(3.7768, 1)	(3.7786, 0)	(3.7804, 0)	(3.7822, 0)	(3.7839, 0)	(3.7857, 0)
(3.7875, 0)	(3.7893, 0)	(3.7911, 1)	(3.7929, 0)	(3.7947, 3)	(3.7965, 2)
(3.7983, 4)	(3.8001, 4)	(3.8018, 8)	(3.8036, 22)	(3.8054, 13)	(3.8072, 14)
(3.8090, 11)	(3.8108, 7)	(3.8126, 11)	(3.8144, 6)	(3.8162, 9)	(3.8179, 10)
(3.8197, 11)	(3.8215, 6)	(3.8233, 8)	(3.8251, 16)	(3.8269, 18)	(3.8287, 21)
(3.8305, 30)	(3.8323, 58)	(3.8341, 109)	(3.8358, 91)	(3.8376, 1)	(3.8394, 2)
(3.8412, 0)	(3.8430, 0)	(3.8448, 1)	(3.8466, 0)	(3.8484, 0)	(3.8502, 0)
(3.8519, 0)	(3.8537, 1)	(3.8555, 0)	(3.8573, 0)	(3.8591, 0)	(3.8609, 0)
(3.8627, 0)	(3.8645, 0)	(3.8663, 1)			

and are plotted in Figs. 6.3 and 6.4. Also listed in the figures and tables are the average of the 500 posterior means and standard deviations. Sample calculations for the average of the posterior mean and standard deviation for the ^{226}Ra half-life calculated with independent compartmental data (see Appendix C) are:

$$\text{Average PM} = \sum \text{PM}_i / 500 = (1596.14 + 1600.56 + \dots) / 500 = 1599.86 \text{ years}$$

$$\text{Average SD} = \sum \text{SD}_i / 500 = (3.41198 + 2.84396 + \dots) / 500 = 2.89 \text{ years}$$

The spread of the frequency distribution is narrow and skewed to the left of the mode: 1602.5 years for ^{226}Ra and 3.834 days for ^{222}Rn . Considering the large difference between the parent half-life and observation intervals, the average mean half-lives were very close to the published values: 1599.86 ± 2.89 years for ^{226}Ra and 3.8251 ± 0.0096 days for ^{222}Rn . Because the highest frequency also occurred around the published half-lives used to generate the data sets, this indicates that the Box – Draper parameter estimation technique is working properly.

When the analyses were repeated using lumped compartmental data and Eqn. (6.9), the estimates were imprecise. The resulting frequency distributions of the posterior mean of the ^{226}Ra and ^{222}Rn half-lives are listed in Tables 6.4 and 6.5, and plotted in Figs. 6.5 and 6.6. The frequency distributions spreads are widen and centered around 1480 years for ^{226}Ra and around 1.4 days for ^{222}Rn . This increased the average mean half-lives and standard deviations to 1707.01 ± 531.5 years for ^{226}Ra and 5.5646 ± 7.0933 days for ^{222}Rn .

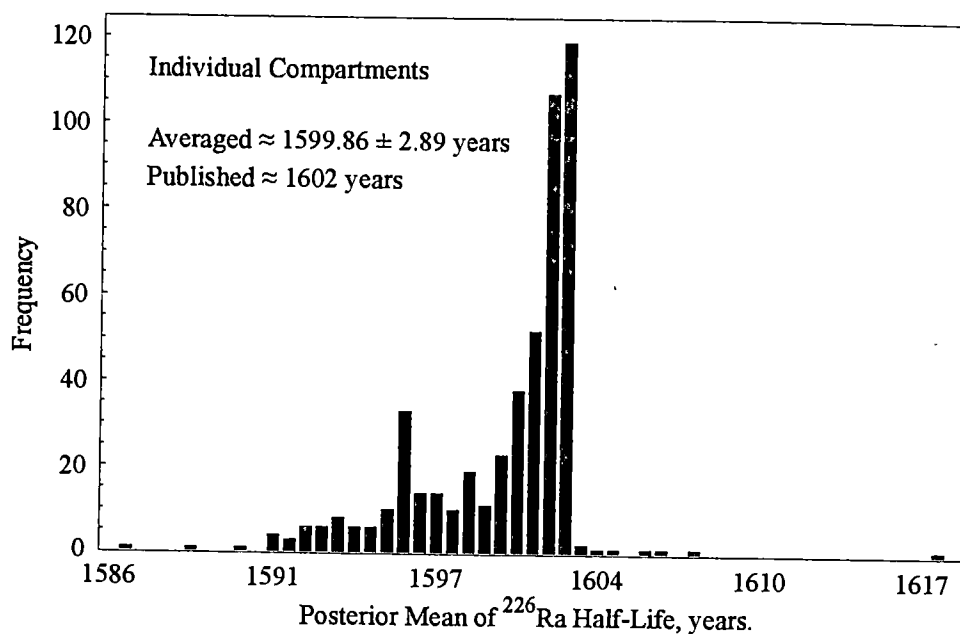


Figure 6.3. Histogram of the posterior mean for the ^{226}Ra half-lives in years for 500 simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data. The average of the posterior mean of the half-life is 1599.86 ± 2.89 years.

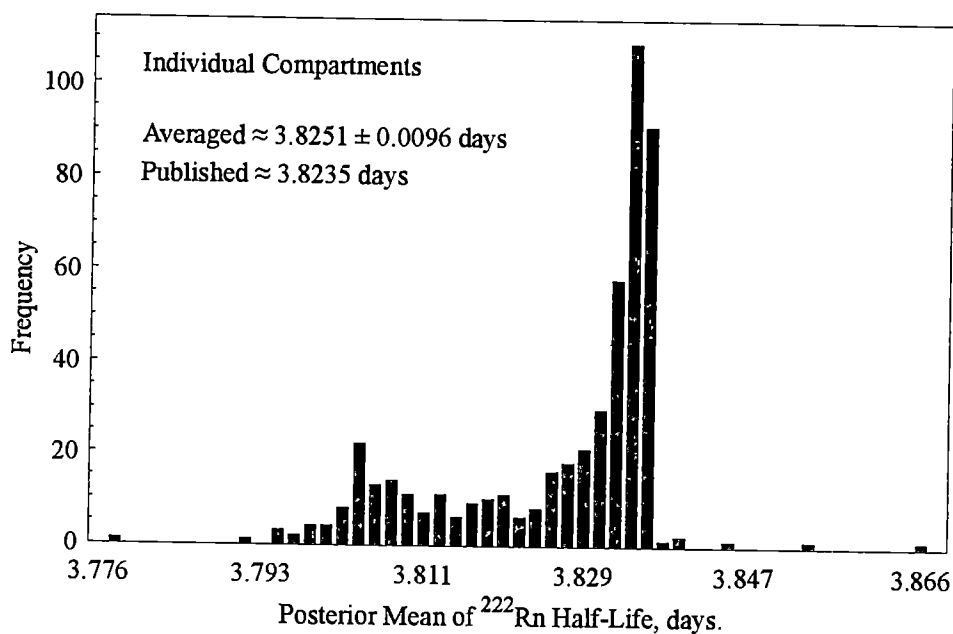


Figure 6.4. Histogram of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data. The average of the posterior mean of the half-life is 3.8251 ± 0.0096 days.

Table 6.4. Frequency table of the posterior mean for the ^{226}Ra half-lives in years for 500 simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data. They are given in the format of (bin midpoint, frequency). The average of the posterior mean of the half-life is 1707.01 ± 531.5 years.

(555.67, 1)	(591.34, 2)	(627.01, 1)	(662.68, 2)	(698.35, 3)	(734.02, 4)
(769.69, 4)	(805.37, 8)	(841.04, 6)	(876.71, 7)	(912.38, 5)	(948.05, 8)
(983.72, 8)	(1019.39, 10)	(1055.06, 12)	(1090.73, 11)	(1126.40, 8)	(1162.07, 14)
(1197.74, 10)	(1233.41, 20)	(1269.08, 11)	(1304.76, 15)	(1340.43, 13)	(1376.10, 18)
(1411.77, 20)	(1447.44, 21)	(1483.11, 23)	(1518.78, 20)	(1554.45, 18)	(1590.12, 14)
(1625.79, 20)	(1661.46, 15)	(1697.13, 16)	(1732.80, 14)	(1768.47, 25)	(1804.14, 15)
(1839.82, 13)	(1875.49, 11)	(1911.16, 12)	(1946.83, 5)	(1982.50, 10)	(2018.17, 8)
(2053.84, 5)	(2089.51, 4)	(2125.18, 2)	(2160.85, 2)	(2196.52, 2)	(2232.19, 2)
(2267.86, 1)	(2303.53, 0)	(2339.21, 1)			

Table 6.5. Frequency table of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data. They are given in the format of (bin midpoint, frequency). The average of the posterior mean of the half-life is 5.5646 ± 7.0933 days.

(1.2177, 53)	(1.4855, 126)	(1.7532, 102)	(2.0210, 65)	(2.2887, 43)	(2.5565, 23)
(2.8242, 22)	(3.0920, 14)	(3.3597, 5)	(3.6275, 9)	(3.8952, 5)	(4.1630, 10)
(4.4307, 4)	(4.6984, 1)	(4.9662, 1)	(5.2339, 1)	(5.5017, 2)	(5.7694, 2)
(6.0372, 1)	(6.3049, 2)	(6.5727, 2)	(6.8404, 0)	(7.1082, 3)	(7.3759, 0)
(7.6437, 0)	(7.9114, 0)	(8.1791, 0)	(8.4469, 1)	(8.7146, 0)	(8.9824, 0)
(9.2501, 0)	(9.5179, 0)	(9.7856, 0)	(10.0534, 1)	(10.3211, 0)	(10.5889, 1)
(10.8566, 0)	(11.1244, 0)	(11.3921, 0)	(11.6598, 0)	(11.9276, 0)	(12.1953, 0)
(12.4631, 0)	(12.7308, 0)	(12.9986, 0)	(13.2663, 0)	(13.5341, 0)	(13.8018, 0)
(14.0696, 0)	(14.3373, 0)	(14.6051, 1)			

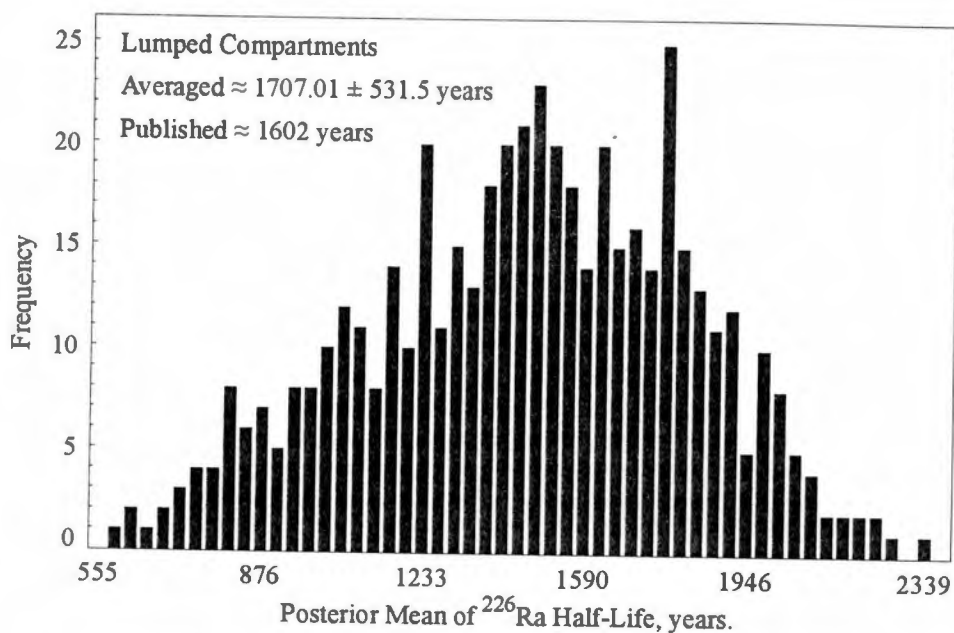


Figure 6.5. Histogram of the posterior mean for the ^{226}Ra half-lives in years for 500 simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data. The average of the posterior mean of the half-life is 1707.01 ± 531.5 years.

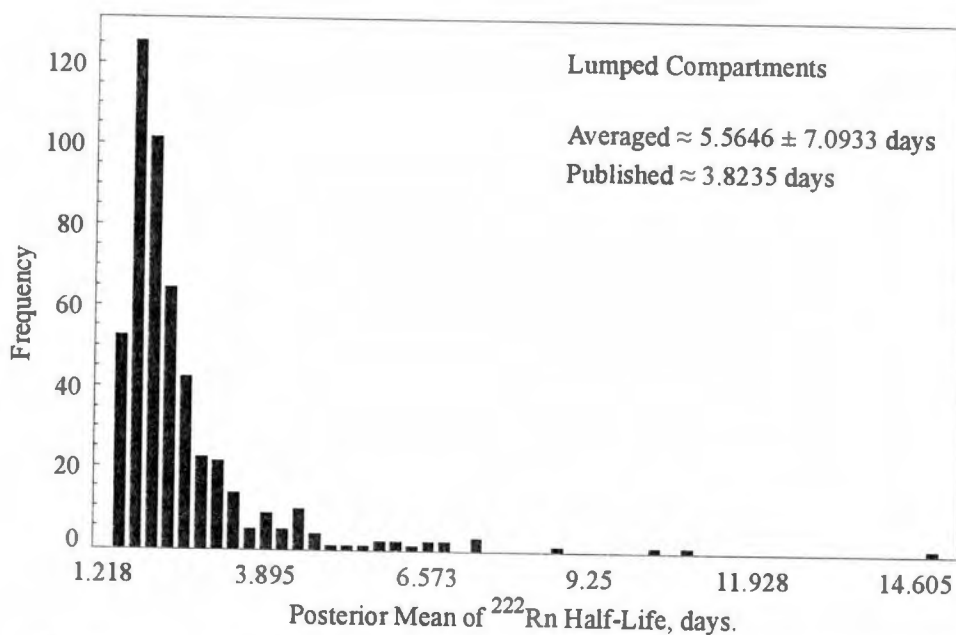


Figure 6.6. Histogram of the posterior mean of the ^{222}Rn half-lives in days for 500 simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data. The average of the posterior mean of the half-life is 5.5646 ± 7.0933 days.

6.3.2 Decay of ^{222}Rn to ^{218}Po

For the decay of ^{222}Rn to ^{218}Po , the results were better than for the decay of ^{226}Ra to ^{222}Rn . This is because the data are observed hourly and the changes in the activities are easily detectable. Whereas in the previous analysis, daily observation maybe insufficient to see any changes in the ^{226}Ra 's activity, whose half-life is about 1602 years. The frequency distributions of the posterior mean for the ^{222}Rn and ^{218}Po half-lives, calculated from individual compartmental observations, are listed in Tables 6.6 and 6.7, and plotted in Figs. 6.7 and 6.8. Centered around 3.822 days, the spread of the ^{222}Rn posterior mean half-lives is narrow. It gave an average posterior mean half-life of about 3.8229 ± 0.0193 days, very close to the published/input value of 3.8235 days. On the other hand, the frequency distribution of the ^{218}Po half-lives is spread widely around 3.02 minutes with an average posterior mean half-life of about 3.0318 ± 0.0708 minutes.

When the analyses were repeated using lumped compartmental data and Eqn. (6.5), the results were mixed. The frequency distributions of the posterior mean for the ^{222}Rn and ^{218}Po half-lives are listed in Tables 6.8 and 6.9, and plotted in Figs. 6.9 and 6.10. Although the data were lumped together, the ^{222}Rn half-life results were good. It gave an average posterior mean half-life of about 3.8276 ± 0.0234 days with the frequency distribution centered around 3.82 days. The results for the ^{218}Po half-life were imprecise. The frequency distribution is skewed to the right of the mode (1.7 minutes), and gave us an average posterior mean half-life is about 2.197 ± 2.078 minutes.

Table 6.6. Frequency table of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data. They are given in the format of (bin midpoint, frequency). The average of the posterior mean of the half-life is 3.8229 ± 0.0193 days.

(3.7809, 3)	(3.7839, 7)	(3.7868, 6)	(3.7898, 3)	(3.7927, 11)	(3.7957, 6)
(3.7986, 3)	(3.8016, 11)	(3.8045, 14)	(3.8075, 14)	(3.8104, 21)	(3.8133, 23)
(3.8163, 28)	(3.8192, 44)	(3.8222, 81)	(3.8251, 61)	(3.8281, 35)	(3.8310, 19)
(3.8340, 9)	(3.8369, 11)	(3.8398, 17)	(3.8428, 15)	(3.8457, 5)	(3.8487, 4)
(3.8516, 7)	(3.8546, 7)	(3.8575, 4)	(3.8605, 11)	(3.8634, 2)	(3.8664, 3)
(3.8693, 3)	(3.8722, 5)	(3.8752, 6)	(3.8781, 0)	(3.8811, 0)	(3.8840, 0)
(3.8870, 0)	(3.8899, 0)	(3.8929, 0)	(3.8958, 0)	(3.8987, 0)	(3.9017, 0)
(3.9046, 0)	(3.9076, 0)	(3.9105, 0)	(3.9135, 0)	(3.9164, 0)	(3.9194, 0)
(3.9223, 0)	(3.9253, 0)	(3.9282, 1)			

Table 6.7. Frequency table of the posterior mean for the ^{218}Po half-lives in minutes for 500 simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data. They are given in the format of (bin midpoint, frequency). The average of the posterior mean of the half-life is 3.0318 ± 0.0708 minutes.

(2.8438, 1)	(2.8526, 0)	(2.8614, 0)	(2.8703, 2)	(2.8791, 5)	(2.8879, 2)
(2.8967, 7)	(2.9055, 3)	(2.9143, 3)	(2.9231, 6)	(2.9319, 8)	(2.9408, 12)
(2.9496, 7)	(2.9584, 17)	(2.9672, 20)	(2.9760, 24)	(2.9848, 16)	(2.9936, 28)
(3.0025, 25)	(3.0113, 20)	(3.0201, 32)	(3.0289, 23)	(3.0377, 24)	(3.0465, 25)
(3.0553, 17)	(3.0642, 15)	(3.0730, 14)	(3.0818, 28)	(3.0906, 13)	(3.0994, 21)
(3.1082, 20)	(3.1170, 9)	(3.1258, 11)	(3.1347, 3)	(3.1435, 5)	(3.1523, 6)
(3.1611, 4)	(3.1699, 6)	(3.1787, 1)	(3.1875, 6)	(3.1964, 3)	(3.2052, 3)
(3.2140, 1)	(3.2228, 1)	(3.2316, 1)	(3.2404, 0)	(3.2492, 0)	(3.2581, 0)
(3.2669, 0)	(3.2757, 1)	(3.2845, 1)			

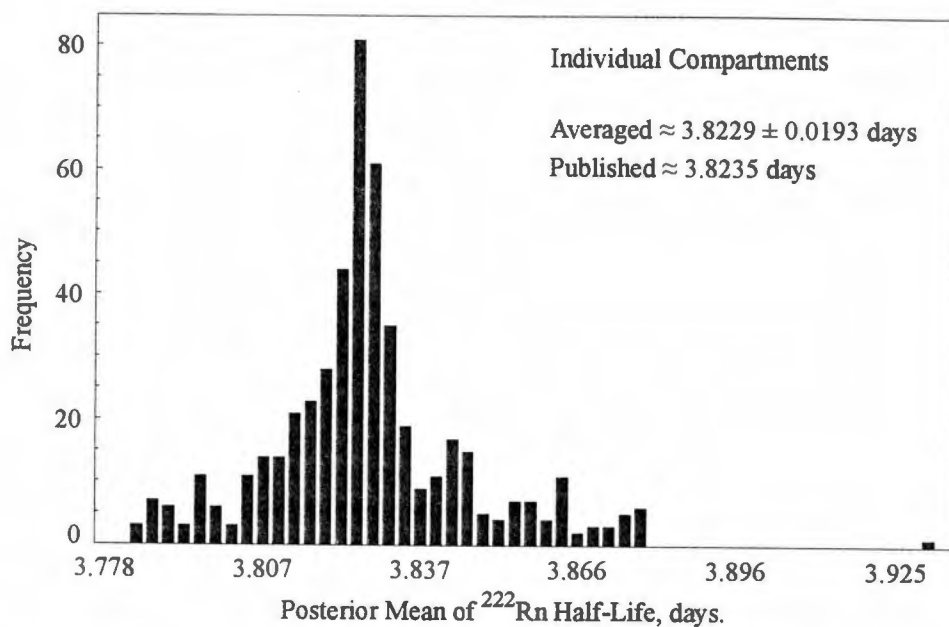


Figure 6.7. Histogram of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data. The average of the posterior mean of the half-life is 3.8229 ± 0.0193 days.

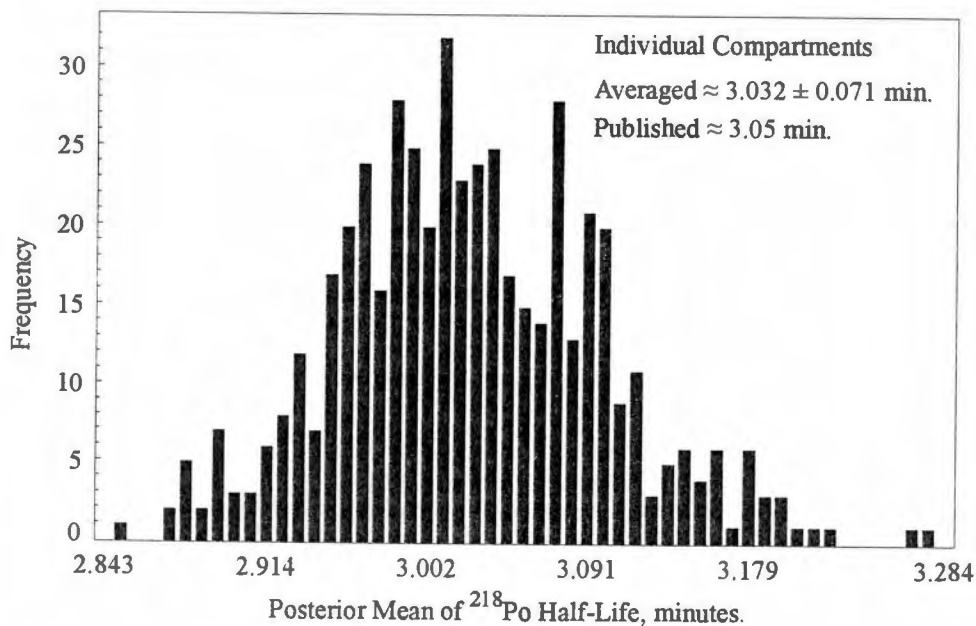


Figure 6.8. Histogram of the posterior mean for the ^{218}Po half-lives in minutes for 500 simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data. The average of the posterior mean of the half-life is 3.032 ± 0.071 minutes.

Table 6.8. Frequency table of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data. They are given in the format of (bin midpoint, frequency). The average of the posterior mean of the half-life is 3.8276 ± 0.0234 minutes.

(3.7457, 1)	(3.7495, 0)	(3.7532, 0)	(3.7569, 0)	(3.7606, 0)	(3.7644, 0)
(3.7681, 1)	(3.7718, 0)	(3.7755, 0)	(3.7793, 0)	(3.7830, 3)	(3.7867, 1)
(3.7905, 8)	(3.7942, 8)	(3.7979, 8)	(3.8016, 9)	(3.8054, 10)	(3.8091, 20)
(3.8128, 25)	(3.8166, 27)	(3.8203, 56)	(3.8240, 72)	(3.8277, 47)	(3.8315, 35)
(3.8352, 31)	(3.8389, 21)	(3.8426, 14)	(3.8464, 13)	(3.8501, 15)	(3.8538, 13)
(3.8576, 15)	(3.8613, 10)	(3.8650, 9)	(3.8687, 16)	(3.8725, 5)	(3.8762, 6)
(3.8799, 0)	(3.8836, 0)	(3.8874, 0)	(3.8911, 0)	(3.8948, 0)	(3.8986, 0)
(3.9023, 0)	(3.9060, 0)	(3.9097, 0)	(3.9135, 0)	(3.9172, 0)	(3.9209, 0)
(3.9247, 0)	(3.9284, 0)	(3.9321, 1)			

Table 6.9. Frequency table of the posterior mean for the ^{218}Po half-lives in minutes for 500 simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data. They are given in the format of (bin midpoint, frequency). The average of the posterior mean of the half-life is 2.197 ± 2.078 minutes.

(1.3056, 31)	(1.5292, 86)	(1.7529, 107)	(1.9765, 87)	(2.2001, 47)	(2.4237, 39)
(2.6474, 20)	(2.8710, 14)	(3.0946, 11)	(3.3182, 6)	(3.5418, 6)	(3.7655, 5)
(3.9891, 4)	(4.2127, 3)	(4.4363, 5)	(4.6600, 4)	(4.8836, 1)	(5.1072, 4)
(5.3308, 1)	(5.5544, 2)	(5.7781, 2)	(6.0017, 3)	(6.2253, 2)	(6.4489, 2)
(6.6726, 2)	(6.8962, 0)	(7.1198, 1)	(7.3434, 0)	(7.5670, 0)	(7.7907, 0)
(8.0143, 0)	(8.2379, 0)	(8.4615, 0)	(8.6852, 0)	(8.9088, 1)	(9.1324, 1)
(9.3560, 0)	(9.5796, 0)	(9.8033, 0)	(10.0269, 1)	(10.2505, 0)	(10.4741, 0)
(10.6978, 0)	(10.9214, 0)	(11.1450, 0)	(11.3686, 0)	(11.5922, 1)	(11.8159, 0)
(12.0395, 0)	(12.2631, 0)	(12.4867, 1)			

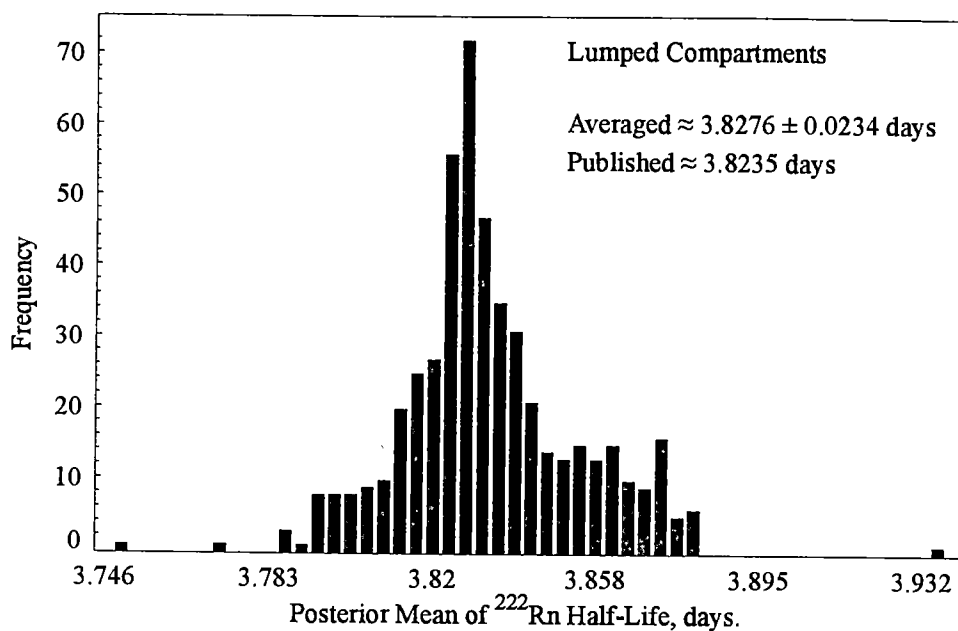


Figure 6.9. Histogram of the posterior mean for the ^{222}Rn half-lives in days for 500 simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data. The average of the posterior mean of the half-life is 3.8276 ± 0.0234 days.

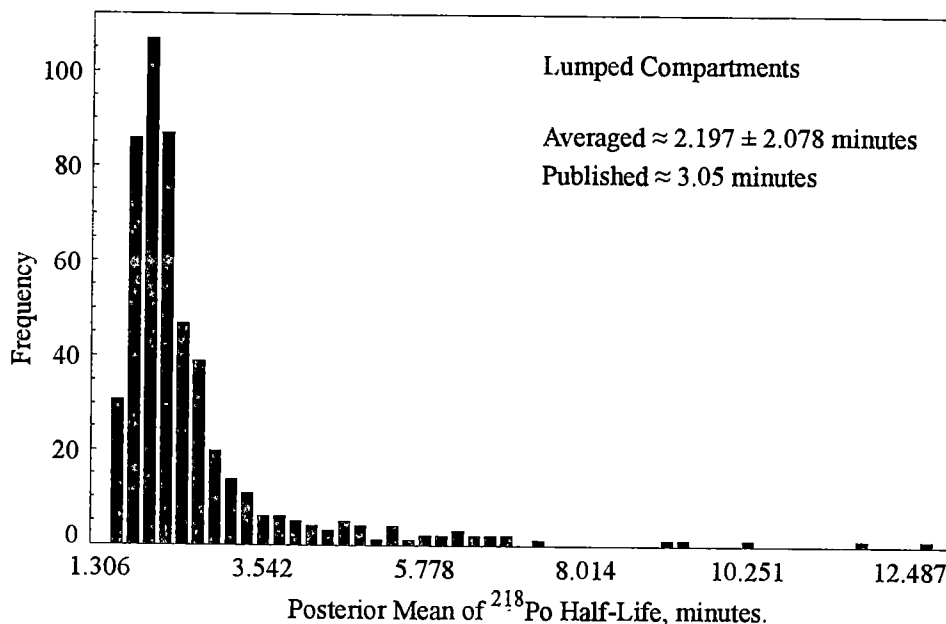


Figure 6.10. Histogram of the posterior mean for the ^{218}Po half-lives in minutes for 500 simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data. The average of the posterior mean of the half-life is 2.197 ± 2.078 minutes.

Finally, we showed that radioactive decay can be described using compartmental models and the radioactive half-life estimated using Box and Draper method. As with any estimation procedures, the amount of data and the observation interval is important. Instead of histograms, traditional Bayesian plots, such as marginal posterior densities, can also be used to examine individual data set, if desired. As always, the most precise estimates were obtained using independent compartmental data. However, the estimates for the short-lived isotopes were reasonably precise when calculated using lumped decay data with short counting interval.

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE WORK

This dissertation described and demonstrated the use of Bayes' Theorem, with the Box and Draper likelihood, to estimate the parameters of compartmental models. This method is a good replacement for current "ad hoc" parameter estimation methods. It has several novel features that improve parameter estimation. One such feature is that the estimation uncertainty is given by the posterior probability density, which cannot be derived with standard methods. Secondly, information from previous analyses and/or expert judgement can be incorporated using prior probability densities. Another novel feature is the use of highest posterior densities (HPD) contours to characterize the uncertainty of parameter pairs. This provides additional information about the parameter estimation with reduced data and/or different models. In situations where open contours are present, the estimation variances are large and can sometime be infinite.

We first provided background information on the compartmental model and the theoretical concepts used. Next, the procedure was applied to examples in biology and physics: the exchange of calcium at bone surfaces in beagles, human cerebral glucose metabolism, the exchange of serum albumin in human, and the estimation of ^{226}Ra , ^{222}Rn and ^{218}Po half-lives from simulated decay data. In addition, different reduced data sets were also examined for each model to show parameter estimation with limited data.

In summary, the Bayesian parameter estimation technique was applied to two and three-compartment models. The presence of bimodality and "divergent" behavior in the

posterior densities for the biokinetic models was unanticipated. They are due to the likelihood and can be changed using prior information and/or the different data sets. For the bone calcium study, the divergent behavior was eliminated when Normal priors were used. However, the Normal priors also introduced bimodality for all three parameters and made the posterior densities more complicated.

For the cerebral glucose metabolism study, the results were poor. Since the biokinetic model used is widely accepted, we question the quality of the clinical data. Another interesting behavior was observed in the exchange of serum albumin analysis. The exclusion of the extravascular space data increased the estimation precision in three of the four parameters, as indicated by the smaller HPD contours, not diminished it as one generally would expect. This could mean that the extravascular space data are imprecise or that an inappropriate model was used.

Finally, we showed that compartmental model can be used to describe radioactive decay and the half-life estimated using Box and Draper method. The estimation precision is sensitive to the amount of data and the length of the observation interval. Generally, the most precise estimates were obtained using data from individual compartments. However, reasonably precise half-lives were estimated for the short-lived radon daughters using lumped decay data and short counting interval.

In conclusion, we understand that the likelihood is the main cause of bimodality and divergent behavior found in the analyses. The following research is proposed to further analyze the behavior of the Box and Draper parameter estimation method.

1). Verification of the cerebral glucose metabolism model. Since the model used is widely accepted and our analysis of the clinical data gave poor fits, additional analyses of the clinical data are needed to determine the validity of the model.

2). Prediction of compartmental concentrations. The joint posterior density of the parameters can be used to predict missing observation or compartmental concentration at arbitrary time to verify the accuracy of the model and/or the parameter estimates (Box; Draper; Hunter, 1970). The method involves multiplying the solution of the differential equations for the compartment of interest and the posterior density, derived using the Box and Draper method, to get the "prediction" density. Since the resulting equation depends on the parameters and time, we can input the desired time and integrate over the parameters to get the concentration.

3). More complicated models. Apply the Box and Draper method to models that are more complicated and incorporating more elaborated numerical integration methods to reduce the calculation time. An example of the model is the ICRP model for the movement of radionuclides through the gastrointestinal tract (Raabe, 1995).

REFERENCES

REFERENCES

1. Berson, S. A.; Yalow, R. S. "The Distribution of I131 Labeled Human Serum Albumin Introduced into Ascitic Fluid: Analysis of the Kinetics of a Three Compartment Catenary Transfer System in Man and Speculations on Possible Sites of Degradation." *Journal of Clinical Investigation*, 33: 377-387; 1954.
2. Box, G. E. P.; Draper, N. R. "The Bayesian Estimation of Common Parameters from Several Responses." *Biometrika*, 52: 355-365; 1965.
3. Box, G. E. P.; Draper, N. R. "Missing Values in Multiresponse Nonlinear Model." *Technometrics*, 12: 613-629; 1970.
4. Box, G. E. P.; Tiao, C. "Bayesian Inference in Statistical Analysis." Reading Massachusetts: Addison Wesley; 1973.
5. Cox, D. R.; Miller, H. D. "The Theory of Stochastic Process." New York: Wiley and Sons; 1965.
6. Crowder, M. J.; Kimber, A. C.; Smith, R. L.; Sweeting, T. J. "Statistical Analysis of Reliability Data." New York: Chapman and Hall; 1991.
7. Groer, P. G.; Marshall, J. H. "Mechanism of Calcium Exchange at Bone Surface." *Calcified Tissue Research*, 12: 175-192; 1973.
8. Huang, S. C. et. al. "Non-Invasive Determination of Local Cerebral Metabolic Rate of Glucose in Man." *American Journal of Physiology*, 238: E69-E82; 1980.
9. Jacquez, J. A. "Compartmental Analysis in Biology and Medicine." 2nd ed. Ann Arbor Michigan: University of Michigan Press; 1985.
10. Lo, Y. "Measurement of Airborne Radon Daughters – A Bayesian Approach." Thesis: University of Tennessee – Knoxville; 1996.

11. Nagle, R. K.; Saff, E. B. "Fundamental of Differential Equations." New York: Benjamin-Cumming; 1989.
12. Raabe, O. G. "Internal Radiation Dosimetry: 1994 Summer School." Madison Wisconsin: Medical Physics Publishing; 1996.
13. Randolph, B. V. "Bayesian estimation of Biokinetic Parameters for a Two Compartment Model Describing Calcium – 45 Exchange." Thesis: University of Tennessee – Knoxville; 1997.
14. Rowland, R. E. "Exchangeable Bone Calcium." Clinical Orthopedics and Related Research, 49: 233-248; 1966.
15. Sander, P.; Badoux, R. "Bayesian Methods in Reliability." Norwell Massachusetts: Kluwer Academic Publishers; 1991.
16. Smith, G. T. Personal communications; University of Tennessee Medical Center in Knoxville – Nuclear Medicine Department; 1997.
17. Vander, A. J. et. al. "Human Physiology: The Mechanisms of Body Function." New York: McGraw-Hill; 1990.
18. Wolfram Research Inc. "Mathematica Version 3.0 for Apple Macintosh." Champaign Illinois; 1998.

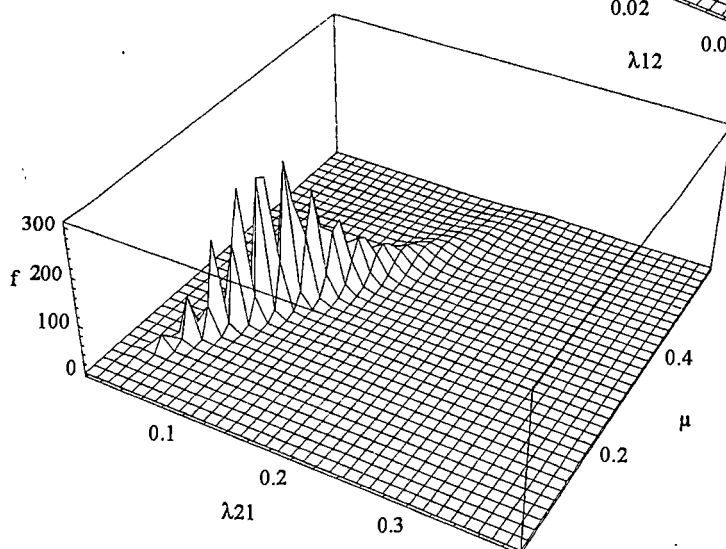
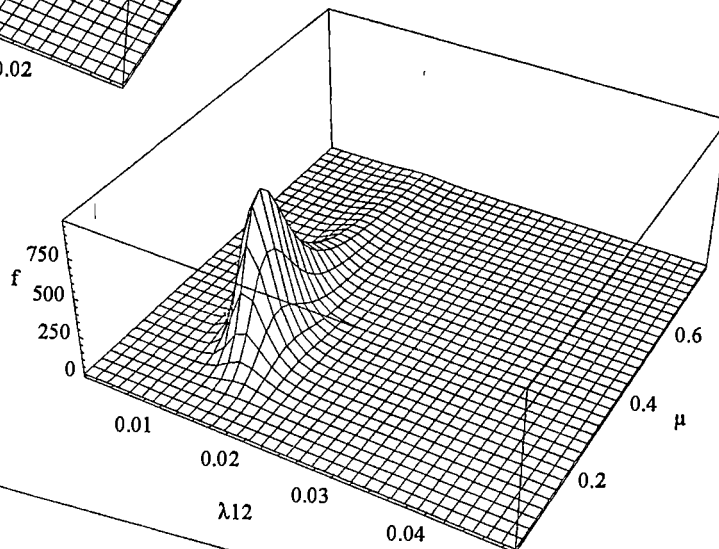
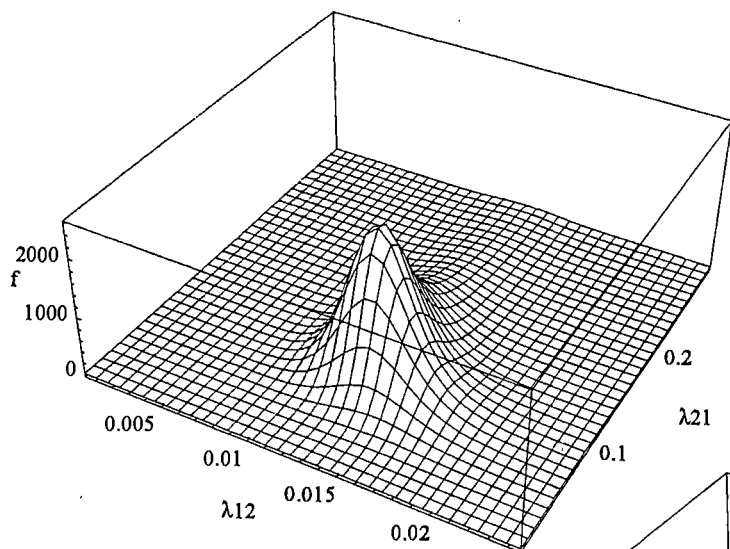
APPENDICES

APPENDIX A

NORMALIZED POSTERIOR SURFACE DENSITY PLOTS

This appendix contains all of the normalized posterior surface density plots used in this dissertation. These plots were generated using the same integration limits that were used in the respective analyses and formatted to show the most important portion of the density. Because of the graphics software used, a small number of plotting points were used to generate these figures. Hence, some of the surfaces are rough and can be smoothed by using more plotting points.

Normalized posterior surface density plots for the calcium exchange rates at bone surface in beagle calculated using all data with uniform priors.



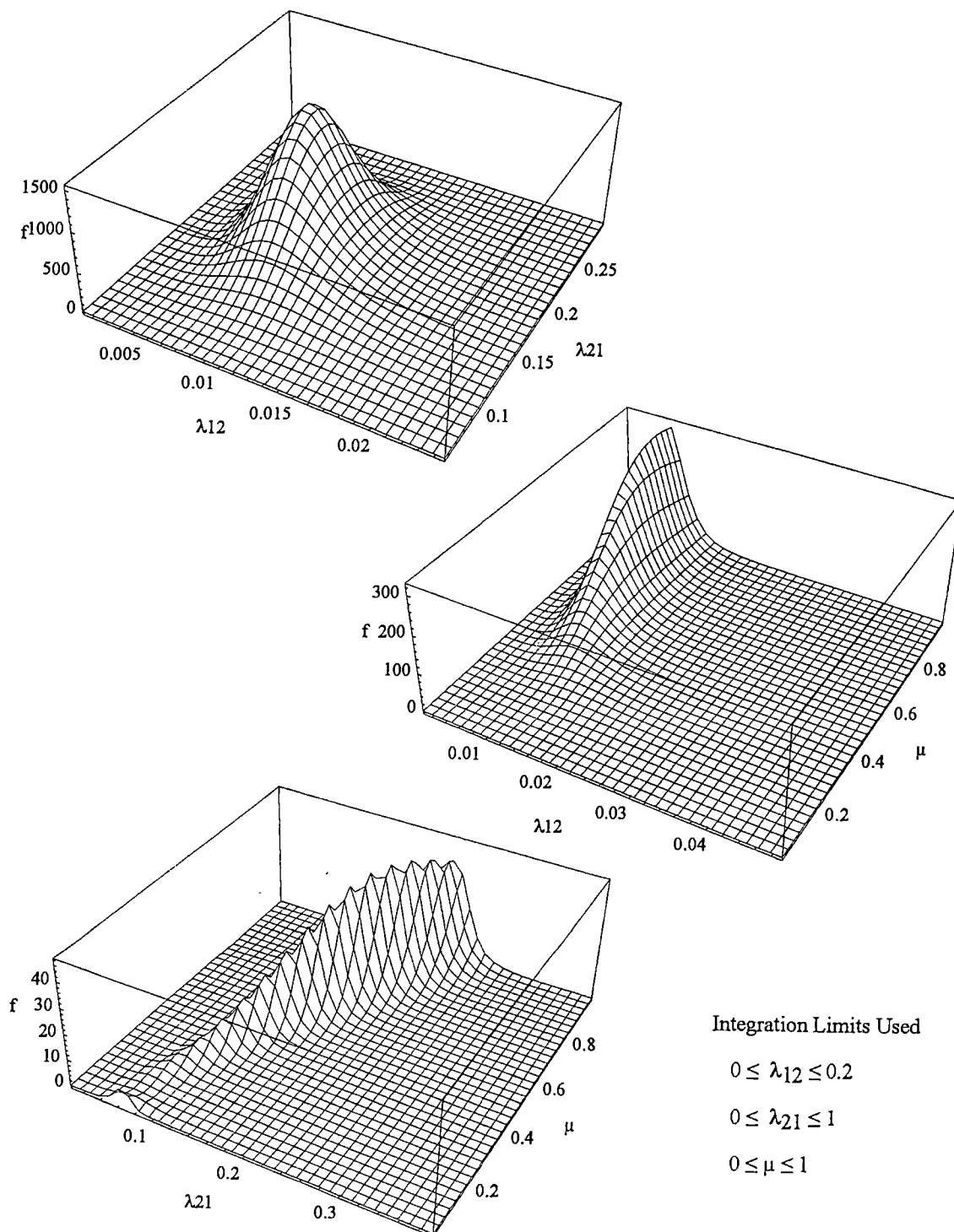
Integration Limits Used

$$0 \leq \lambda_{12} \leq 0.2$$

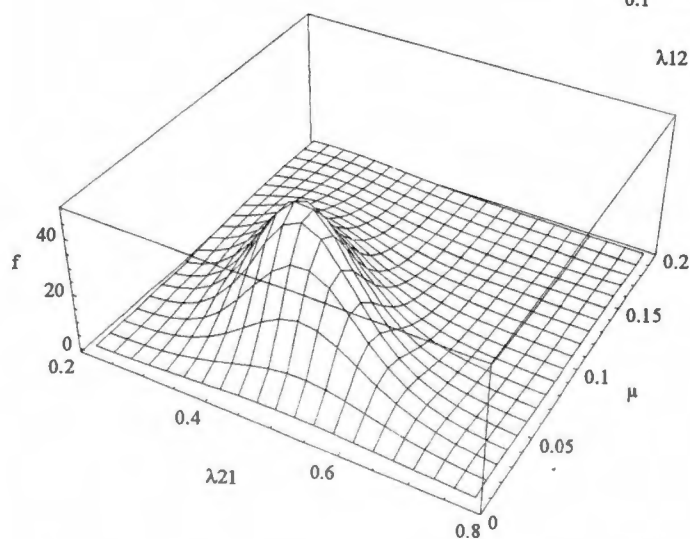
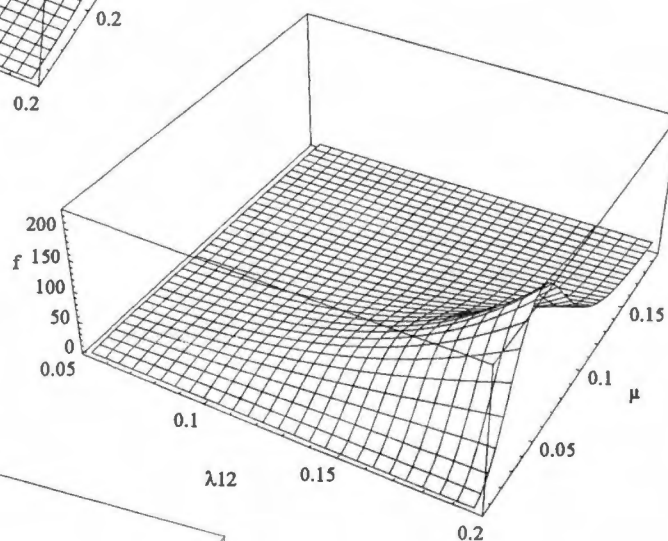
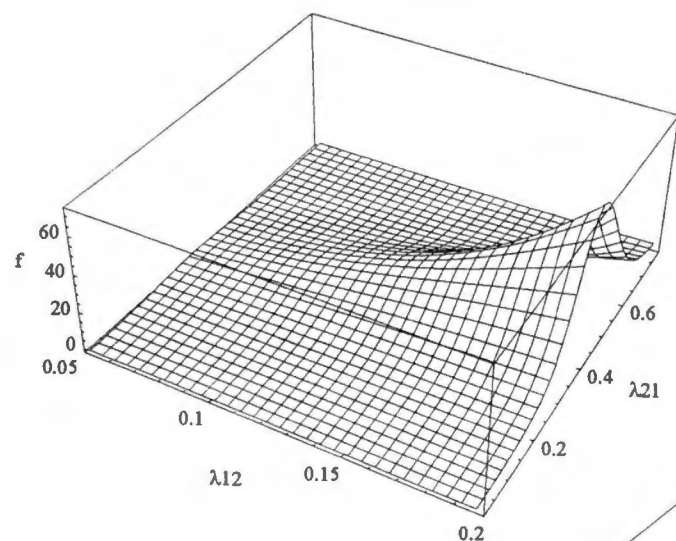
$$0 \leq \lambda_{21} \leq 1$$

$$0 \leq \mu \leq 1$$

Normalized posterior surface density plots for the calcium exchange rates at bone surface in beagle calculated using bone surface data with uniform priors.



Normalized posterior surface density plots for the calcium exchange rates at bone surface in beagle calculated using plasma data with uniform priors.



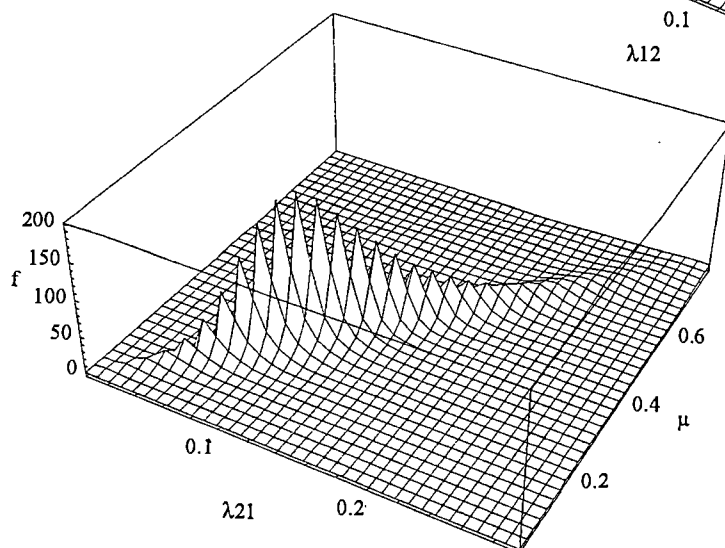
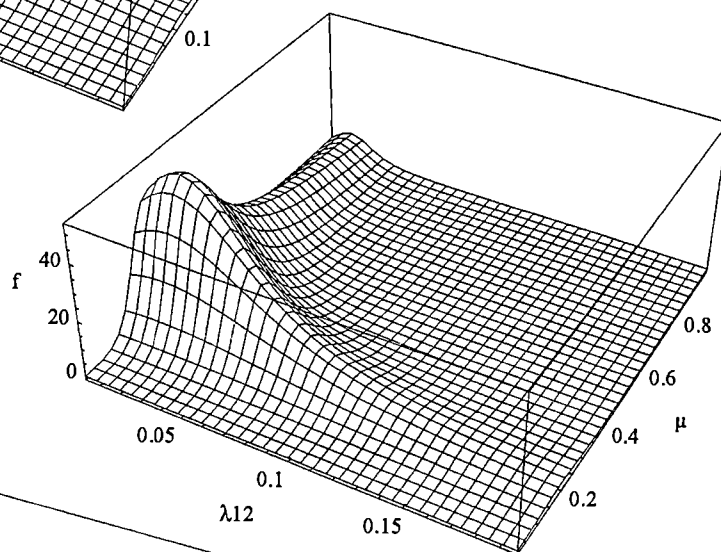
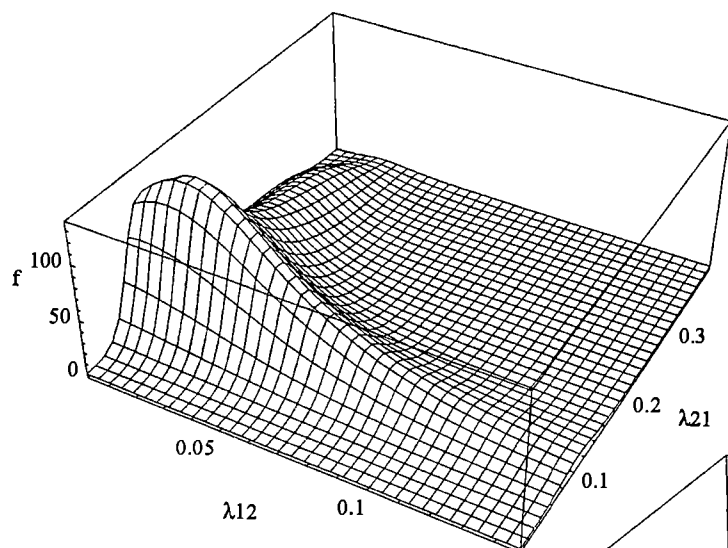
Integration Limits Used

$$0 \leq \lambda_{12} \leq 0.2$$

$$0 \leq \lambda_{21} \leq 1$$

$$0 \leq \mu \leq 1$$

Normalized posterior surface density plots for the calcium exchange rates at bone surface in beagle calculated using first six data with uniform priors.



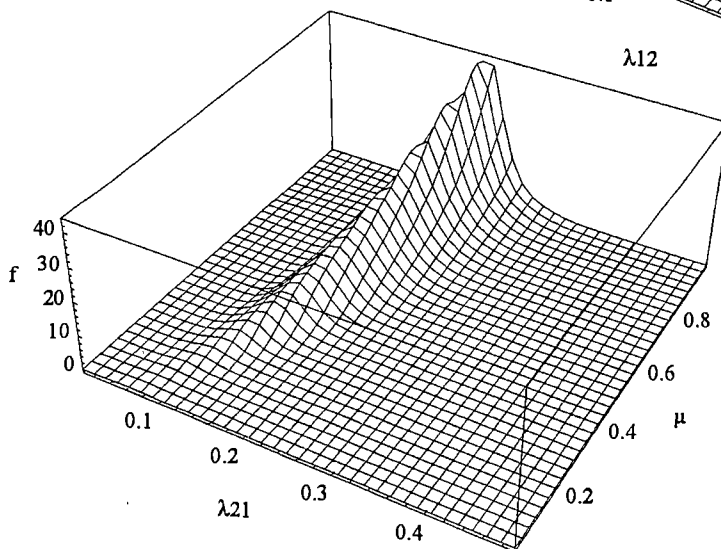
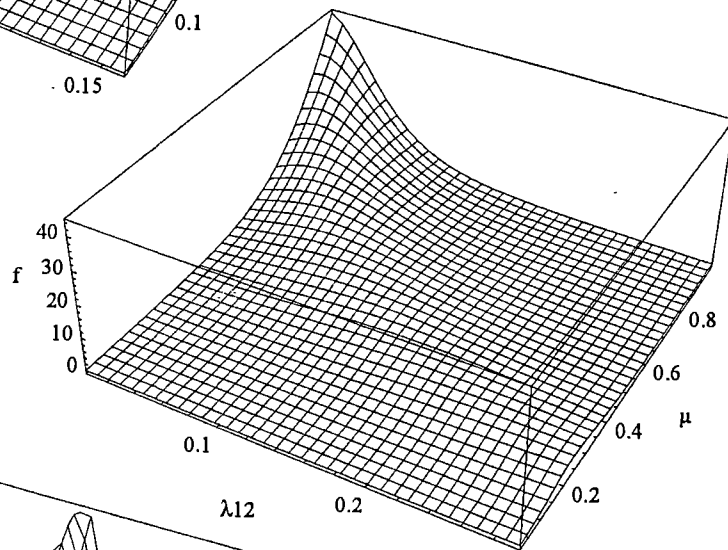
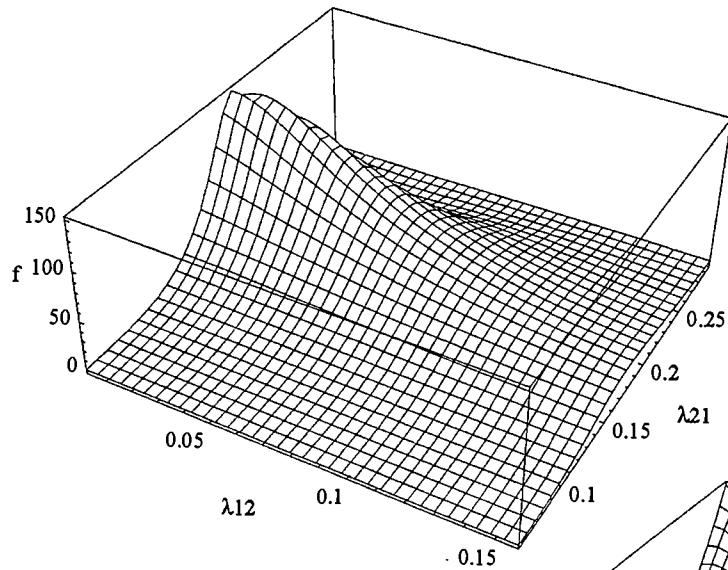
Integration Limits Used

$$0 \leq \lambda_{12} \leq 0.2$$

$$0 \leq \lambda_{21} \leq 1$$

$$0 \leq \mu \leq 1$$

Normalized posterior surface density plots for the calcium exchange rates at bone surface in beagle calculated using first six bone surface data with uniform priors.



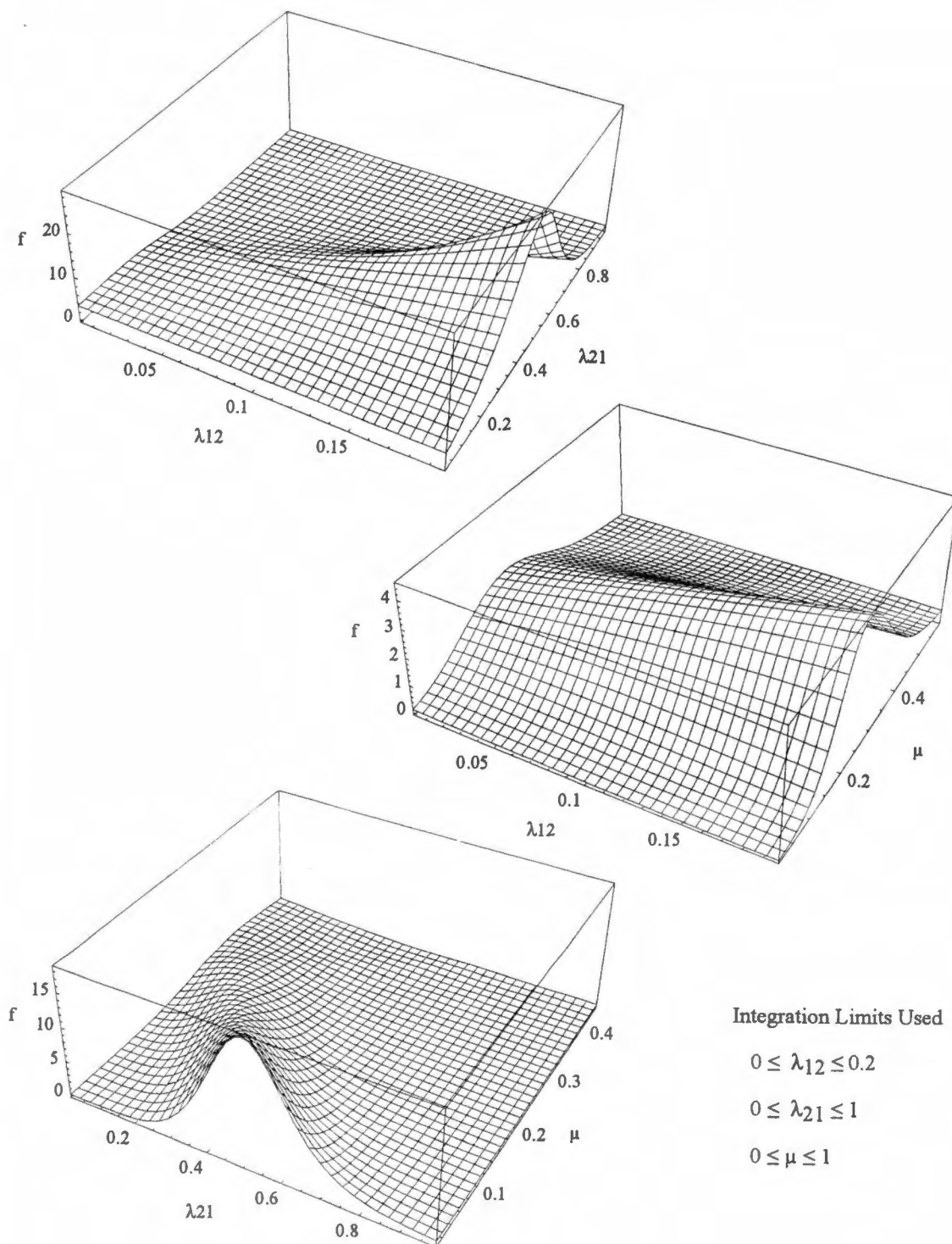
Integration Limits Used

$$0 \leq \lambda_{12} \leq 0.2$$

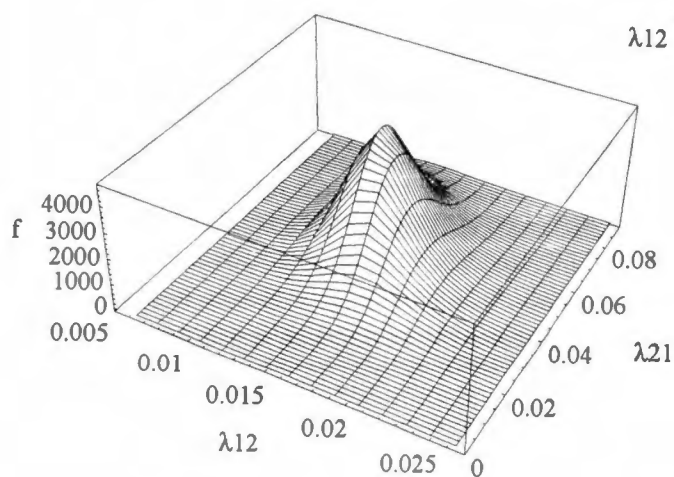
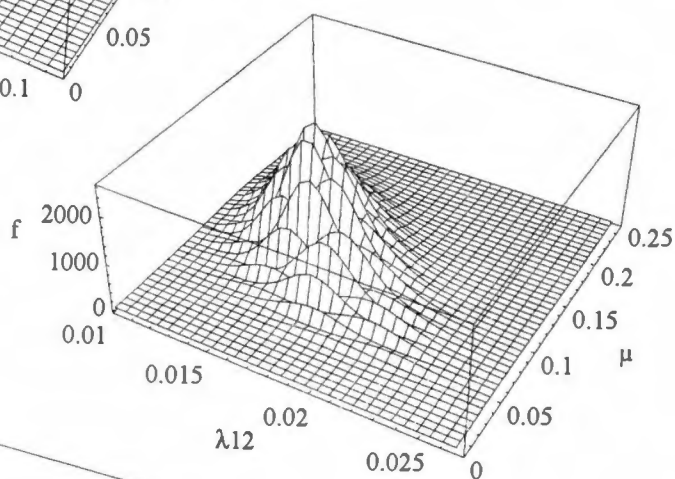
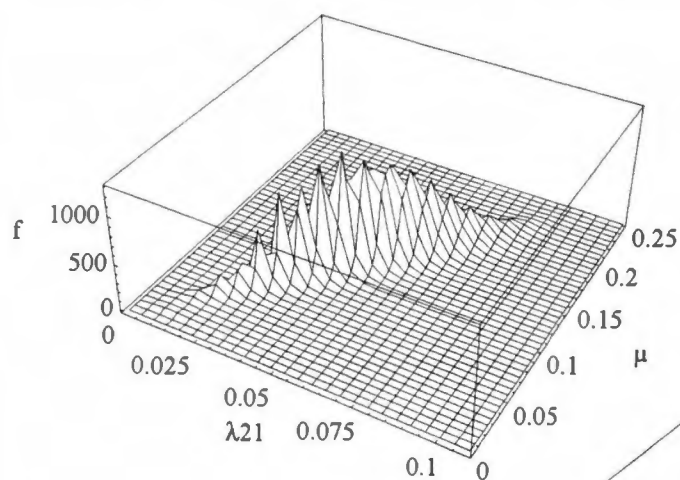
$$0 \leq \lambda_{21} \leq 1$$

$$0 \leq \mu \leq 1$$

Normalized posterior surface density plots for the calcium exchange rates at bone surface in beagle calculated using first six plasma data with uniform priors.



Normalized posterior surface density plots for the calcium exchange rates at bone surface in beagle calculated using all data with normal priors.



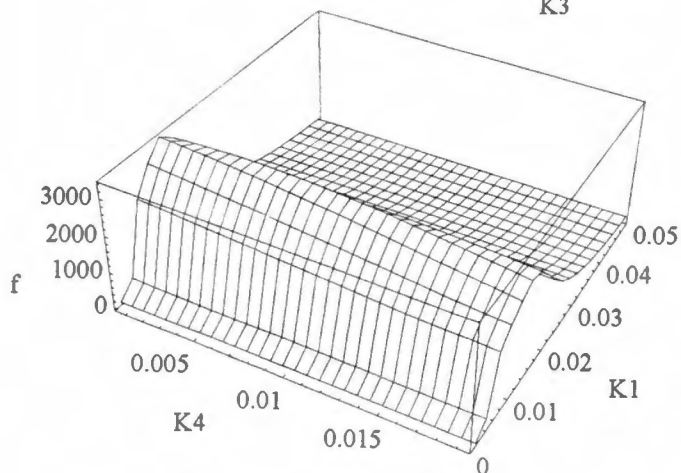
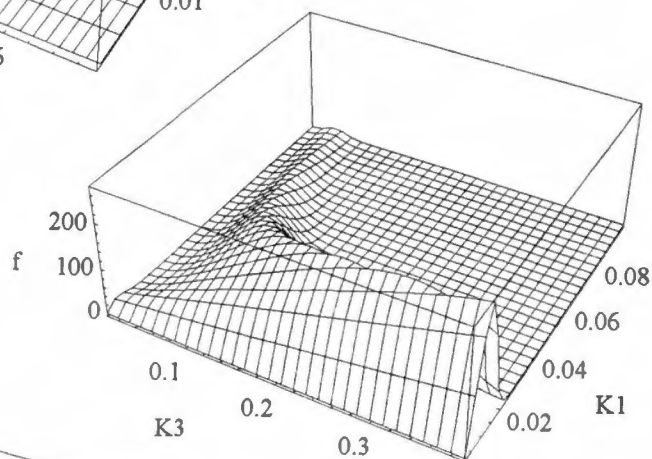
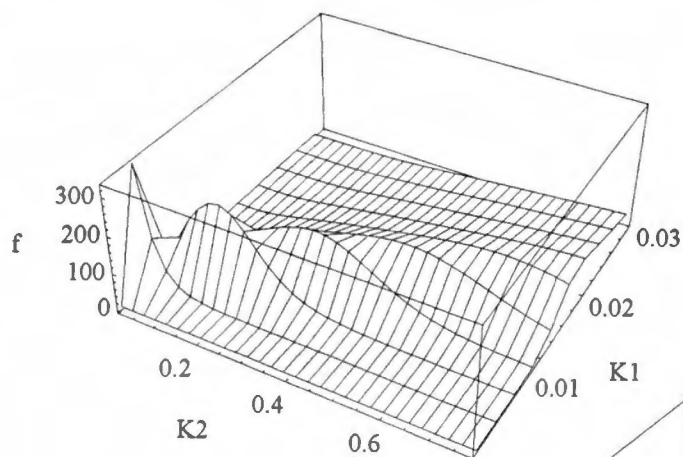
Integration Limits Used

$$0 \leq \lambda_{12} \leq 2$$

$$0 \leq \lambda_{21} \leq 2$$

$$0 \leq \mu \leq 0.4$$

Normalized posterior surface density plots for the local human cerebral glucose exchange rates calculated using clinical data with uniform priors, part 1.



Integration Limits Used

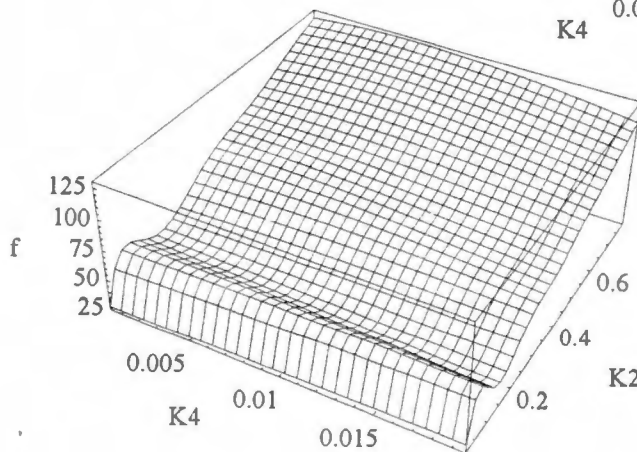
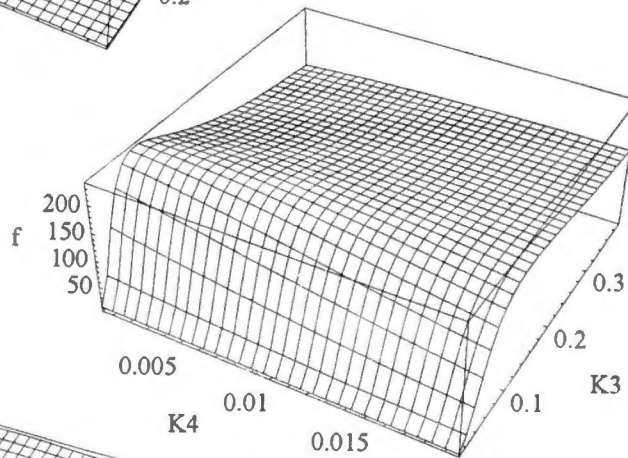
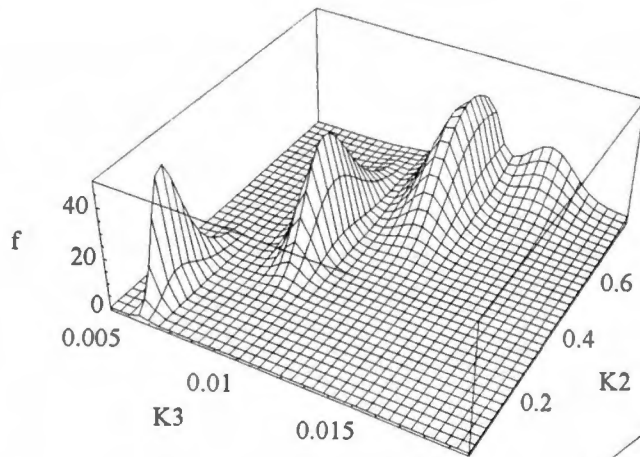
$$0 \leq K_1 \leq 0.4$$

$$0 \leq K_2 \leq 0.8$$

$$0 \leq K_3 \leq 0.04$$

$$0 \leq K_4 \leq 0.02$$

Normalized posterior surface density plots for the local human cerebral glucose exchange rates calculated using clinical data with uniform priors, part 2.



Integration Limits Used

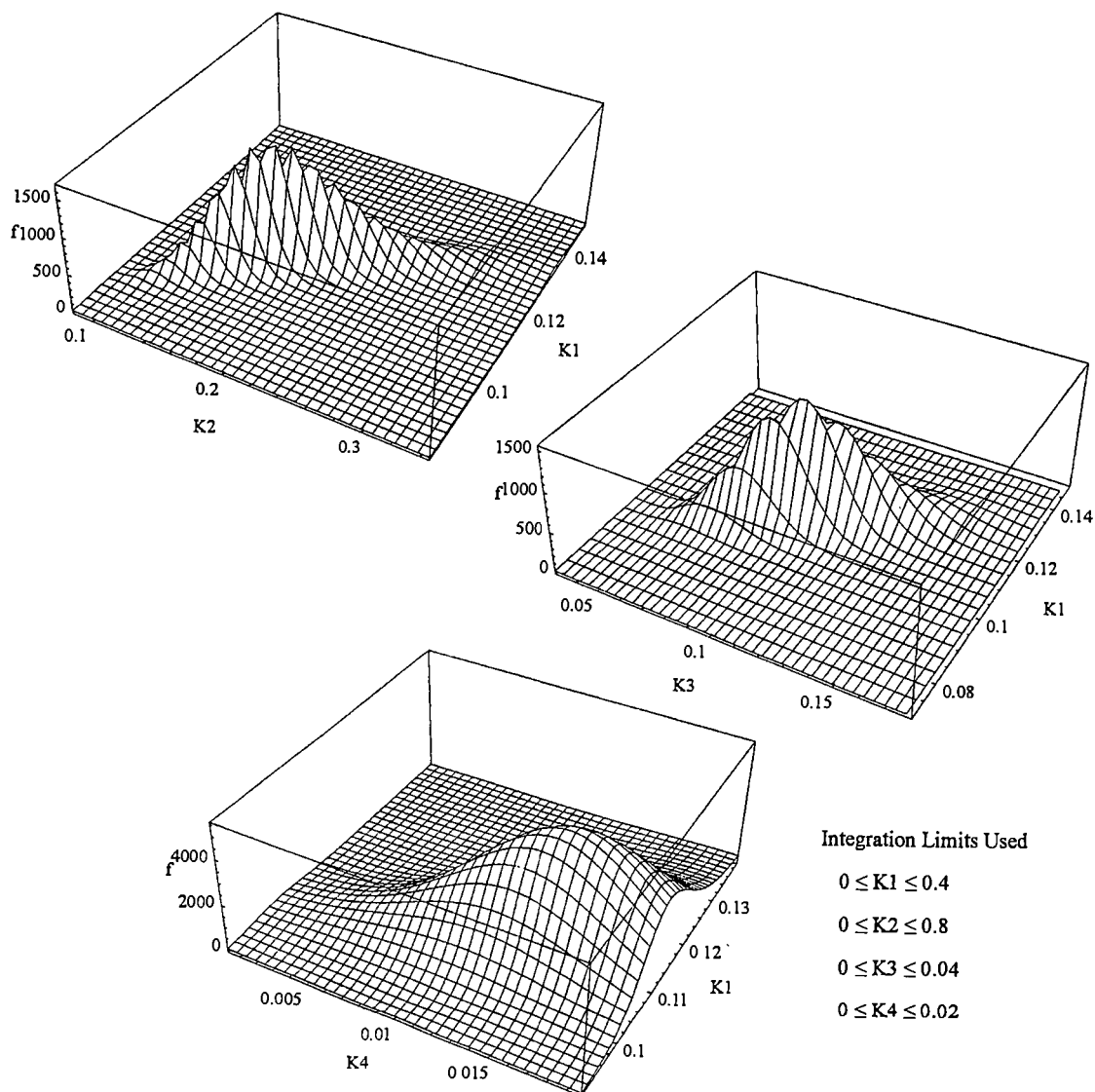
$$0 \leq K_1 \leq 0.4$$

$$0 \leq K_2 \leq 0.8$$

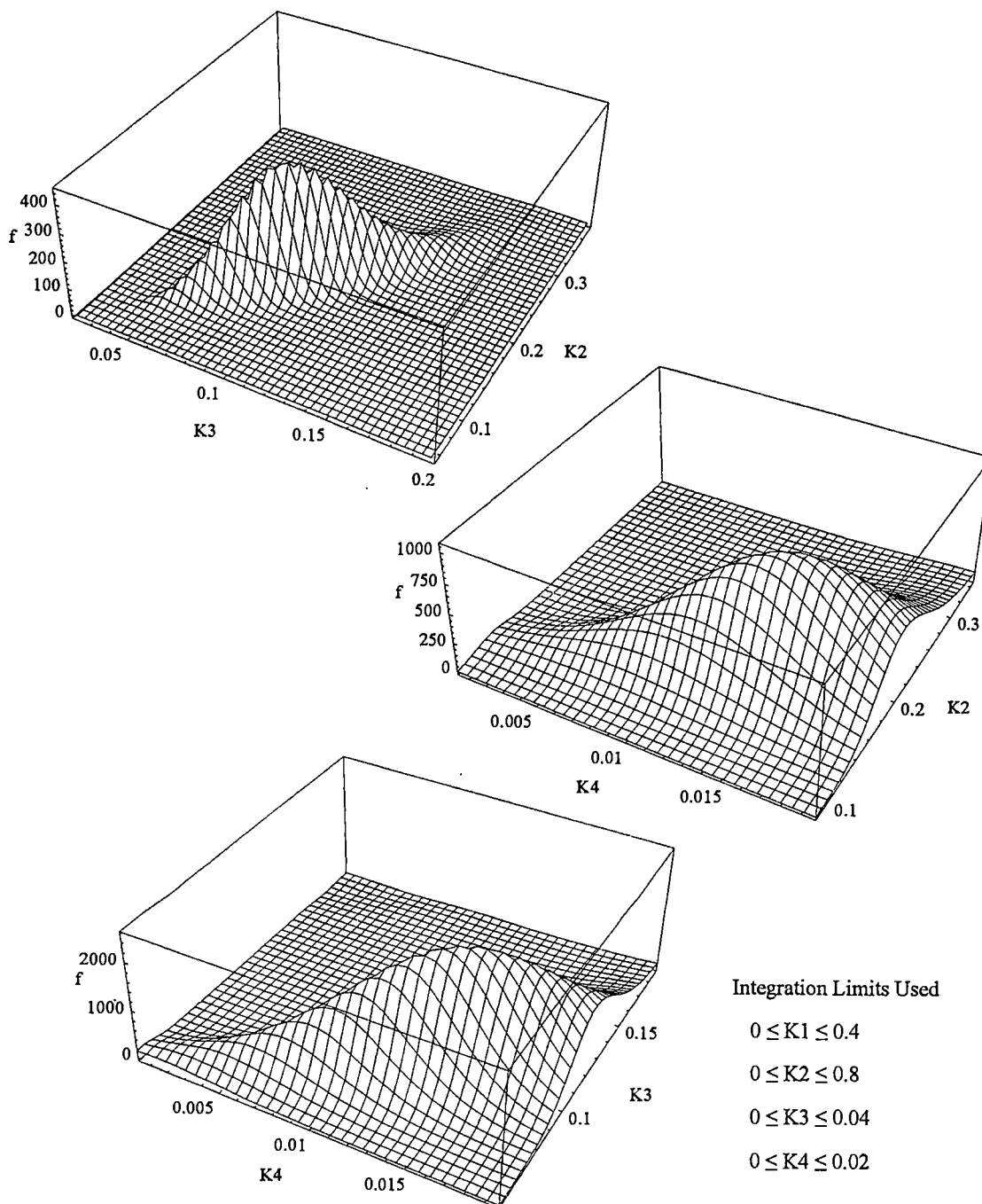
$$0 \leq K_3 \leq 0.04$$

$$0 \leq K_4 \leq 0.02$$

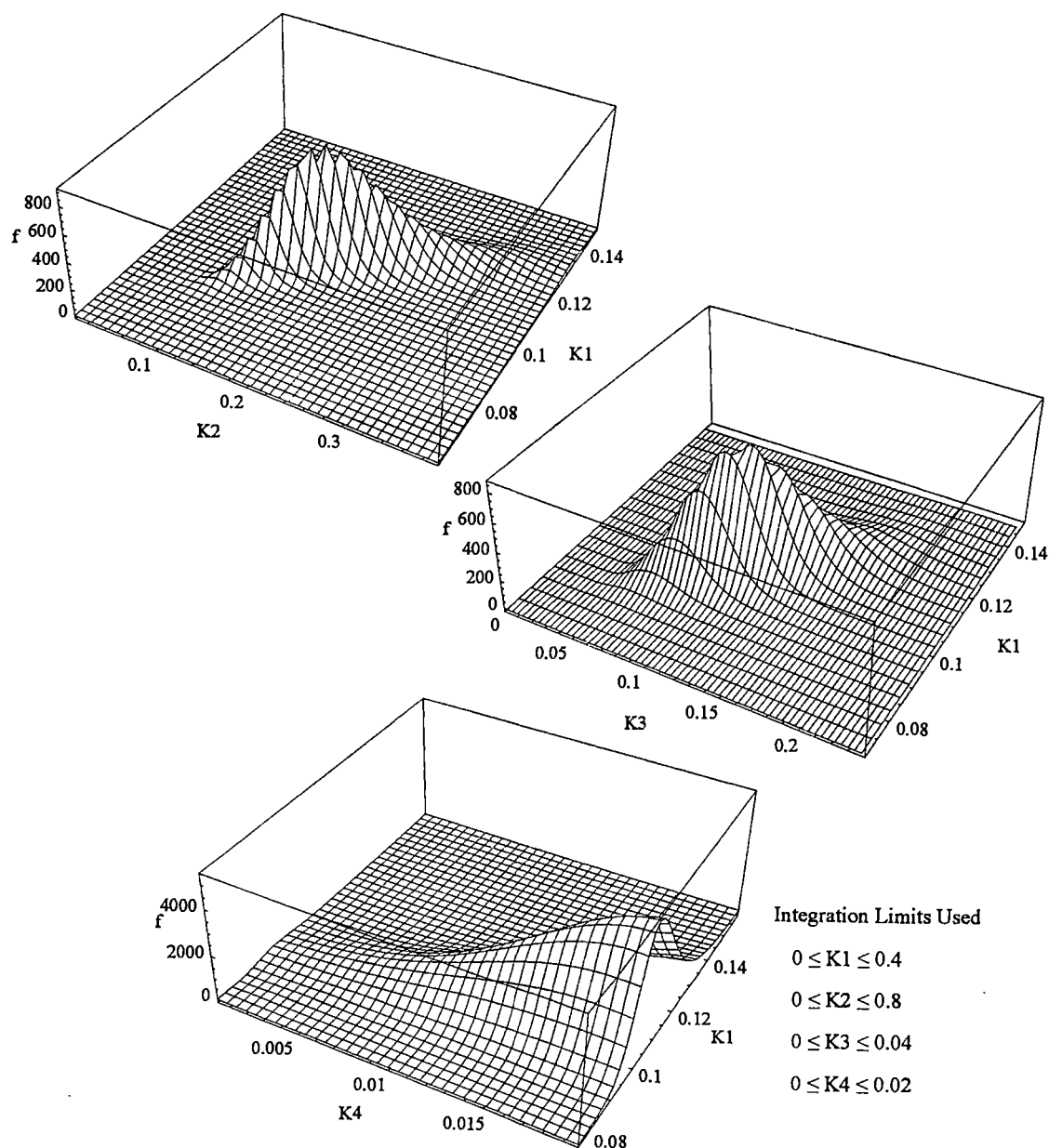
Normalized posterior surface density plots for the local human cerebral glucose exchange rates calculated using simulated data set with 5% Normal random noise and uniform priors, part 1.



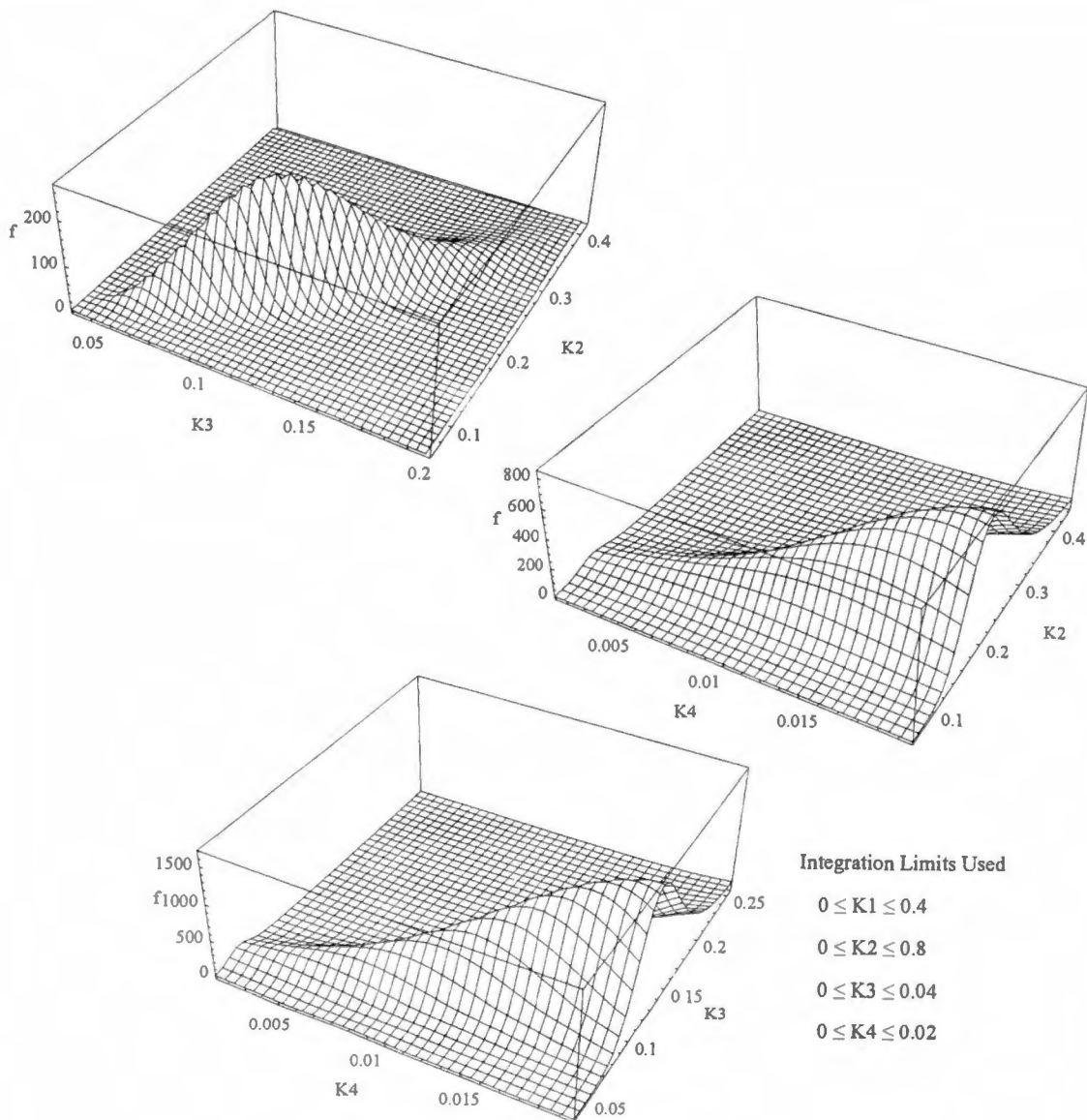
Normalized posterior surface density plots for the local human cerebral glucose exchange rates calculated using simulated data set with 5% Normal random noise and uniform priors, part 2.



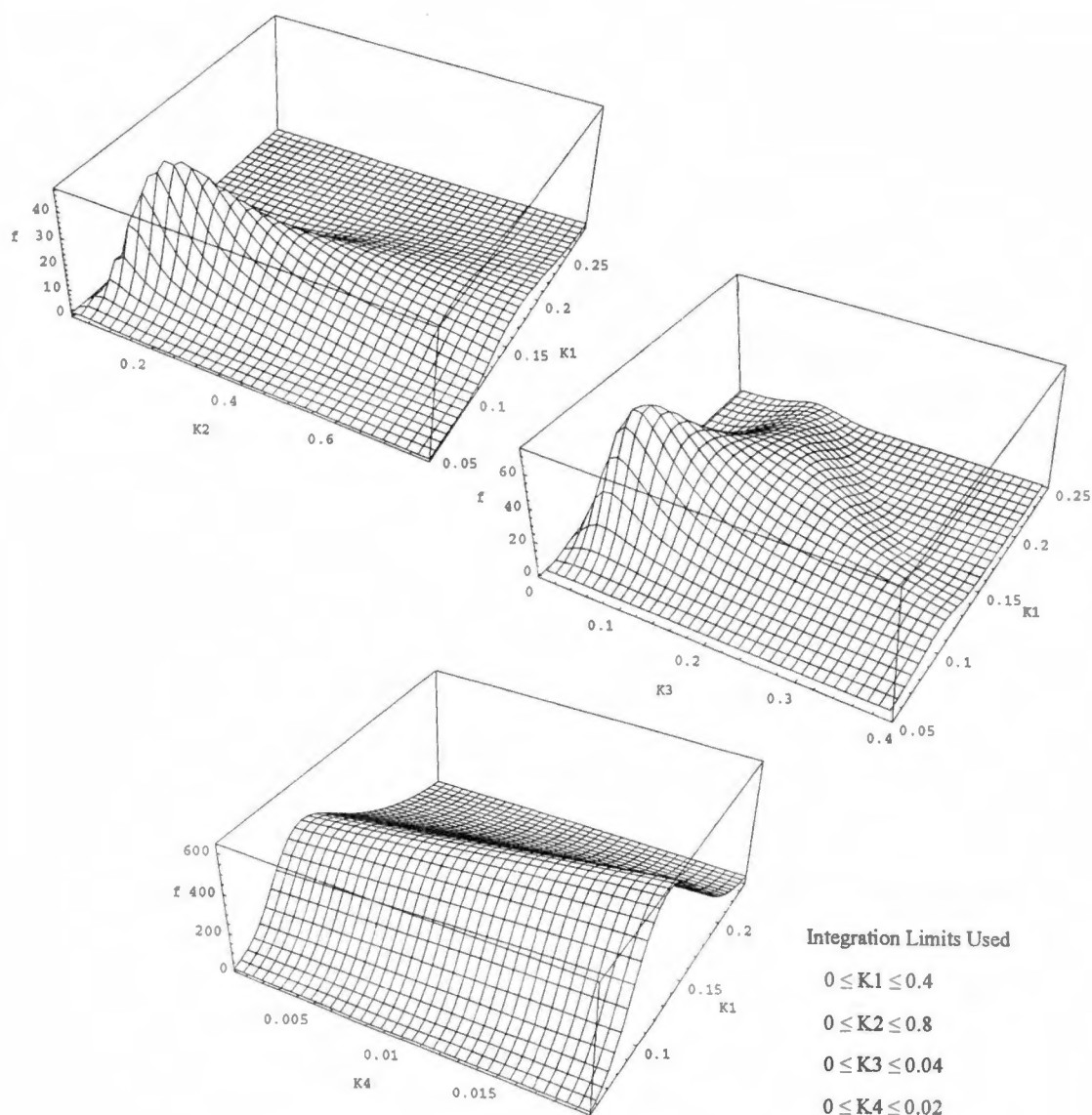
Normalized posterior surface density plots for the local human cerebral glucose exchange rates calculated using simulated data set with 10% Normal random noise and uniform priors, part 1.



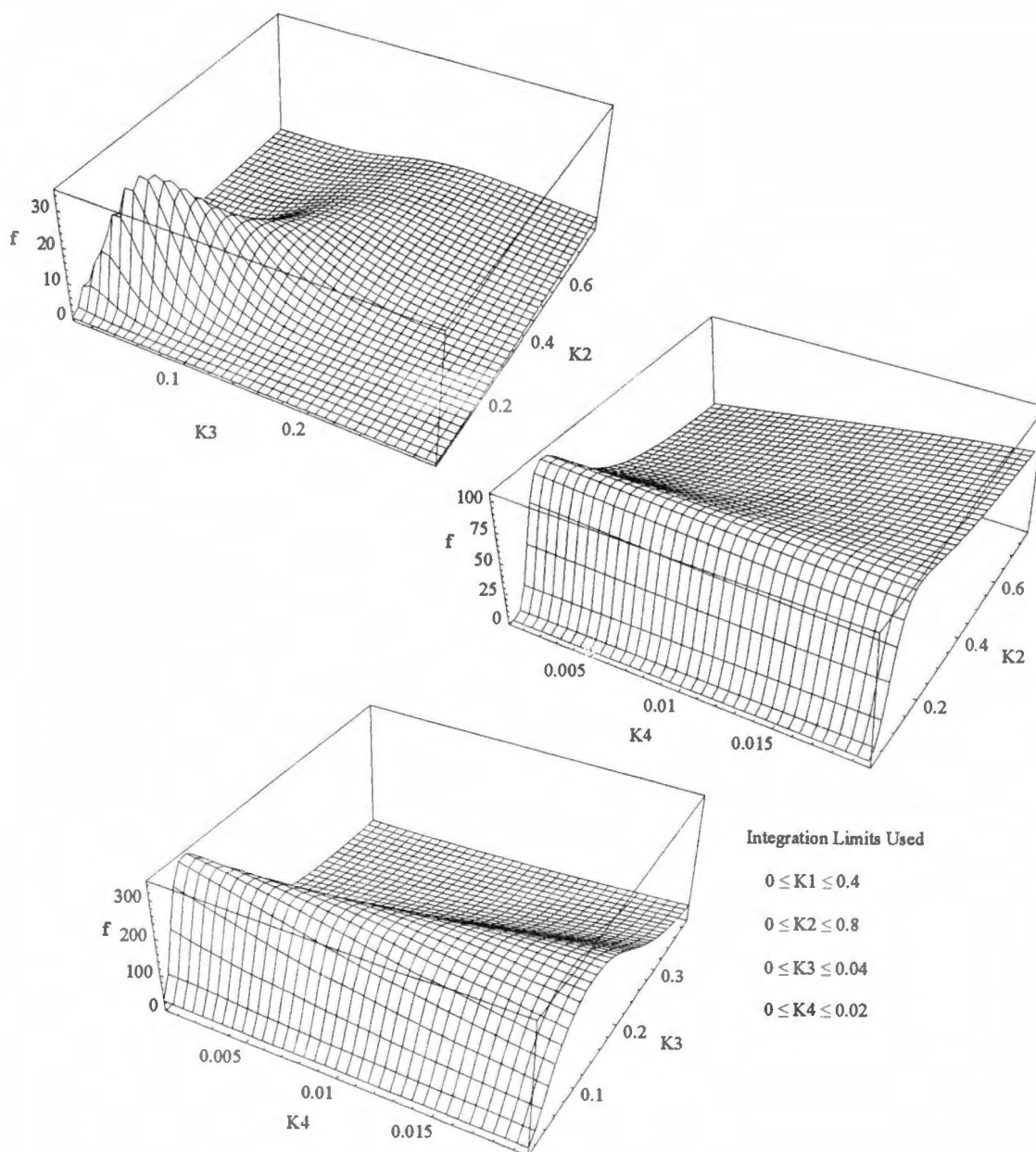
Normalized posterior surface density plots for the local human cerebral glucose exchange rates calculated using simulated data set with 10% Normal random noise and uniform priors, part 2.



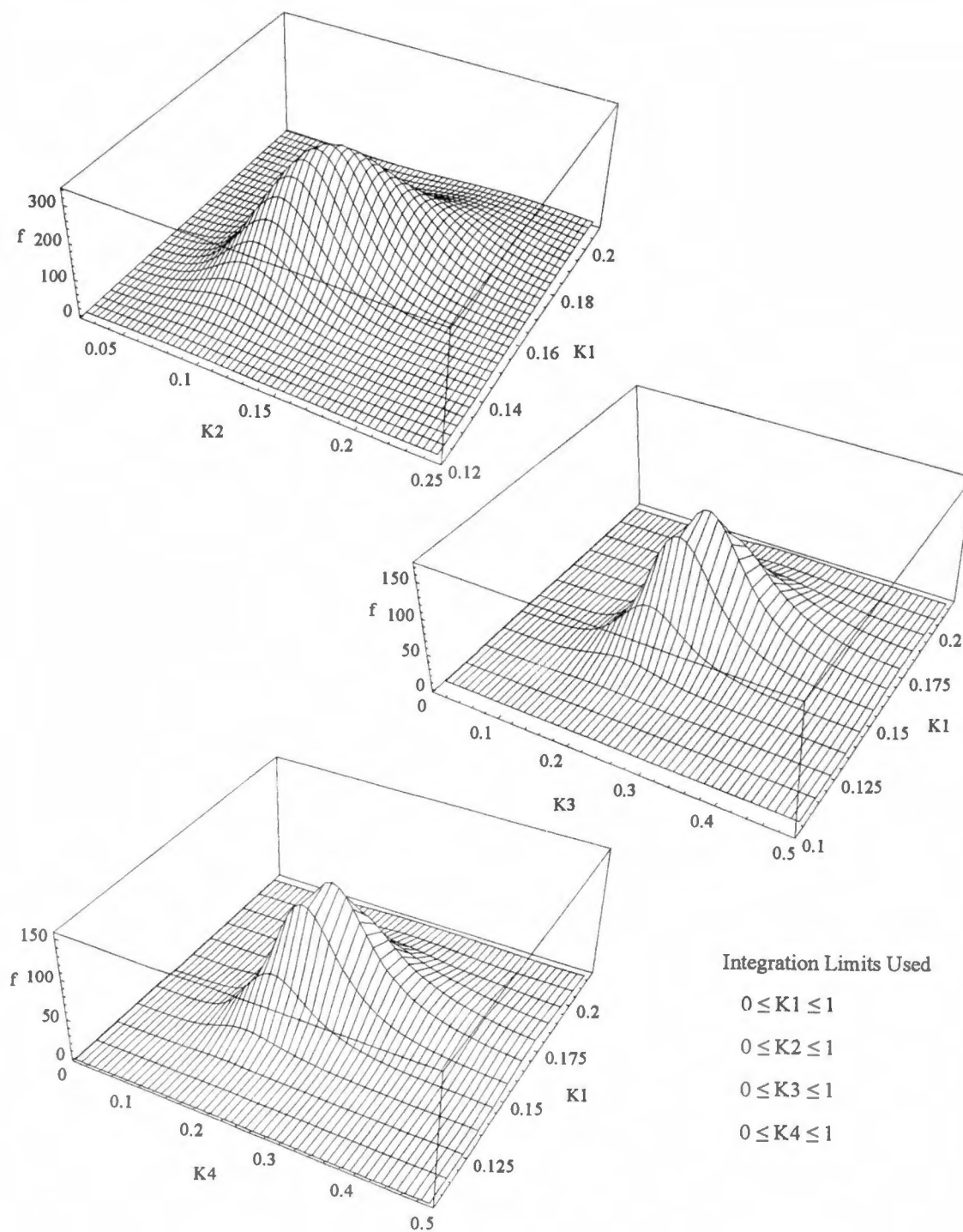
Normalized posterior surface density plots for the local human cerebral glucose exchange rates calculated using simulated data set with 25% Normal random noise and uniform priors, part 1.



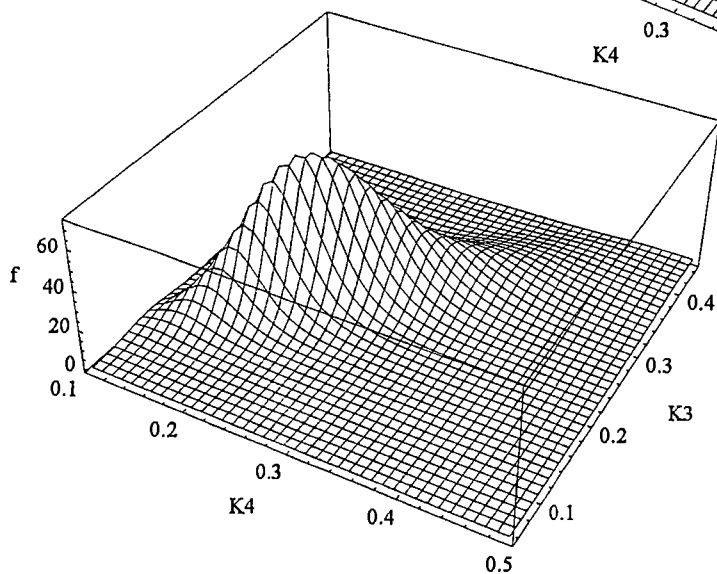
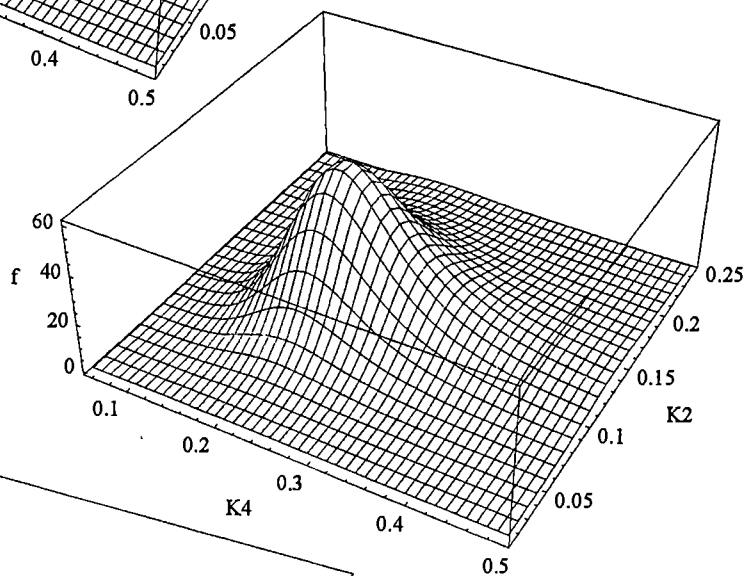
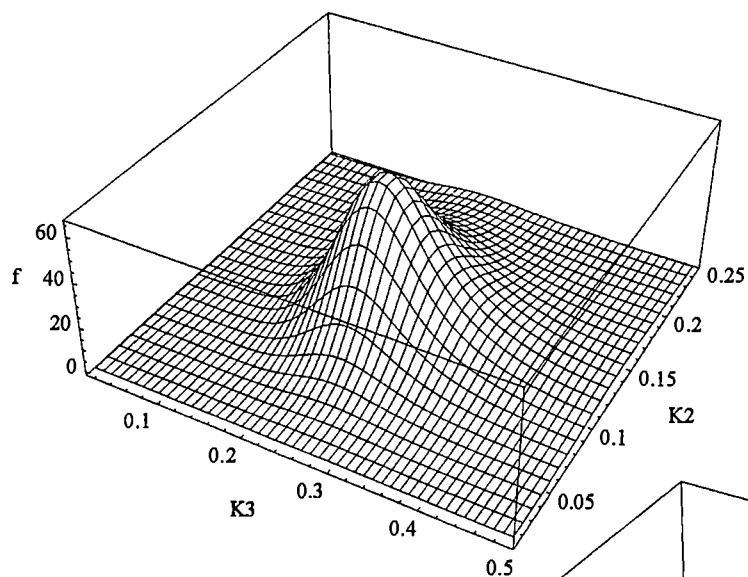
Normalized posterior surface density plots for the local human cerebral glucose exchange rates calculated using simulated data set with 25% Normal random noise and uniform priors, part 2.



Normalized posterior surface density plots for the human serum albumin exchange rates calculated using all data with uniform priors, part 1.



Normalized posterior surface density plots for the human serum albumin exchange rates calculated using all data with uniform priors, part 2.



Integration Limits Used

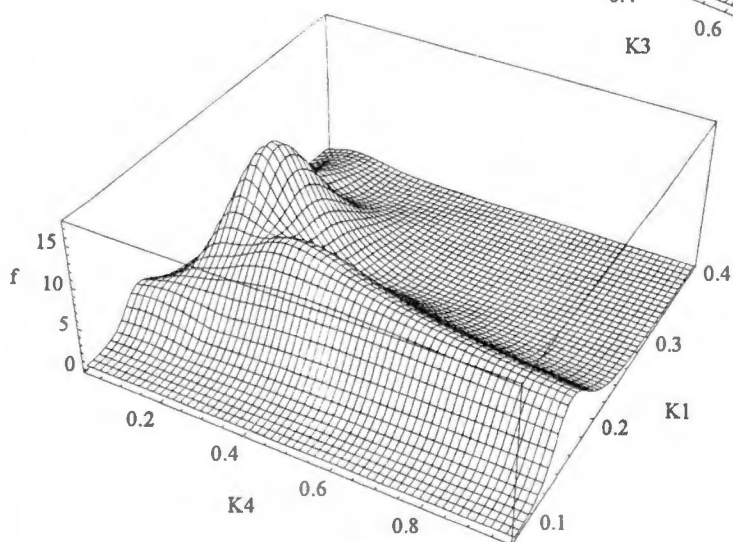
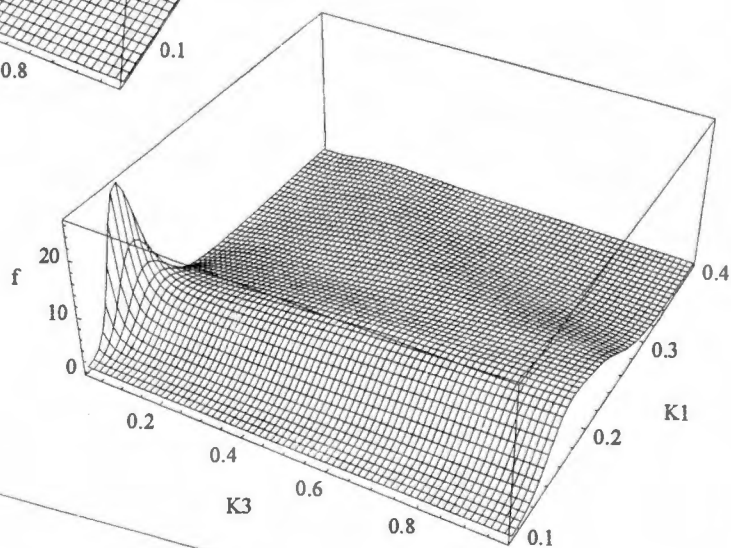
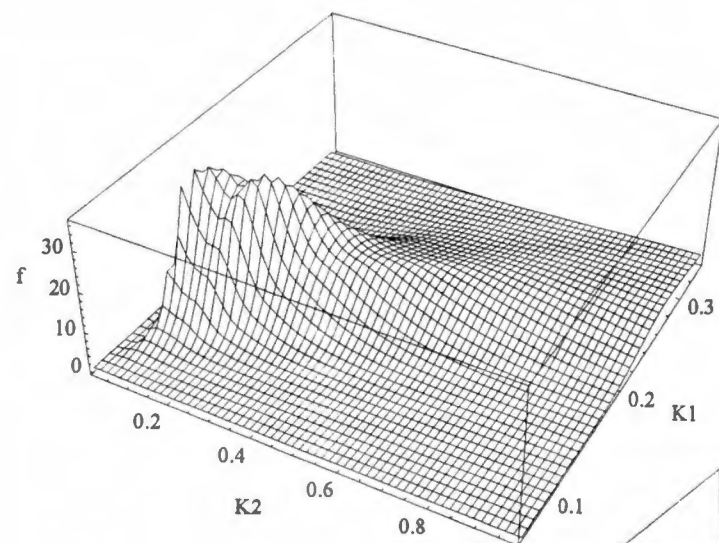
$$0 \leq K_1 \leq 1$$

$$0 \leq K_2 \leq 1$$

$$0 \leq K_3 \leq 1$$

$$0 \leq K_4 \leq 1$$

Normalized posterior surface density plots for the human serum albumin exchange rates calculated using ascitic fluid data with uniform priors, part 1.



Integration Limits Used

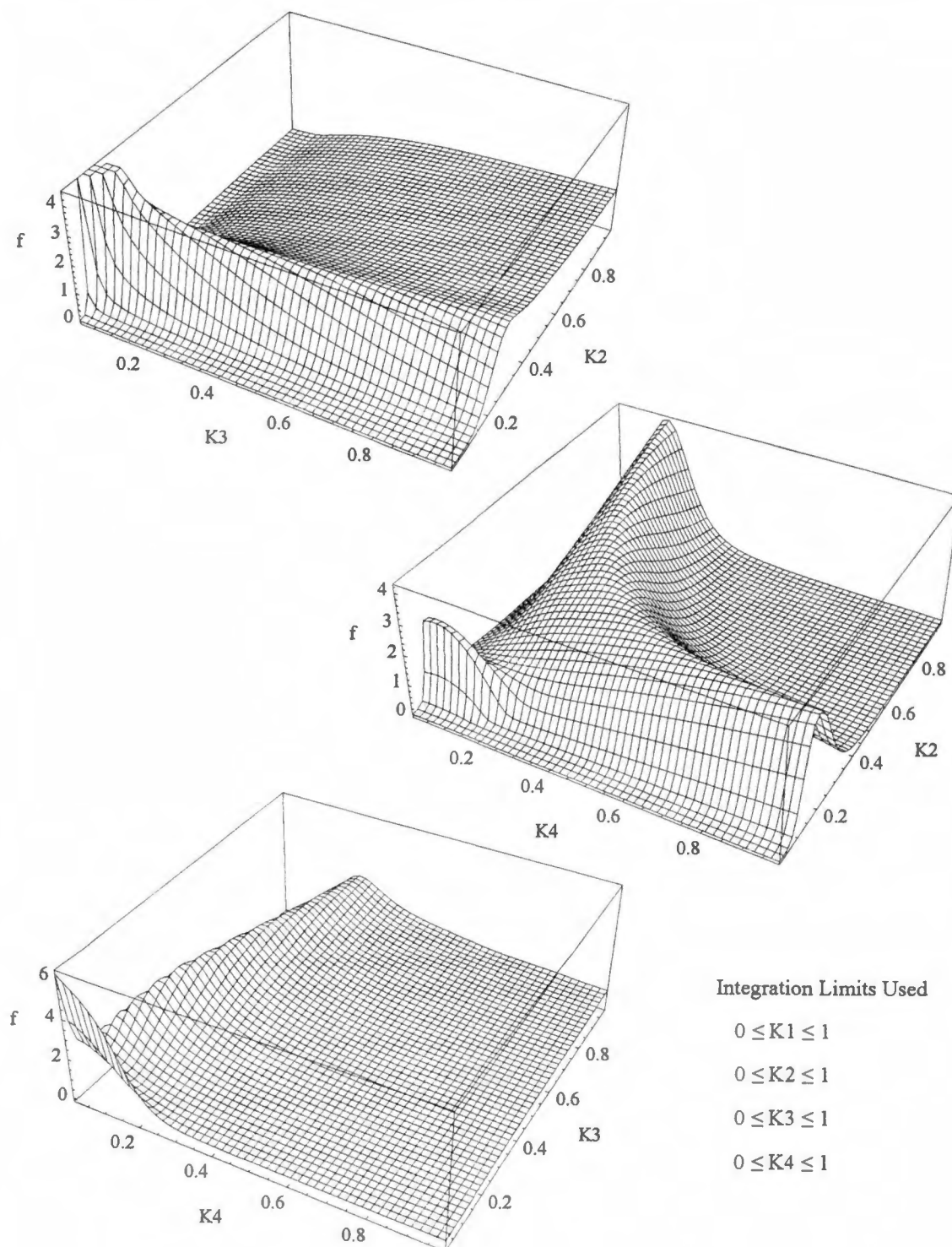
$$0 \leq K1 \leq 1$$

$$0 \leq K2 \leq 1$$

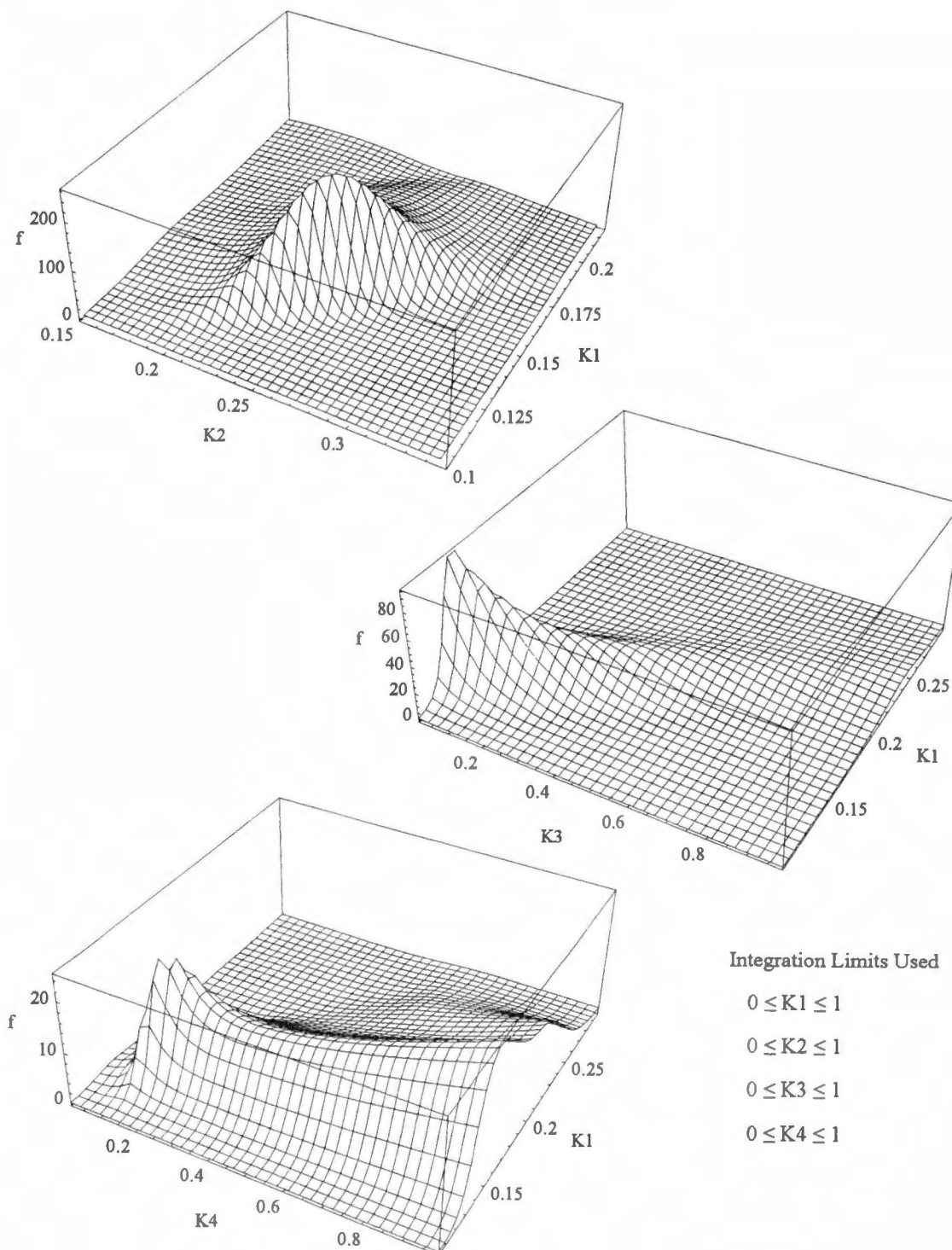
$$0 \leq K3 \leq 1$$

$$0 \leq K4 \leq 1$$

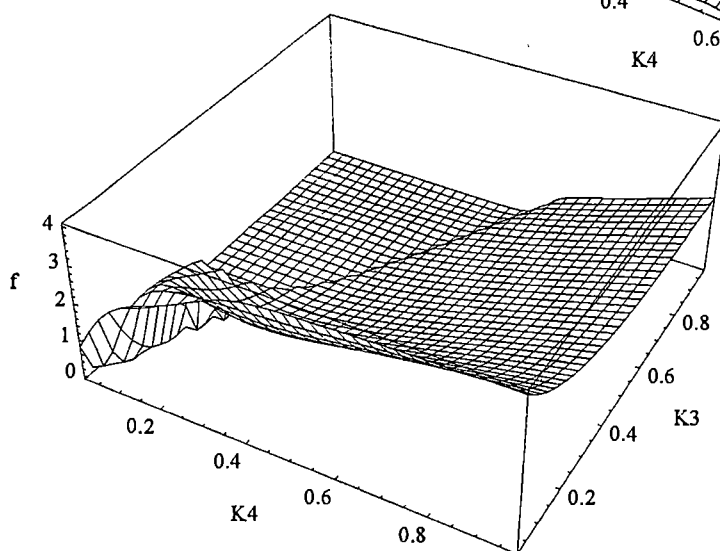
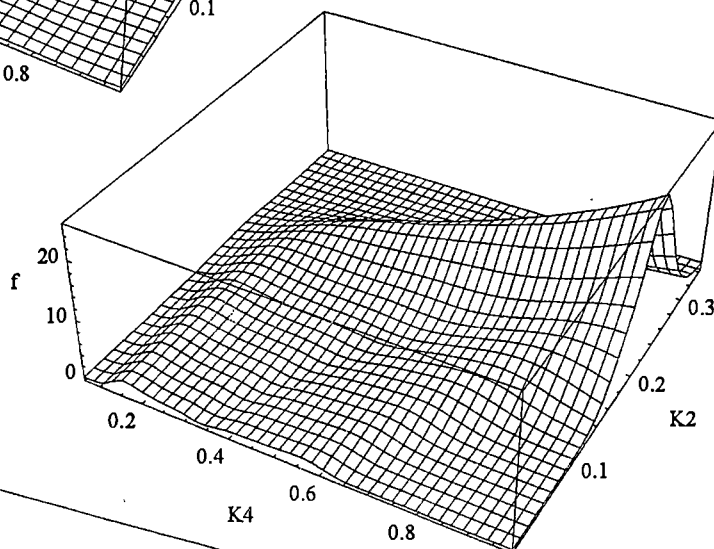
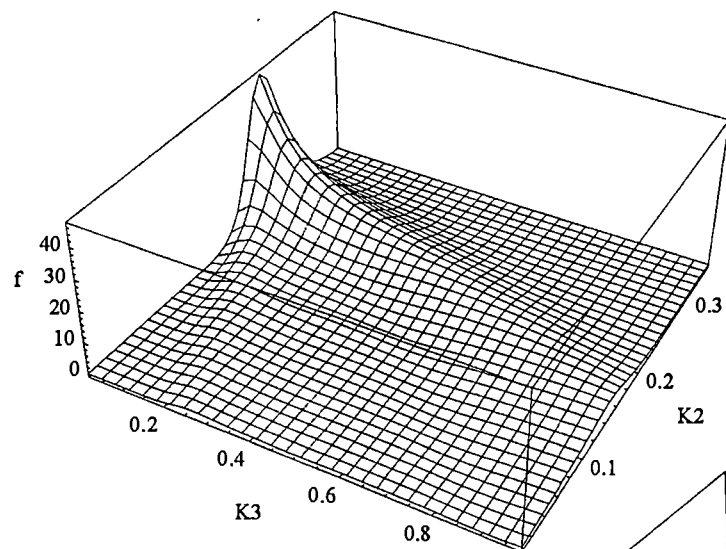
Normalized posterior surface density plots for the human serum albumin exchange rates calculated using ascitic fluid data with uniform priors, part 2.



Normalized posterior surface density plots for the human serum albumin exchange rates calculated using plasma data with uniform priors, part 1.



Normalized posterior surface density plots for the human serum albumin exchange rates calculated using plasma data with uniform priors, part 2.



Integration Limits Used

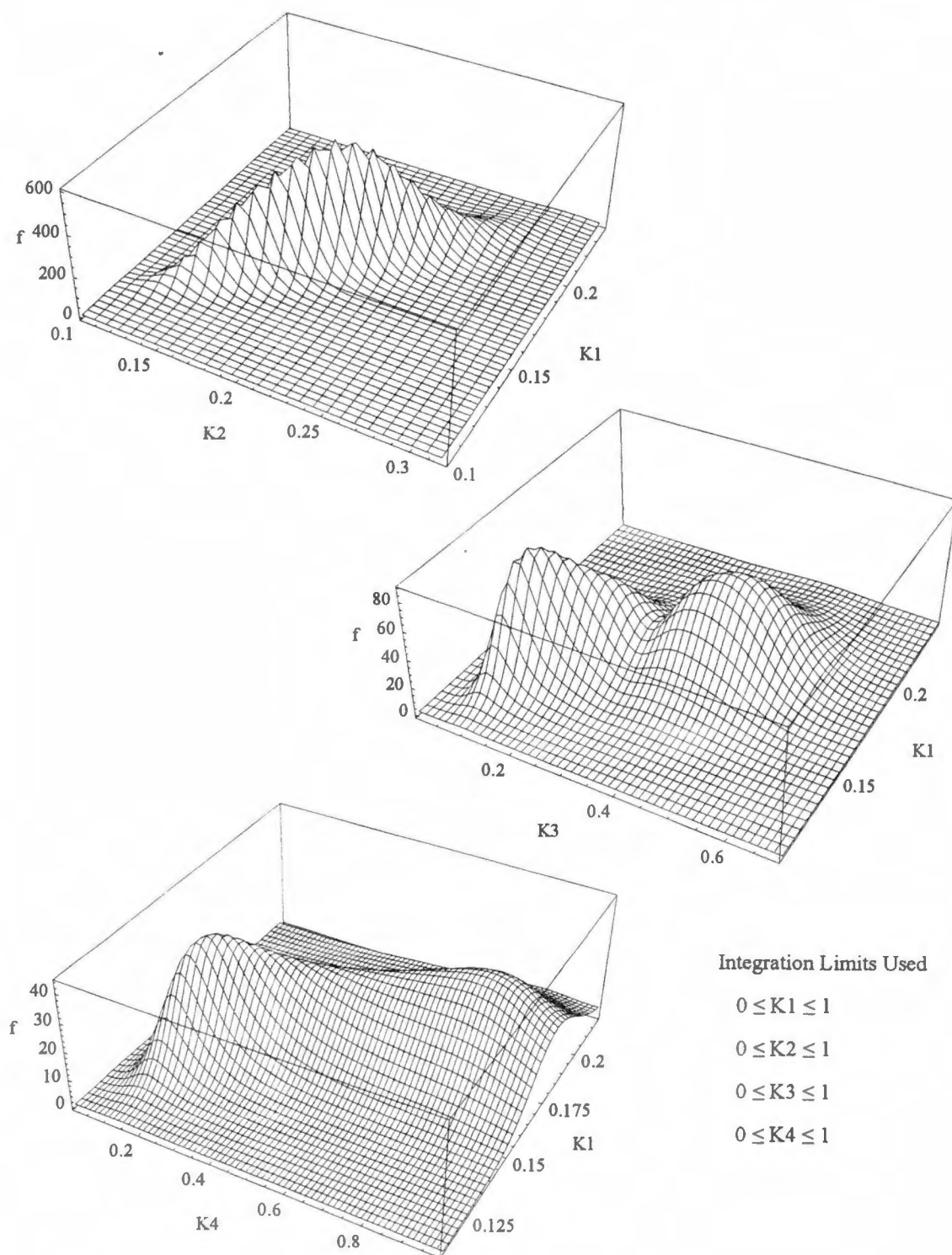
$$0 \leq K_1 \leq 1$$

$$0 \leq K_2 \leq 1$$

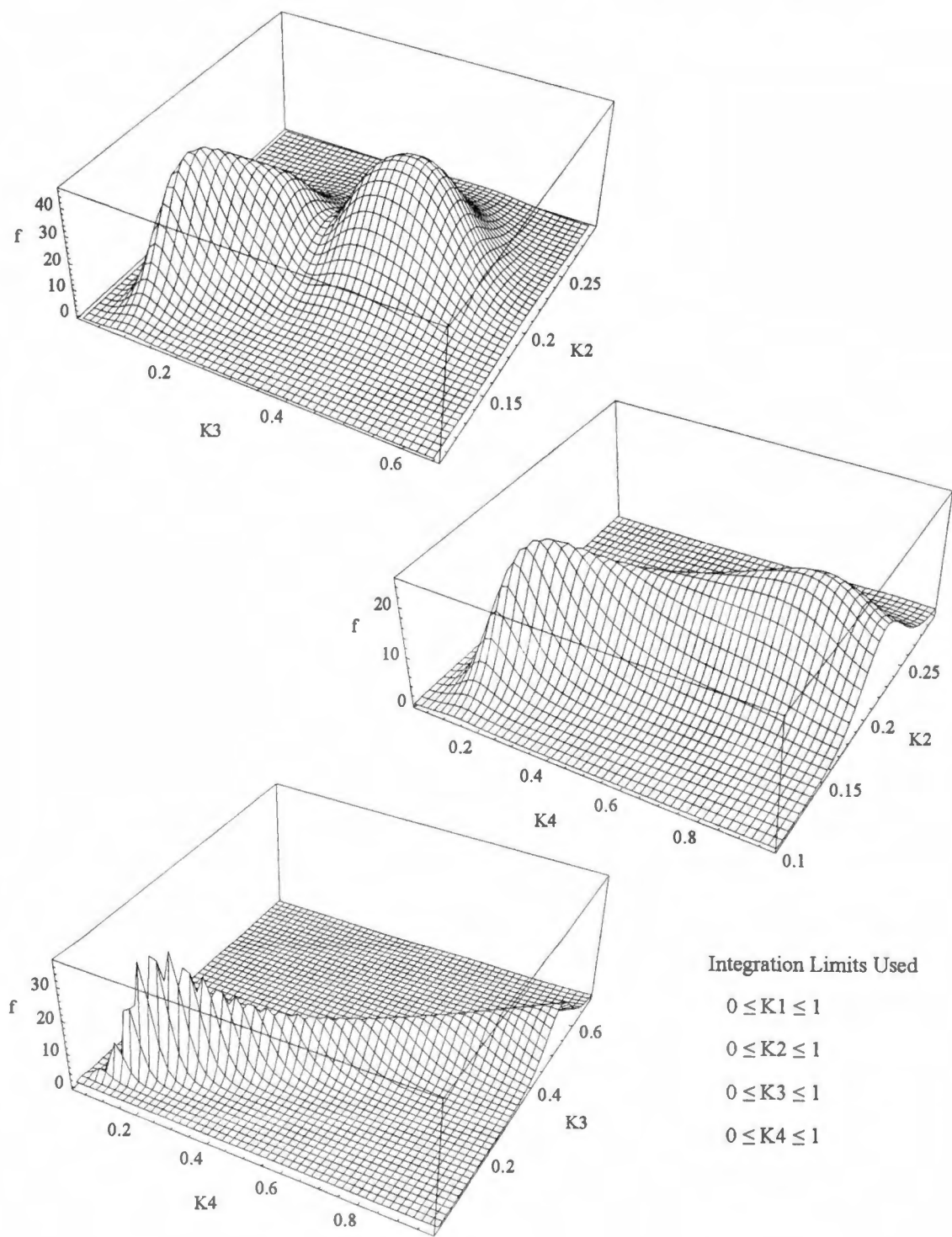
$$0 \leq K_3 \leq 1$$

$$0 \leq K_4 \leq 1$$

Normalized posterior surface density plots for the human serum albumin exchange rates calculated using ascitic fluid and plasma data with uniform priors, part 1.



Normalized posterior surface density plots for the human serum albumin exchange rates calculated using ascitic fluid and plasma data with uniform priors, part 2.



APPENDIX B

SAMPLE COMPUTER CODES IN C AND MATHEMATICA®

This appendix contains some of the computer codes written in C and *Mathematica*® that were used in this dissertation. Because the codes used in shared the similar layout, only selected examples are shown here along with examples for the two numerical integration methods used: midpoint and Gaussian quadrature.

Equal segment midpoint:
$$\int_a^b f(x) dx \equiv \frac{(b-a)}{n} \sum_{i=1}^n f(x_i)$$

Gaussian quadrature:
$$\int_a^b f(x) dx \equiv \sum_{i=1}^n w_i f(x_i)$$

with n segments, abscissas x_i and weights w_i . The C codes listed are for finding: posterior means and variances, marginal densities, and HPD contours. The *Mathematica*® codes listed are for the various plotting commands, for calculating the Gaussian quadrature numerical integration points and weights, and for simulating data.

Volume, posterior mean and variances calculation

/*

Box and Draper Bayesian parameter estimation for the exchange of calcium at bone surface in beagle with uniform priors. This program calculates the normalization constant (volume of the density), posterior means, variances and standard deviations.

This code first calculates the normalization constant and uses it to find the posterior means and standard deviations of the estimates. Midpoint numerical integration rule was used. It is simple and the results are comparable to the more advance methods.

Codes used to find marginal densities, HPD contours and 3D surfaces are based on this layout. Only the order of integration, numerical integration methods and the likelihood were changed.

Written by Yunnhon Lo, Dept. of Nuclear Engineering, University of
Tennessee - Knoxville (c) 1996-2000

```

*/

#include <stdio.h>
#include <math.h>
main()
{
/* Declaring dummy variables used */
int sw;
double func,i,j,k,icm,ik,ijk,immx,jmmy,kmnz,ijmm,m1,m2,m3,mx,my,mz;
double mmx,mmy,mmz,nc,p,q,r,S11,S12,S22,xmin,xmax,ymin,ymax,zmin,zmax;
double volume,immx4,den,mxmymz,mxmymznc,meana,mean2a,vara,sda;
double meanb,mean2b,varb,sdb,meanc,mean2c,varc,sdc;
double y1,y2,y4,y6,y24,y48,y120,y408,y052,y02;
double z1,z2,z4,z6,z24,z48,z120,z408,z052,z02;
double u0,u1,u2,u3,u4,u5,u6,u7,u8,u9,w0,w1,w2,w3,w4,w5,w6,w7,w8,w9;

/* Integration limit: x = L12, y = L21, z = mu */
xmin=0.0;   ymin=0.0;   zmin=0.0;   xmax=0.2;   ymax=1.0;   zmax=1.0;

/* Numerical integration: midpoint rule. */
mx=0.0002; my=0.002;   mz=0.002;   mmx=mx/2;   mmy=my/2;   mmz=mz/2;
mxmymz=mx*my*mz;

/* Initialize counting variables */
meana=0.0; meanb=0.0; meanc=0.0; mean2a=0.0; mean2b=0.0;
mean2c=0.0; func=0.0;   volume=0.0;

/* Volume and posterior mean calculation switch statement.
   If sw = 0 find volume (this comes first),
   If sw = 1 find means, standard deviations. */
for (sw=0; sw<2; sw++)
{
    if(sw>0)    { mxmymznc=mxmymz/volume; }
    else        { volume=0.0; }

/* Start midpoint numerical integration
   Counting variables i,j,k denotes L12, L21, mu.
   Begin integration loop for parameter L12 */
    for (i=0; i<xmax-mmx; i+=mx)
    {
        immx=i+mmx;
        immx4=immx*4.0;

/* Begin integration loop for parameter L21 */
        for (j=0; j<ymax-mmy; j+=my)
        {
            jmmy=j+mmy; ijmm=immx+jmmy;

/* Begin integration loop for parameter mu */
            for (k=0; k<zmax-mmz; k+=mz)
            {
                kmnz=k+mmz;
                ik=immx4*kmnz;
                ijk=ijmm+kmnz;
                m3=sqrt(ijk*ijk-ik);

```

```

m1=(ijk+m3)/2;
m2=(ijk-m3)/2;
icm=27.1/m3;
p=icm*jimmy;
q=icm*(immx-m2);
r=icm*(immx-m1);

/* Exponential portion of the solution of ODE. */
y052=exp(-0.52*m2);      y02=exp(-0.2*m2);
y1=exp(-m2);              y2=y1*y1;
y4=y2*y2;                  y6=y2*y4;
y24=y6*y6*y6*y6;          y48=y24*y24;
y120=y48*y48*y24;
y408=y120*y120*y120*y48;
z052=exp(-0.52*m1);      z02=exp(-0.2*m1);
z1=exp(-m1);              z2=z1*z1;
z4=z2*z2;                  z6=z2*z4;
z24=z6*z6*z6*z6;          z48=z24*z24;
z120=z48*z48*z24;
z408=z120*z120*z120*z48;

/* Box-Draper S11 component */
u0=0.21-(y408-z408)*p;    u1=1.97-(y120-z120)*p;
u2=4.16-(y48-z48)*p;      u3=5.79-(y24-z24)*p;
u4=4.89-(y6-z6)*p;        u5=4.37-(y4-z4)*p;
u6=3.53-(y2-z2)*p;        u7=3.39-(y1-z1)*p;
u8=2.81-(y052-z052)*p;    u9=1.1-(y02-z02)*p;

/* Box-Draper S22 component */
w0=0.1-q*y408+r*z408;     w1=1.3-q*y120+r*z120;
w2=2.3-q*y48+r*z48;       w3=5.0-q*y24+r*z24;
w4=8.0-q*y6+r*z6;         w5=9.5-q*y4+r*z4;
w6=14.0-q*y2+r*z2;        w7=15.0-q*y1+r*z1;
w8=17.0-q*y052+r*z052;    w9=22.0-q*y02+r*z02;

S11=u0*u0+u1*u1+u2*u2+u3*u3+u4*u4+u5*u5+u6*u6+u7*u7+u8*u8+u9*u9;
S12=u0*w0+u1*w1+u2*w2+u3*w3+u4*w4+u5*w5+u6*w6+u7*w7+u8*w8+u9*w9;
S22=w0*w0+w1*w1+w2*w2+w3*w3+w4*w4+w5*w5+w6*w6+w7*w7+w8*w8+w9*w9;
den=S11*S22-S12*S12;

/* Calculate posterior mean and volume */
if(sw>0)
{ func=mxmymznc/(den*den*den*den*den);
  meana=(immx*func)+meana;  mean2a=(immx*immx*func)+mean2a;
  meanb=(jimmy*func)+meanb; mean2b=(jimmy*jimmy*func)+mean2b;
  meanc=(kmmz*func)+meanc;  mean2c=(kmmz*kmmz*func)+mean2c;
}
else
{ volume=(mxmymz/(den*den*den*den*den))+volume; }
}

/* Calculate variances and standard deviations. */
vara=mean2a-(meana*meana);  varb=mean2b-(meanb*meanb);
varc=mean2c-(meanc*meanc);  sda=sqrt(abs(vara));
sdb=sqrt(abs(varb));         sdc=sqrt(abs(varc));

/* Output the results to the screen */
printf("The exchange of Ca-45 at bone surface in beagle.\n");

```

```

printf("calculated using all data and uniform priors.\n\n");
printf("Volume or normalization constant: \t %e\n\n\n",volume);
printf("Parm: E(T)\t\t\tE(T^2)\t\t\tVariance\t\t\tStd. Dev\n");
printf("L12 : %e\t%e\t%e\t%e\n",meana,mean2a,vara,sda);
printf("L21 : %e\t%e\t%e\t%e\n",meanb,mean2b,varb,sdb);
printf("mu : %e\t%e\t%e\t%e\n",meanc,mean2c,varc,sdc);
}
/* end of program */

```

Normalized marginal posterior density of lambda12

/* Marginal posterior density of lambda12 (L12).
This code used the normalization constant calculated in previous code and midpoint numerical integration to generate the marginal posterior density of lambda12. The output is in the form of { L12, P(L12|data) } from 0 to 0.2 at 0.0002 interval. The output can then be formatted, and plotted using other graphic software.

Written by Yunnhon Lo, University of Tennessee - Knoxville
Department of Nuclear Engineering (c) 1996-2000
*/

```

#include <stdio.h>
#include <math.h>
main()
{
/* Declaring dummy variables used */
double func,i,j,k,icm,ik,ijk,immx,jmny,kmnz,ijmm,m1,m2,m3,mx,my,mz,mmx;
double mny,mnz,mymznc,nc,p,q,r,S11,S12,S22,xmin,xmax,ymin,ymax,zmin;
double zmax,volume,immx4,den,y1,y2,y4,y6,y24,y48,y120,y408,y052,y02;
double z1,z2,z4,z6,z24,z48,z120,z408,z052,z02;
double u0,u1,u2,u3,u4,u5,u6,u7,u8,u9,w0,w1,w2,w3,w4,w5,w6,w7,w8,w9;

/* Normalization constant */
nc=1.799709e-16;

/* Integration limit: x = L12, y = L21, z = mu */
xmin=0.0;   ymin=0.0;   zmin=0.0;   xmax=0.2;   ymax=1.0;   zmax=1.0;

/* Numerical integration: midpoint rule */
mx=0.0002; my=0.002;   mz=0.002;   mmx=mx/2;   mny=my/2;   mnz=mz/2;
mymznc=my*mz/nc;

/* Printing output headers and variable definition for Mathematica.
   The output file needs to be re-edited. */

printf("( * \n");
printf(" Marginal density for lambda12.\n");
printf(" Calcium, uniform priors, all data.\n");
printf(" Midpoint Rule with widths mx, my, mz: %f,%f,%f \n",mx,my,mz);
printf("( * )\n\n");
printf("CaMargL12All:={\n");

/* Start numerical integration using midpoint rule.

```

Evaluate the integral at every L12

*/

```

for (i=xmin; i<xmax-mmx; i+=mx)
{
    func=0.0;
    immx=i+mmx;      immx4=4*immx;

    for (j=ymin; j<ymax-mmy; j+=my)
    {
        jmmx=j+mmy; ijmm=immx+jmmy;

        for (k=zmin; k<zmax-mnz; k+=mz)
        {
            kmnz=k+mnz;      ik=immx4*kmnz;      ijk=ijmm+kmnz;
            m3=sqrt(ijk*ijk-ik);      m1=(ijk+m3)/2;      m2=(ijk-m3)/2;
            icm=27.1/m3;      p=icm*jmmx;      q=icm*(immx-m2);
            r=icm*(immx-m1);

            y052=exp(-0.52*m2);      y02=exp(-0.2*m2);      y1=exp(-m2);
            y2=y1*y1;      y4=y2*y2;      y6=y2*y4;
            y24=y6*y6*y6*y6;      y48=y24*y24;      y120=y48*y48*y24;
            y408=y120*y120*y120*y48;      z052=exp(-0.52*m1);      z02=exp(-0.2*m1);
            z1=exp(-m1);      z2=z1*z1;      z4=z2*z2;
            z6=z2*z4;      z24=z6*z6*z6*z6;      z48=z24*z24;
            z120=z48*z48*z24;      z408=z120*z120*z120*z48;

            u0=0.21-(y408-z408)*p;      u1=1.97-(y120-z120)*p;      u2=4.16-(y48-z48)*p;
            u3=5.79-(y24-z24)*p;      u4=4.89-(y6-z6)*p;      u5=4.37-(y4-z4)*p;
            u6=3.53-(y2-z2)*p;      u7=3.39-(y1-z1)*p;      u8=2.81-(y052-z052)*p;
            u9=1.1-(y02-z02)*p;

            w0=0.1-q*y408+r*z408;      w1=1.3-q*y120+r*z120;      w2=2.3-q*y48+r*z48;
            w3=5.0-q*y24+r*z24;      w4=8.0-q*y6+r*z6;      w5=9.5-q*y4+r*z4;
            w6=14.0-q*y2+r*z2;      w7=15.0-q*y1+r*z1;      w8=17.0-q*y052+r*z052;
            w9=22.0-q*y02+r*z02;

            S11=u0*u0+u1*u1+u2*u2+u3*u3+u4*u4+u5*u5+u6*u6+u7*u7+u8*u8+u9*u9;
            S12=u0*w0+u1*w1+u2*w2+u3*w3+u4*w4+u5*w5+u6*w6+u7*w7+u8*w8+u9*w9;
            S22=w0*w0+w1*w1+w2*w2+w3*w3+w4*w4+w5*w5+w6*w6+w7*w7+w8*w8+w9*w9;

            den = S11*S22 - S12*S12;
            /* Calculate the posterior density at current L12 */
            func=mymznc/(den*den*den*den)+func;
        }
    }
}
/* Output p(L12|data) at current L12 in form {L12,P(L12)} */
printf("{%f,%f},\n", immx, func);
}
/* end of program */

```

HPD contour z value for lambda12 - lambda21

/* HPD contour z value calculation for lambda12 - lambda21.
The lambda12 - lambda21 axis is divided into series small grids.
x axis = 1000 segments, y and z axis = 500 segments The integral is
evaluated at the center of each square to determine if the p(L12,L21)

is above the z plane. Thus, numerical integration is performed over μ . This code used the normalization constant previously calculated.

Written by Yunnhon Lo, University of Tennessee - Knoxville
Department of Nuclear Engineering (c) 1996-2000
*/

```
#include <stdio.h>
#include <math.h>
main()
{
/* Declaring dummy variables used */
float cvalue;
double area,func,i,j,k,icm,ik,ijk,immx,jmmy,ijmmx,m1,m2,m3,mx,my,mz;
double mmx ,mmy,mmz,mznc,S11,S12,S22,xmin,xmax,ymin,ymax,zmin,zmax,nc;
double p,q,r,volume,immx4,den,y1,y2,y4,y6,y24,y48,y120,y408,y052,y02;
double z1,z2,z4,z6,z24,z48,z120,z408,z052,z02;
double u0,u1,u2,u3,u4,u5,u6,u7,u8,u9,w0,w1,w2,w3,w4,w5,w6,w7,w8,w9;

/* CONTOUR LEVEL INPUT */
printf("Enter contour level, use 0.0 for volume calculation =");
scanf("%f", &cvalue);

/* Normalization constant */
nc=1.799709e-16;

/* Integration limit: x = L12, y = L21, z = mu */
xmin=0.0; ymin=0.0; zmin=0.0; xmax=0.2; ymax=1.0; zmax=1.0;

/* Numerical integration: midpoint rule */
mx=0.0002; my=0.002; mz=0.002; mmx=mx/2; mmy=my/2; mmz=mz/2;
area=mx*my; mznc=mz/nc; volume=0.0;

printf("Calculating.....\n");

for (i=xmin; i<xmax-mmx; i+=mx)
{
    immx=i+mmx;          immx4=immx*4.0;
    for (j=ymin; j<ymax-mmy; j+=my)
    {
        func=0.0;
        jmmy=j+mmy;      ijmmx=immx+jmmy;

/* Begin numerical integration loop for parameter mu */
        for (k=zmin; k<zmax-mmz; k+=mz)
        {
            ijk=ijmmx+k+mmz;          ik=immx4*(k+mmz);          m3=sqrt(ijk*ijk-ik);
            m1=(ijk+m3)/2;             m2=(ijk-m3)/2;             icm=27.1/m3;
            p=icm*jmmy;                q=icm*(immx-m2);          r=icm*(immx-m1);

            y052=exp(-0.52*m2);        y02=exp(-0.2*m2);        y1=exp(-m2);
            y2=y1*y1;                  y4=y2*y2;              y6=y2*y4;
            y24=y6*y6*y6*y6;          y48=y24*y24;          y120=y48*y48*y24;
            y408=y120*y120*y120*y48;  z052=exp(-0.52*m1);    z02=exp(-0.2*m1);
            z1=exp(-m1);               z2=z1*z1;              z4=z2*z2;
            z6=z2*z4;                  z24=z6*z6*z6*z6;      z48=z24*z24;
            z120=z48*z48*z24;          z408=z120*z120*z120*z48;
        }
    }
}
```

```

u0=0.21-(y408-z408)*p;   u1=1.97-(y120-z120)*p;   u2=4.16-(y48-z48)*p;
u3=5.79-(y24-z24)*p;   u4=4.89-(y6-z6)*p;   u5=4.37-(y4-z4)*p;
u6=3.53-(y2-z2)*p;   u7=3.39-(y1-z1)*p;   u8=2.81-(y052-z052)*p;
u9=1.1-(y02-z02)*p;   w0=0.1-q*y408+r*z408;   w1=1.3-q*y120+r*z120;
w2=2.3-q*y48+r*z48;   w3=5.0-q*y24+r*z24;   w4=8.0-q*y6+r*z6;
w5=9.5-q*y4+r*z4;   w6=14.0-q*y2+r*z2;   w7=15.0-q*y1+r*z1;
w8=17.0-q*y052+r*z052;   w9=22.0-q*y02+r*z02;

```

```

S11=u0*u0+u1*u1+u2*u2+u3*u3+u4*u4+u5*u5+u6*u6+u7*u7+u8*u8+u9*u9;
S12=u0*w0+u1*w1+u2*w2+u3*w3+u4*w4+u5*w5+u6*w6+u7*w7+u8*w8+u9*w9;
S22=w0*w0+w1*w1+w2*w2+w3*w3+w4*w4+w5*w5+w6*w6+w7*w7+w8*w8+w9*w9;

```

```

den=S11*S22-S12*S12;
func=mznc/(den*den*den*den*den)+func;
}
if(func >= cvalue)
    volume=area*func+volume;
}
}

```

```

/* Calculate appropriate cv volume and display the result */
if(cvalue > 0)
    { printf("f, volume = %f\t%f\n",cvalue,volume); }
else
    { printf("Calculated total hypervolume is: %e\n",volume); }
}
/* End of program */

```

HPD contour/surface density plot for lambda12 - lambda21

/* Generating the 3D surface density for the parameters L12 and L21 at equal spaces. They are formatted for plotting contours and surface densities on Mathematica. Therefore, no (x,y) coordinates were used. The points are equally spaced according to the Mathematica's range specifications. This code used the normalization constant previously calculated and midpoint numerical integration rules.

Written by Yunnhon Lo, University of Tennessee - Knoxville
 Department of Nuclear Engineering (c) 1996-2000
 */

```

#include <stdio.h>
#include <math.h>
main()
{
double area,func,i,j,k,icm,ik,ijk,immx,jmmy,ijmmx,m1,m2,m3,mx,my,mz;
double mmy,mmz,mznc,nc,p,q,r,S11,S12,S22,xmin,xmax,ymin,ymax,zmin,zmax;
double mmx,volume,immx4,den,y1,y2,y4,y6,y24,y48,y120,y408,y052,y02;
double z1,z2,z4,z6,z24,z48,z120,z408,z052,z02;
double u0,u1,u2,u3,u4,u5,u6,u7,u8,u9,w0,w1,w2,w3,w4,w5,w6,w7,w8,w9;

nc=1.799709e-16;
/* Lambda12: x = horizontal, Lambda21: y = vertical, mu = z*/
xmin=0.0;   xmax=0.2;   ymin=0.0;   ymax=1.0;   zmin=0.0;   zmax=1.0;

mx=0.002;   /* Lambda12 segment width */
my=0.02;    /* Lambda21 segment width */
mz=0.0005;  /* mu segment width integrating over this axis */

```

```

mmx=mx/2;   mmy=my/2;   mmz=mz/2;   mznz=mz/nc;

/* Headers. Information about the data. To be used with Mathematica.
See Mathematica for contour plotting commands and formatting. */
printf("( * \n");
printf("Segment width: %f \t %f \t %f \n", mx,my,mz);
printf("Mesh Ranges: L12-L21 {{%f,%f},{%f,%f}} *)\n",
      xmin+mmx,xmax-mmz,ymin+mmy,ymax-mmy);
printf("l12k21:={\n");

for (j=ymin; j<yymax-mmy; j+=mmy)
{
  /* this will make j as y axis */
  jmmj=j+mmy;
  printf(")\n");
  for (i=xmin; i<xmax-mmz; i+=mx)
  {
    func=0.0;   /* reset func at i,j to zero. */
    /* this will make i as x axis */
    immx=i+mmx;   immx4=immx*4.0;   ijmj=immx+jmmj;

    for (k=zmin; k<zmax-mmz; k+=mz)
    {
      /* Integrate over mu */
      ijk=ijmj+k+mmz;   ik=immx4*(k+mmz);   m3=sqrt(ijk*ijk-ik);
      m1=(ijk+m3)/2;   m2=(ijk-m3)/2;   icm=27.1/m3;
      p=icm*jmmj;   q=icm*(immx-m2);   r=icm*(immx-m1);

      y052=exp(-0.52*m2);   y02=exp(-0.2*m2);   y1=exp(-m2);
      y2=y1*y1;   y4=y2*y2;   y6=y2*y4;
      y24=y6*y6*y6*y6;   y48=y24*y24;   y120=y48*y48*y24;
      y408=y120*y120*y120*y48;   z052=exp(-0.52*m1);   z02=exp(-0.2*m1);
      z1=exp(-m1);   z2=z1*z1;   z4=z2*z2;
      z6=z2*z4;   z24=z6*z6*z6*z6;   z48=z24*z24;
      z120=z48*z48*z24;   z408=z120*z120*z120*z48;

      u0=0.21-(y408-z408)*p;   u1=1.97-(y120-z120)*p;   u2=4.16-(y48-z48)*p;
      u3=5.79-(y24-z24)*p;   u4=4.89-(y6-z6)*p;   u5=4.37-(y4-z4)*p;
      u6=3.53-(y2-z2)*p;   u7=3.39-(y1-z1)*p;   u8=2.81-(y052-z052)*p;
      u9=1.1-(y02-z02)*p;   w0=0.1-q*y408+r*z408;   w1=1.3-q*y120+r*z120;
      w2=2.3-q*y48+r*z48;   w3=5.0-q*y24+r*z24;   w4=8.0-q*y6+r*z6;
      w5=9.5-q*y4+r*z4;   w6=14.0-q*y2+r*z2;   w7=15.0-q*y1+r*z1;
      w8=17.0-q*y052+r*z052;   w9=22.0-q*y02+r*z02;

      S11=u0*u0+u1*u1+u2*u2+u3*u3+u4*u4+u5*u5+u6*u6+u7*u7+u8*u8+u9*u9;
      S12=u0*w0+u1*w1+u2*w2+u3*w3+u4*w4+u5*w5+u6*w6+u7*w7+u8*w8+u9*w9;
      S22=w0*w0+w1*w1+w2*w2+w3*w3+w4*w4+w5*w5+w6*w6+w7*w7+w8*w8+w9*w9;

      den=S11*S22-S12*S12;
      func=mznz/(den*den*den*den)+func;
    }
    /* Print value of integral */
    printf("%f,", func);
  }
  printf(")}\n");
}
/* End of program */

```

Volume/normalization constant with Normal priors calculation

/* Volume (normalization constant) calculation using Normal priors. The data came from Rowland and Groer-Marshall. It uses Gaussian-quadrature numerical integration method with 400 points.

Written by Yunnhon Lo, Department of Nuclear Engineering, University of Tennessee - Knoxville (c) 1996-2000 */

```
#include <stdio.h>
#include <math.h>
main()
{
    int i,j,k;
    double func,ijk,icm,kmmz,ij,m1,m2,m3,p,q,r,S11,S12,S22,immx4,den;
    double priora,priorb,priorc,pmeana,pmeanb,pmeanc,pvara,pvarb,pvarc;
    double y1,y2,y4,y6,y24,y48,y120,y408,y052,y02;
    double z1,z2,z4,z6,z24,z48,z120,z408,z052,z02;
    double u0,u1,u2,u3,u4,u5,u6,u7,u8,u9,w0,w1,w2,w3,w4,w5,w6,w7,w8,w9;

    /* Abbreviated Gaussian quadrature abscissas (x) and weights (c).
       The integration interval is 0 to 2 for parameter Lambda12, Lambda21.
       0 to 0.4 for mu. */

    static double x[400]={0.0001762295834980909934,0.000927374689911765156,
        ...,1.999823770190865148};
    static double xmu[400]={0.00003524591669961819,0.000185474937982353031,
        ...,0.3999647540381730295};
    static double c[400]={0.000452127385157969744,0.001049827946206253127,
        ...,0.0004521273851579697444};
    static double cmu[400]={0.000090425477031593948,0.00020996558924125062,
        ...,0.00009042547703159394886};

    /* Normal distribution parameters from rabbit data.
       Since  $f = 1/(SD * \sqrt{2\pi}) \exp[-0.5 ((x-\text{mean})/SD)^2]$ 
       f is proportional  $\exp[-(x-\text{pmean})^2 / \text{pvar}]$  under Bayes Theorem with
        $\text{pvar}=2 * SD^2$ . pmean = prior mean, pvar = prior variance,
       a = lambda12, b = lambda21, c = mu */

    pmeana= 0.1485349;      pvara= 0.329740768*0.329740768*2;
    pmeanb= 0.1899742;      pvarb= 0.312158955*0.312158955*2;
    pmeanc= 0.04072596;     pvarc= 0.048547304*0.048547304*2;
    func=0.0;

    for (i=0; i<400; i++)
    {
        immx4=4*x[i];
        /* Normal prior (constants dropped) for lambda12 */
        priora=exp(-(x[i]-pmeana)*(x[i]-pmeana)/pvara);

        for (j=0; j<400; j++)
        {
            ij=x[i] + x[j];
            /* Normal prior (constants dropped) for lambda21 */
            priorb=exp(-(x[j]-pmeanb)*(x[j]-pmeanb)/pvarb);

            for (k=0; k<400; k++)
```

```

{
    /* Normal prior (constants dropped) for mu */
    priorc=exp(-(xmu[k]-pmeanc)*(xmu[k]-pmeanc)/pvarc);
    ijk=ij+xmu[k];    m3=sqrt(ijk*ijk-(immx4*xmu[k]));    m1=(ijk+m3)/2;
    m2=(ijk-m3)/2;    icm=27.1/m3;    p=icm*x[j];    q=icm*(x[i]-m2);
    r=icm*(x[i]-m1);

    y052=exp(-0.52*m2);    y02=exp(-0.2*m2);    y1=exp(-m2);
    y2=y1*y1;    y4=y2*y2;    y6=y2*y4;
    y24=y6*y6*y6*y6;    y48=y24*y24;    y120=y48*y48*y24;
    y408=y120*y120*y120*y48; z052=exp(-0.52*m1);    z02=exp(-0.2*m1);
    z1=exp(-m1);    z2=z1*z1;    z4=z2*z2;
    z6=z2*z4;    z24=z6*z6*z6*z6;    z48=z24*z24;
    z120=z48*z48*z24;    z408=z120*z120*z120*z48;

    u0=0.21-(y408-z408)*p;    u1=1.97-(y120-z120)*p;    u2=4.16-(y48-z48)*p;
    u3=5.79-(y24-z24)*p;    u4=4.89-(y6-z6)*p;    u5=4.37-(y4-z4)*p;
    u6=3.53-(y2-z2)*p;    u7=3.39-(y1-z1)*p;    u8=2.81-(y052-z052)*p;
    u9=1.1-(y02-z02)*p;    w0=0.1-q*y408+r*z408;    w1=1.3-q*y120+r*z120;
    w2=2.3-q*y48+r*z48;    w3=5.0-q*y24+r*z24;    w4=8.0-q*y6+r*z6;
    w5=9.5-q*y4+r*z4;    w6=14.0-q*y2+r*z2;    w7=15.0-q*y1+r*z1;
    w8=17.0-q*y052+r*z052;    w9=22.0-q*y02+r*z02;

    S11=u0*u0+u1*u1+u2*u2+u3*u3+u4*u4+u5*u5+u6*u6+u7*u7+u8*u8+u9*u9;
    S12=u0*w0+u1*w1+u2*w2+u3*w3+u4*w4+u5*w5+u6*w6+u7*w7+u8*w8+u9*w9;
    S22=w0*w0+w1*w1+w2*w2+w3*w3+w4*w4+w5*w5+w6*w6+w7*w7+w8*w8+w9*w9;

    den = S11*S22 - S12*S12;
    func=priora*priorb*priorc*c[i]*c[j]*cmu[k]/(den*den*den*den)+func;
}
}
printf("Normalization constant with Normal priors\n");
printf("%e\n", func);
}
/* End of program */

```

Posterior mean & variance for simulated ²²⁶Ra-²²²Rn decay data.

/* Posterior mean and variance calculations for 500 simulated Ra226 - Rn222 decay data. Modified for direct half-life calculations and uses Gaussian quadrature numerical integration methods with 400 points.

Written by Yunnhon Lo, Department of Nuclear Engineering, University of Tennessee - Knoxville (c) 1996-2000 */

```

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

```

```

main()
{
    int i,j,dset;
    double S11,S12,S22,n10,k21,k1n10,coef,k1,k2,den,func,ln2;
    double a1,a2,a3,a4,a5,a6,a7,a8,a9,a10,a11,a12,a13;
    double a14,a15,a16,a17,a18,a19,a20,a21,a22,a23,a24;
    double b1,b2,b3,b4,b5,b6,b7,b8,b9,b10,b11,b12,b13;
    double b14,b15,b16,b17,b18,b19,b20,b21,b22,b23,b24;
    double u1,u2,u3,u4,u5,u6,u7,u8,u9,u10,u11,u12,u13;

```

```

double u14,u15,u16,u17,u18,u19,u20,u21,u22,u23,u24;
double w1,w2,w3,w4,w5,w6,w7,w8,w9,w10,w11,w12,w13;
double w14,w15,w16,w17,w18,w19,w20,w21,w22,w23,w24;
double ex1,ex2,ex3,ex4,ex5,ex6,ex7,ex8,ex9,ex10,ex11,ex12,ex13;
double ex14,ex15,ex16,ex17,ex18,ex19,ex20,ex21,ex22,ex23,ex24;
double ey1,ey2,ey3,ey4,ey5,ey6,ey7,ey8,ey9,ey10,ey11,ey12,ey13;
double ey14,ey15,ey16,ey17,ey18,ey19,ey20,ey21,ey22,ey23,ey24;
double meana,mean2a,vara,sda,meanb,mean2b,varb,sdb;

/* Abbreviated Numerical integration variables */
static double xx1[400]={2.64343543416113e-10,...,5.99894262582633e-6};
static double xx2[400]={3.52458057888138e-5,...,0.999911885485527};
static double cc1[400]={4.83614945780519e-10,...,1.93445978312208e-9};
static double cc2[400]={6.4481992770736e-5,...,1.61204981926839e-4};

/* Abbreviated 500 simulated Ra-226 decay data at each 24 periods */
static double aa1[500]={26934242493,26933940877, ... ,26934223649};
static double aa2[500]={26934285561,26933931670, ... ,26934478904};
...
static double aa24[500]={26933448542,26933462387, ... ,26933322489};

/* Abbreviated 500 simulated Rn-222 decay data at each 24 periods */
static double bb1[500]={29368,29189, ... ,29164};
static double bb2[500]={53903,53597, ... ,53787};
...
static double bb24[500]={173140,173743, ... ,173764};

/* Normalization constant. Calculated in another program */
static double nc[500]={1.95747e-233,2.816584e-226, ... ,4.535577e-232};

/* Initial number of Ra-226 atoms present. Same for all data set */
n10=2.693412383921e10;

/* Natural log of 2 */
ln2=0.6931471805599453;

printf("Posterior means and standard deviations.\n");
printf("E(T),E(T^2),Variance,Std.Dev\n");

/* 500 simulated data sets */
for (dset=0; dset<500; dset++)
{
a1=aa1[dset];      a2=aa2[dset];      a3=aa3[dset];      a4=aa4[dset];
a5=aa5[dset];      a6=aa6[dset];      a7=aa7[dset];      a8=aa8[dset];
a9=aa9[dset];      a10=aa10[dset];     a11=aa11[dset];     a12=aa12[dset];
a13=aa13[dset];     a14=aa14[dset];     a15=aa15[dset];     a16=aa16[dset];
a17=aa17[dset];     a18=aa18[dset];     a19=aa19[dset];     a20=aa20[dset];
a21=aa21[dset];     a22=aa22[dset];     a23=aa23[dset];     a24=aa24[dset];

b1=bb1[dset];      b2=bb2[dset];      b3=bb3[dset];      b4=bb4[dset];
b5=bb5[dset];      b6=bb6[dset];      b7=bb7[dset];      b8=bb8[dset];
b9=bb9[dset];      b10=bb10[dset];     b11=bb11[dset];     b12=bb12[dset];
b13=bb13[dset];     b14=bb14[dset];     b15=bb15[dset];     b16=bb16[dset];
b17=bb17[dset];     b18=bb18[dset];     b19=bb19[dset];     b20=bb20[dset];
b21=bb21[dset];     b22=bb22[dset];     b23=bb23[dset];     b24=bb24[dset];

/* Reset counting variables for each data set */
func=0.0;

```

```

        meana=0.0; mean2a=0.0; vara=0.0; sda=0.0;
        meanb=0.0; mean2b=0.0; varb=0.0; sdb=0.0;

        /* Integration loop for Ra226 */
        for (i=0; i<400; i++)
        {
            k1=xx1[i];          k1n10=k1*n10;
            /* Exponent portion of the Box-Draper likelihood */
            ex1 =exp(-k1);      ex2 =ex1*ex1;      ex3 =ex2*ex1;      ex4 =ex3*ex1;
            ex5 =ex4*ex1;      ex6 =ex5*ex1;      ex7 =ex6*ex1;      ex8 =ex7*ex1;
            ex9 =ex8*ex1;      ex10=ex9*ex1;      ex11=ex10*ex1;    ex12=ex11*ex1;
            ex13=ex12*ex1;      ex14=ex13*ex1;      ex15=ex14*ex1;    ex16=ex15*ex1;
            ex17=ex16*ex1;      ex18=ex17*ex1;      ex19=ex18*ex1;    ex20=ex19*ex1;
            ex21=ex20*ex1;      ex22=ex21*ex1;      ex23=ex22*ex1;    ex24=ex23*ex1;
            /* S11 component */
            u1=a1-n10*ex1;      u2=a2-n10*ex2;      u3=a3-n10*ex3;      u4=a4-n10*ex4;
            u5=a5-n10*ex5;      u6=a6-n10*ex6;      u7=a7-n10*ex7;      u8=a8-n10*ex8;
            u9=a9-n10*ex9;      u10=a10-n10*ex10;    u11=a11-n10*ex11;    u12=a12-n10*ex12;
            u13=a13-n10*ex13;    u14=a14-n10*ex14;    u15=a15-n10*ex15;    u16=a16-n10*ex16;
            u17=a17-n10*ex17;    u18=a18-n10*ex18;    u19=a19-n10*ex19;    u20=a20-n10*ex20;
            u21=a21-n10*ex21;    u22=a22-n10*ex22;    u23=a23-n10*ex23;    u24=a24-n10*ex24;
            /* S11 placed here to speed up calculation */
            S11=u1*u1+u2*u2+u3*u3+u4*u4+u5*u5+u6*u6+u7*u7+u8*u8+u9*u9+u10*u10+
                u11*u11+u12*u12+u13*u13+u14*u14+u15*u15+u16*u16+u17*u17+u18*u18+
                u19*u19+u20*u20+u21*u21+u22*u22+u23*u23+u24*u24;

            /* Integration loop for Rn222 */
            for (j=0; j<400; j++)
            {
                k2=xx2[j];          coef=k1n10/(k2-k1);
                /* Exponent portion of the Box-Draper likelihood */
                ey1 =exp(-k2);      ey2 =ey1*ey1;      ey3 =ey2*ey1;      ey4 =ey3*ey1;
                ey5 =ey4*ey1;      ey6 =ey5*ey1;      ey7 =ey6*ey1;      ey8 =ey7*ey1;
                ey9 =ey8*ey1;      ey10=ey9*ey1;      ey11=ey10*ey1;    ey12=ey11*ey1;
                ey13=ey12*ey1;      ey14=ey13*ey1;      ey15=ey14*ey1;    ey16=ey15*ey1;
                ey17=ey16*ey1;      ey18=ey17*ey1;      ey19=ey18*ey1;    ey20=ey19*ey1;
                ey21=ey20*ey1;      ey22=ey21*ey1;      ey23=ey22*ey1;    ey24=ey23*ey1;
                /* S22 component */
                w1=b1-coef*(ex1-ey1);  w2=b2-coef*(ex2-ey2);  w3=b3-coef*(ex3-ey3);
                w4=b4-coef*(ex4-ey4);  w5=b5-coef*(ex5-ey5);  w6=b6-coef*(ex6-ey6);
                w7=b7-coef*(ex7-ey7);  w8=b8-coef*(ex8-ey8);  w9=b9-coef*(ex9-ey9);
                w10=b10-coef*(ex10-ey10);  w11=b11-coef*(ex11-ey11);
                w12=b12-coef*(ex12-ey12);  w13=b13-coef*(ex13-ey13);
                w14=b14-coef*(ex14-ey14);  w15=b15-coef*(ex15-ey15);
                w16=b16-coef*(ex16-ey16);  w17=b17-coef*(ex17-ey17);
                w18=b18-coef*(ex18-ey18);  w19=b19-coef*(ex19-ey19);
                w20=b20-coef*(ex20-ey20);  w21=b21-coef*(ex21-ey21);
                w22=b22-coef*(ex22-ey22);  w23=b23-coef*(ex23-ey23);
                w24=b24-coef*(ex24-ey24);

                S12=w1*u1+w2*u2+w3*u3+w4*u4+w5*u5+w6*u6+w7*u7+w8*u8+w9*u9+w10*u10+
                    w11*u11+w12*u12+w13*u13+w14*u14+w15*u15+w16*u16+w17*u17+w18*u18+
                    w19*u19+w20*u20+w21*u21+w22*u22+w23*u23+w24*u24;
                S22=w1*w1+w2*w2+w3*w3+w4*w4+w5*w5+w6*w6+w7*w7+w8*w8+w9*w9+w10*w10+
                    w11*w11+w12*w12+w13*w13+w14*w14+w15*w15+w16*w16+w17*w17+w18*w18+
                    w19*w19+w20*w20+w21*w21+w22*w22+w23*w23+w24*w24;
            }
        }

```

```

den = S11*S22 - S12*S12;

```

```

func=(cc1[i]*cc2[j]/(nc[dset]*den*den*den*den*
den*den*den*den*den*den*den));
meana=(ln2/(k1*365)*func)+meana;
meanb=(ln2 /k2*func)+meanb;
mean2a=((ln2 /(k1*365))*(ln2/(k1*365))*func)+mean2a;
mean2b=((ln2/k2)*(ln2/k2)*func)+mean2b;
    }    }
vara=fabs((mean2a-(meana*meana)));          sda=sqrt(vara);
varb=fabs((mean2b-(meanb*meanb)));          sdb=sqrt(varb);

/* Output the results in half-lives */
printf("Set,%d,%,%e,%e,%e,%e,%e,%e,%e,%e\n",
dset,meana,mean2a,vara,sda,meanb,mean2b,varb,sdb);
}    }
/* End of program */

```

Mathematica® plotting commands.

```

(* Marginal density plot of lambda12 (solid line), lambda21 (dash line)
and mu (dot-dash line) from a list of (x, y, f) values      *)

mpl12=ListPlot[margl12data,PlotJoined->True,Frame->True,PlotRange->
All,FrameLabel->{"L12","f(L12|data)","",""}]
mpl21=ListPlot[margl21data,PlotJoined->True,Frame->True,PlotRange->
All,FrameLabel->{"L21","f(L21|data)","",""},PlotStyle->
Dashing[{0.01,0.01}]]
mpmu= ListPlot[margl21data,PlotJoined->True,Frame->True,PlotRange->
All,FrameLabel->{"L21","f(L21|data)","",""},PlotStyle->
Dashing[{0.02,0.01,0.005}]]
Show[mpl12,mpl21,mpmu,PlotRange->All,RotateLabel->True,FrameLabel->
{"parameter","f(p|data)","",""}]

(* Generate three-dimensional surface density plot from an equal spaced
array of height values with plotting range *)

Show[SurfaceGraphics[Data,{Axes->True,Shading->False,AxesLabel->
{"xlabel","ylabel","zlabel"},MeshRange->{{xmin,xmax},{ymin,ymax}}}]

(* Generate contour plot from an equal spaced array of height
values with mesh range (specifies ranges in x and y) and contour z
values z1 and z2 *)

Show[ContourGraphics[Data,{Contours->{z1,z2},Frame->True,FrameLabel->
{"xlabel","ylabel","",""},ContourLines->True,RotateLabel->True,
ContourShading->False,ContourSmoothing->True,PlotRegion->All,
MeshRange->{{xmin,xmax},{ymin,ymax}}}]

```

Mathematica® commands for finding the Gaussian-Quadrature abscissas and weights.

The first step is to load the *Mathematica*® Gaussian Quadrature (GD) package:

```
<<"NumericalMath`GaussianQuadrature`"
```

Next, find the abscissas and weights for n-point GD formula on the interval (a, b):

```
GaussianQuadratureWeights[n, a, b]
```

and the output is in the form of:

```
{{abscissa1, weight1},{abscissa2, weight2},...,{abscissa-n, weight-n}}
```

To minimize numerical integration error, the integration interval is divided into smaller segments. So for the bone calcium analysis with Normal priors, the integration limit of (0, 2) is divided into 10 smaller segments each with 40 GD points and weights. This gave a total of 400 GD points over the interval (0, 2):

```
GaussianQuadratureWeights[40,0.0,0.2];  
GaussianQuadratureWeights[40,0.2,0.4];  
GaussianQuadratureWeights[40,0.4,0.6];  
GaussianQuadratureWeights[40,0.6,0.8];  
GaussianQuadratureWeights[40,0.8,1.0];  
GaussianQuadratureWeights[40,1.0,1.2];  
GaussianQuadratureWeights[40,1.2,1.4];  
GaussianQuadratureWeights[40,1.4,1.6];  
GaussianQuadratureWeights[40,1.6,1.8];  
GaussianQuadratureWeights[40,1.8,2.0];
```

For `GaussianQuadratureWeights[40,0.0,0.2]`, the first five points are:

```
{{0.0001762295834980909934, 0.0004521273851579697443},  
{0.0009273746899117651563, 0.001049827946206253127},  
{0.002274006632271595763, 0.001642109207685722506},...,}
```

Formatted for C as static array variables:

```
/* Abscissa, 400 points */  
static double x[400]={0.000176229583498090993,0.0009273746899117651563,  
0.00227400663227159576,0.004208316950274962958, ... ,}
```

```

/* Weights, 400 points */
static double c[400]={0.000452127385157969744,0.001049827946206253127,
0.001642109207685722506,0.002224578662521202741, ... ,}

```

Mathematica® commands for simulating FDG data decay data based on Normal random error.

```

<<Statistics`ContinuousDistributions`
mean1=f1[ObservationPeriods]; sd1=PercentNoise*mean1;
mean2=f2[ObservationPeriods]; sd2=PercentNoise*mean2;
mean3=f3[ObservationPeriods]; sd3=PercentNoise*mean3;
CA=Table[Random[NormalDistribution[mean1[[j]],sd1[[j]],{j,1,14}]];
CB=Table[Random[NormalDistribution[mean2[[j]],sd2[[j]],{j,1,14}]];
CC=Table[Random[NormalDistribution[mean3[[j]],sd3[[j]],{j,1,14}]];
PlasmaData=CA*0.9;
TissueData=CA*0.1+CB+CC;

```

Mathematica® commands for simulating ^{226}Ra - ^{222}Rn and ^{222}Rn - ^{218}Po decay data based on Normal random error.

```

(* Since the observation times are the same for the two series, only
different units, they will be defined only once. *)

```

```

(* Observation Times, in day or hour *)
Ti={1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24};

```

```

(* Solution of the ODE. f1=Parent, f2=Daughter *)
f1[t_]=n10*Exp[-lambda1*t];
f2[t_]=lambda1*n10*(Exp[-lambda1*t]-Exp[-lambda2*t])/(lambda2-lambda1);

```

```

(* Loads the continuous statistical distributions library *)
<<Statistics`ContinuousDistributions`

```

```

(* Decay of Ra226 to Rn222: initial number of Ra226 present *)
n10=0.37*1602*31536000/Log[2];

```

```

(* Decay constants (1/day)      lambda1=Ra226, lambda2=Rn222 *)
lambda1=Log[2]/(1602*365);      lambda2=Log[2]/(3.8235);

```

```

(* Parameter mu and sigma of a Normal distribution *)
mean1=f1[ObserveTime];          mean2=f2[ObserveTime];

```

```

sd1=Sqrt[m1];
sd2=Sqrt[m2];

(* 500 simulated number of Ra226 atoms present every day for 24 days *)
ListA=IntegerPart[Table[Table[Random[
  NormalDistribution[mean1[[j]],sd1[[j]] ]],{j,1,24}],{x,1,500}]];

(* 500 simulated number of Rn222 atoms present every day for 24 days *)
ListB=IntegerPart[Table[Table[Random[
  NormalDistribution[mean2[[j]],sd2[[j]] ]],{j,1,24}],{x,1,500}]];

(* Combined data for lumped compartmental sampling and save the data *)
ListC=ListA + ListB;
Save["RaRn_compartmentRa", ListA];
Save["RaRn_compartmentRn", ListB];
Save["RaRn_compartmentLump", ListC];

(* Decay of Ra222 to Po218: initial number of Rn222 present *)
n10=0.37*3600*3.8235*24/Log[2];

(* Decay constants (1/hour) *)
lambda1=Log[2]/(3.8235*24); lambda2=Log[2]/(3.05*60);

(* Parameter mu and sigma of a Normal distribution *)
mean1=f1[ObserveTime]; mean2=f2[ObserveTime];
sd1=Sqrt[m1]; sd2=Sqrt[m2];

(* 500 simulated number of Rn222 atoms present every hour for 1 day *)
ListA=IntegerPart[Table[Table[Random[
  NormalDistribution[mean1[[j]],sd1[[j]] ]],{j,1,24}],{x,1,500}]];

(* 500 simulated number of Po218 atoms present every hour for 1 day *)
ListB=IntegerPart[Table[Table[Random[
  NormalDistribution[mean2[[j]],sd2[[j]] ]],{j,1,24}],{x,1,500}]];

(* Combined data for lumped compartmental sampling and save the data *)
ListC=ListA + ListB;
Save["RnPo_compartmentRn", ListA];
Save["RnPo_compartmentPo", ListB];
Save["RnPo_compartmentLump", ListC];

```

APPENDIX C

SAMPLE ^{226}Ra , ^{222}Rn AND ^{218}Po SIMULATED DECAY

DATA SETS AND RESULTS

This appendix contains the samples of the simulated ^{226}Ra , ^{222}Rn and ^{218}Po decay data sets and results. They were calculated using the methodology described in Chapter 6 and algorithms listed in Appendix B.

First four simulated ^{226}Ra – ^{222}Rn decay data sets: number of atoms present.

Time	Simulated Data Set							
	1		2		3		4	
	^{226}Ra	^{222}Rn	^{226}Ra	^{222}Rn	^{226}Ra	^{222}Rn	^{226}Ra	^{222}Rn
0	26934123839	0	26934123839	0	26934123839	0	26934123839	0
1	26934242493	29368	26934131198	29189	26934159900	29374	26933981363	29307
2	26934285561	53903	26933931670	53597	26934071311	53543	26934255224	53729
3	26934288634	74198	26934064633	74140	26934347101	73937	26933891015	73982
4	26934157529	90755	26934023093	90665	26933674448	91367	26934056712	90970
5	26934109447	105268	26933901495	104857	26933928641	105026	26934057735	105655
6	26933963429	117655	26933782482	117095	26933941825	116728	26933942230	117293
7	26933930675	126735	26934151312	126731	26933968309	126315	26933535208	127001
8	26933704934	134602	26933991295	134999	26934069313	135500	26933809706	135109
9	26933959160	141549	26933606019	141695	26933919917	142012	26933743188	141662
10	26933973982	147832	26933719930	147838	26933641526	147197	26933411867	148257
11	26933922878	151763	26933805985	152009	26933775102	152271	26933695095	152690
12	26933350907	155811	26933720797	156152	26933626376	157105	26933820982	156315
13	26933815292	159411	26933750475	159898	26933518707	159389	26933705446	159667
14	26933545612	162285	26933733350	162758	26933539612	162344	26933895782	162420
15	26933812418	163935	26933666987	164806	26933625036	164415	26933568230	165049
16	26933329557	166362	26933576754	166220	26933789479	166862	26933815895	167434
17	26933678861	168222	26933523202	168002	26933501146	167939	26933496679	168495
18	26933480669	169279	26933579072	169226	26933564555	169670	26933619012	169999
19	26933450436	171038	26933425659	170530	26933435176	170857	26933620074	170872
20	26933207425	171781	26933602120	171148	26933360471	171705	26933560865	171678
21	26933340120	172319	26933603407	172267	26933482139	172233	26933307398	171383
22	26933319068	173625	26933312634	172950	26933501303	173246	26933314018	173185
23	26933414127	173761	26933469197	174285	26933513626	173434	26933360884	173375
24	26933448542	173140	26933462387	173743	26933060555	174078	26933202387	174223

First five simulated $^{222}\text{Rn} - ^{218}\text{Po}$ decay data sets: number of atoms present.

Simulated Data Set										
Time	1		2		3		4		5	
	^{222}Rn	^{218}Po	^{222}Rn	^{218}Po	^{222}Rn	^{218}Po	^{222}Rn	^{218}Po	^{222}Rn	^{218}Po
0	176340	0	176340	0	176340	0	176340	0	176340	0
1	175165	104	174901	112	175151	95	175133	103	174948	86
2	174019	115	173187	100	174475	89	173452	89	174517	103
3	171540	113	172248	96	172756	79	172318	112	171981	98
4	171281	102	171097	81	170926	87	170940	97	171030	94
5	170131	94	169955	81	170070	97	169537	78	170222	95
6	168537	100	168411	95	168146	76	168871	103	168408	94
7	166867	103	167091	114	167447	93	168057	93	166868	83
8	165908	103	166066	99	165338	69	166435	90	166011	76
9	164849	100	164811	90	164696	81	165087	87	165394	102
10	163961	100	163058	81	163292	101	163727	79	163434	85
11	162958	92	162520	86	161843	96	162052	74	162525	89
12	161186	76	161224	100	162075	77	160915	94	161466	81
13	160626	93	159366	89	159824	84	159587	84	159894	83
14	159329	71	158387	89	158677	98	158685	92	159041	90
15	156608	92	157543	94	157119	88	157828	78	157043	77
16	156506	76	156083	90	156536	80	156450	95	156072	91
17	155140	76	155222	80	154712	81	154263	98	154907	76
18	154087	65	154007	93	153516	93	154100	101	153870	79
19	152679	71	152749	77	152756	84	152657	83	153274	86
20	151451	77	151836	103	152230	75	151862	84	151901	84
21	150238	81	151085	84	150966	87	149873	75	151092	72
22	148951	83	149446	76	149159	78	149938	92	149299	91
23	148061	110	148199	86	148105	89	148441	95	148739	73
24	146784	79	147101	68	146760	71	146847	85	146981	70

First 20 ^{226}Ra and ^{222}Rn half-lives estimation results calculated with simulated individual $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.

Set	^{226}Ra half-life in years			^{222}Rn half-life in days		
1	1596.14	±	3.41198	3.80451	±	0.01298
2	1600.56	±	2.84396	3.82641	±	0.01399
3	1601.82	±	1.79733	3.83336	±	0.00540
4	1591.73	±	3.11158	3.80419	±	0.00905
5	1600.33	±	3.68059	3.82687	±	0.01418
6	1601.00	±	3.41141	3.83101	±	0.00987
7	1597.96	±	3.89125	3.81425	±	0.01681
8	1602.25	±	2.04465	3.83447	±	0.00519
9	1595.16	±	5.45165	3.81411	±	0.01579
10	1601.61	±	1.94177	3.83184	±	0.00871
11	1597.17	±	5.57334	3.81899	±	0.01687
12	1601.84	±	1.68642	3.83272	±	0.00740
13	1600.73	±	3.90016	3.83009	±	0.01150
14	1599.57	±	3.19717	3.82106	±	0.01608
15	1601.41	±	2.82492	3.83219	±	0.00813
16	1602.09	±	0.75628	3.83417	±	0.00221
17	1591.04	±	1.41279	3.80219	±	0.00403
18	1596.15	±	1.39567	3.80305	±	0.00660
19	1600.50	±	3.71321	3.82776	±	0.01382
20	1592.08	±	5.48638	3.80238	±	0.01755

First 20 ^{226}Ra and ^{222}Rn half-lives estimation results calculated with simulated lumped $^{226}\text{Ra} - ^{222}\text{Rn}$ decay data.

Set	^{226}Ra half-life in years			^{222}Rn half-life in days		
1	1430.50	±	506.75	6.19180	±	7.55358
2	2009.45	±	367.32	2.48018	±	3.70150
3	1587.61	±	460.17	4.47015	±	6.31792
4	1726.41	±	432.18	3.40099	±	5.61493
5	1758.18	±	663.04	6.59273	±	9.53914
6	1886.26	±	787.53	7.52419	±	10.65725
7	1958.76	±	488.91	2.96008	±	5.32302
8	1169.45	±	586.78	12.05855	±	10.86445
9	1627.52	±	445.99	3.82526	±	5.89479
10	1026.36	±	498.91	11.12136	±	9.48247
11	1717.44	±	319.46	2.36106	±	3.38894
12	2633.83	±	945.04	4.76452	±	9.47974
13	2039.52	±	246.79	1.27245	±	1.37825
14	1847.85	±	394.02	2.76485	±	4.61765
15	2114.91	±	769.05	5.55498	±	9.16649
16	1866.29	±	356.05	2.29924	±	3.83283
17	1860.18	±	622.85	5.45629	±	8.62400
18	1305.09	±	629.14	10.96312	±	10.91020
19	2144.08	±	386.46	2.17235	±	3.82320
20	1264.75	±	708.32	11.51846	±	11.54418

First 20 ^{222}Rn and ^{218}Po half-lives estimation results calculated with simulated individual $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.

Set	^{222}Rn half-life in hours			^{218}Po half-life in minutes		
1	3.81676	±	0.01877	3.12217	±	0.08660
2	3.82225	±	0.00413	3.08573	±	0.07061
3	3.82110	±	0.01652	2.91477	±	0.06609
4	3.82355	±	0.01344	3.07207	±	0.07102
5	3.86030	±	0.02326	2.96970	±	0.06263
6	3.81714	±	0.01451	3.02691	±	0.06089
7	3.82488	±	0.01239	3.01275	±	0.05563
8	3.81851	±	0.01386	2.98743	±	0.06106
9	3.82720	±	0.01822	3.20483	±	0.06179
10	3.81182	±	0.01958	2.88015	±	0.07867
11	3.83376	±	0.02610	2.97459	±	0.06637
12	3.82292	±	0.01888	3.12360	±	0.06989
13	3.82166	±	0.00997	2.96833	±	0.07135
14	3.86025	±	0.02355	3.19573	±	0.06829
15	3.82520	±	0.02347	3.05092	±	0.09072
16	3.81735	±	0.01604	3.05646	±	0.07020
17	3.82613	±	0.01665	3.04631	±	0.07257
18	3.83256	±	0.02295	2.93344	±	0.07678
19	3.82383	±	0.01196	2.99942	±	0.07117
20	3.81200	±	0.02587	3.04682	±	0.06368

First 20 ^{222}Rn and ^{218}Po half-lives estimation results calculated with simulated lumped $^{222}\text{Rn} - ^{218}\text{Po}$ decay data.

Set	^{222}Rn half-life in hours			^{218}Po half-life in minutes		
1	3.82173	±	0.02545	2.72546	±	2.97246
2	3.82691	±	0.01542	1.47422	±	0.96361
3	3.82125	±	0.02339	2.41396	±	2.60052
4	3.82941	±	0.02392	2.33811	±	2.29648
5	3.86324	±	0.02224	1.90065	±	1.98257
6	3.79246	±	0.03202	5.92009	±	4.81996
7	3.83746	±	0.02412	1.61340	±	1.25167
8	3.81925	±	0.01594	1.91620	±	1.88785
9	3.83212	±	0.02740	2.50858	±	2.63079
10	3.81883	±	0.01284	1.16541	±	0.77596
11	3.84216	±	0.02970	1.90609	±	2.03374
12	3.83026	±	0.02317	1.44821	±	1.19230
13	3.81155	±	0.02824	4.96163	±	4.40775
14	3.85011	±	0.03344	4.44968	±	4.57239
15	3.82903	±	0.03088	2.68545	±	3.07145
16	3.81952	±	0.01799	1.92473	±	1.94233
17	3.83578	±	0.02517	1.81337	±	1.67376
18	3.84090	±	0.02904	2.25898	±	2.38833
19	3.82372	±	0.02599	3.56309	±	3.39365
20	3.81835	±	0.02687	1.71588	±	1.72333

VITA

Yunnhon (Yohon) Lo was born in Taipei, Taiwan on October 4, 1971. His family moved to Hilton Head Island, South Carolina in the summer of 1981. After graduating from Hilton Head High School in June 1990, he entered the University of Tennessee at Knoxville in August 1990 where, in May 1994, he received his Bachelor of Science in Nuclear Engineering. The following August he returned to the University of Tennessee to pursue his Master of Science in Nuclear Engineering, which he received in May 1996. He remained at the University of Tennessee to continue his studies and received his Doctor of Philosophy in Nuclear Engineering in May 2000.