

INFORMATION TO USERS

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

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

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

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

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

UMI

**A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600**

**A Comparison of Three Trough to Peak Estimators Derived
from Ambulatory Blood Pressure Data**

by

Robert A. Jones

**A dissertation submitted in partial fulfillment
of the requirements for the degree of**

Doctor of Philosophy

University of Washington

1997

Approved by Lloyd Fisher
Chairperson of Supervisory Committee

Program Authorized
to Offer Degree Biostatistics

Date 21 March 1997

UMI Number: 9730054

UMI Microform 9730054
Copyright 1997, by UMI Company. All rights reserved.

**This microform edition is protected against unauthorized
copying under Title 17, United States Code.**

UMI
300 North Zeeb Road
Ann Arbor, MI 48103

In presenting this dissertation in partial fulfillment of the requirements for the Doctoral degree at the University of Washington, I agree that the Library shall make its copies freely available for inspection. I further agree that extensive copying of this dissertation is allowable only for scholarly purpose, consistent with "fair use" as prescribed in the U.S. Copyright Law. Requests for copying or reproduction of this dissertation may be referred to University Microfilms, 1490 Eisenhower Place, P.O. Box 975, Ann Arbor, MI 48106, to whom the author has granted "the right to reproduce and sell (a) copies of the manuscript in microfilm and/or (b) printed copies of the manuscript made from microfilm."

Signature Robert A. Jones

Date March 21, 1997

University of Washington

Abstract

**A Comparison of Three Trough to Peak Estimators Derived
from Ambulatory Blood Pressure Data**

by Robert A. Jones

**Chairperson of the Supervisory Committee
Professor Lloyd Fisher
Department of Biostatistics**

A general multivariate model is proposed to analyze ABPM data obtained from multiple subjects in which two ABPM series, typically at baseline and on randomized therapy in a clinical trial, are obtained on each subject. The model is a specific formulation of the general repeated measures multivariate regression model in which the covariance matrix associated with each of the two ABPM profiles are assumed equal and with unspecified structure. Exact maximum likelihood estimates of the unknown parameters and asymptotic properties for the case of no missing data are derived.

Three methods to estimate the trough to peak ratio using ABPM data are examined in this dissertation. These include a method based on between subject time of day averages, the second method using a fitted Fourier curve using the repeated measures multivariate model, and a third simple Fourier regression model. Asymptotic properties of the three estimators are derived and compared. as well as a Monte Carlo simulation to determine finite sample properties.

TABLE OF CONTENTS

	Page
List of Figures	ii
List of Tables	iv
Introduction	1
Chapter 1: Curve fitting of ABPM Data	4
Maximum Likelihood Estimators of Parameters	9
Asymptotic Properties of M.L.E.	28
Chapter 2: Trough to Peak Ratio	46
Asymptotic Properties of T/P ratio	52
Chapter 3: T/P Estimator Monte - Carlo Simulation	74
Simple Fourier versus M.L.E. Fourier Estimator	87
Hourly Mean versus Simple Fourier Estimator	128
Chapter 4: Summary & Conclusions	213
List of References	216

LIST OF FIGURES

Number	Page
S1. Simulated Drug Effect Curve - Simulation 1	82
S2. Simulated Drug Effect Curve - Simulation 2	83
S3. Simulated Drug Effect Curve - Simulation 3	84
S4. Simulated Drug Effect Curve - Simulation 4	85
S5. Simulated Drug Effect Curve - Simulation 5	86
S1.F1. Avg. Bias Plot, Sim. 1, Init. Value : -3, T/P : 0.75.....	140
S1.F2. Avg. Bias Plot, Sim. 1, Init. Value : -6, T/P : 0.75.....	141
S1.F3. Avg. Bias Plot, Sim. 1, Init. Value : -3, T/P : 0.50.....	142
S1.F4. Avg. Bias Plot, Sim. 1, Init. Value : -6, T/P : 0.50.....	143
S1.F5. Avg. Bias Plot, Sim. 1, Init. Value : -3, T/P : 0.25.....	144
S1.F6. Avg. Bias Plot, Sim. 1, Init. Value : -6, T/P : 0.25.....	145
S1.F7. Ratio of M.S.E. Plot, Sim. 1, Init. Value : -3, T/P : 0.75.....	146
S1.F8. Ratio of M.S.E. Plot, Sim. 1, Init. Value : -6, T/P : 0.75.....	147
S1.F9. Ratio of M.S.E. Plot, Sim. 1, Init. Value : -3, T/P : 0.50.....	148
S1.F10. Ratio of M.S.E. Plot, Sim. 1, Init. Value : -6, T/P : 0.50.....	149
S1.F11. Ratio of M.S.E. Plot, Sim. 1, Init. Value : -3, T/P : 0.25.....	150
S1.F12. Ratio of M.S.E. Plot, Sim. 1, Init. Value : -6, T/P : 0.25.....	151

LIST OF FIGURES
(Continued)

Number	Page
S1.F13. Ratio of M.S.E., Minumum Across Peak Hours, Sim. 1, Init. Value : -3.....	152
S1.F14. Ratio of M.S.E., Minimum Across Peak Hours, Sim. 1, Init. Value : -6.....	153
S1.F15. Ratio of M.S.E., Maximum Across Peak Hours, Sim. 1, Init. Value : -3.....	154
S1.F16. Ratio of M.S.E., Maximum Across Peak Hours, Sim. 1, Init. Value : -6.....	155
S1.F17. Ratio of M.S.E., Average Across Peak Hours, Sim. 1, Init. Value : -3.....	156
S1.F18. Ratio of M.S.E., Average Across Peak Hours, Sim. 1, Init. Value : -6.....	157
S2.F1. Avg. Bias Plot, Sim. 2, Init. Value : -3	173
S2.F2. Avg. Bias Plot, Sim. 2, Init. Value : -6	174
S2.F3. Ratio of M.S.E. Plot, Sim. 2, Init. Value : -3	175
..	
S2.F4. Ratio of M.S.E. Plot, Sim. 2, Init. Value : -6	176
..	
S3.F1. Avg. Bias Plot, Sim. 3, Init. Value : -3	183
S3.F2. Ratio of M.S.E. Plot, Sim. 3, Init. Value : -3	184
S4.F1. Avg. Bias Plot, Sim. 4	191
S4.F2. Ratio of M.S.E. Plot, Sim. 4	192

LIST OF FIGURES
(Continued)

Number	Page
S5.F1. Avg. Bias Plot, Sim. 5, Case = 1.....	199
S5.F2. Avg. Bias Plot, Sim. 5, Case = 2.....	200
S5.F3. Avg. Bias Plot, Sim. 5, Case = 3.....	201
S3.F4. Ratio of M.S.E. Plot, Sim. 3, Case = 1	202
S3.F5. Ratio of M.S.E. Plot, Sim. 3, Case = 2	203
S3.F6. Ratio of M.S.E. Plot, Sim. 3, Case = 3	204

LIST OF TABLES

Number	Page
2.1 Comparison of Asymptotic Variances of Trough to Peak Estimators ...	73
S1.C1R Comparison of Fourier Estimators, Simulation 1	91
S2.C1 Comparison of Fourier Estimators, Simulation 2	93
S3.C1 Comparison of Fourier Estimators, Simulation 3	95
S4.C1 Comparison of Fourier Estimators, Simulation 4	97
S5.C1 Comparison of Fourier Estimators, Simulation 5	98
S1.C2 Bias Differences Simple - M.L.E., Simulation 1	100
S1.C3 M.S.E. Differences Simple - M.L.E., Simulation 1	104
S2.C2 Bias Differences Simple - M.L.E., Simulation 2	108
S2.C3 M.S.E. Differences Simple - M.L.E., Simulation 2	109
S3.C2 Bias Differences Simple - M.L.E., Simulation 3	110
S3.C3 M.S.E. Differences Simple - M.L.E., Simulation 3	111
S4.C2 Bias Differences Simple - M.L.E., Simulation 4	112
S4.C3 M.S.E. Differences Simple - M.L.E., Simulation 4	113
S5.C2 Bias Differences Simple - M.L.E., Simulation 5	114
S5.C3 M.S.E. Differences Simple - M.L.E., Simulation 5	115
S1.C4 Summary Comparison of Fourier Estimators, Simulation 1.....	116
S2.C4 Summary Comparison of Fourier Estimators, Simulation 2	123

LIST OF TABLES
(Continued)

Number	Page
S3.C4 Summary Comparison of Fourier Estimators, Simulation 3	125
S4.C4 Summary Comparison of Fourier Estimators, Simulation 4	126
S5.C4 Summary Comparison of Fourier Estimators, Simulation 5	127
S1.T1 Bias Estimate, Simulation 1	158
S1.T2 Bias Diff. Between Fourier and Hourly Estimate, Simulation 1	160
S1.T3 M.S.E. Diff. Between Fourier and Hourly Estimate, Simulation 1 ..	162
S1.T4 Ratio of M.S.E. (Hourly / Fourier), Simulation 1	164
S1.T5 Bias and M.S.E. Diff. 5 & 7 Term Fourier, Simulation 1	166
S1.T6 Comparison of 5 & 7 Term Fourier Estimators, Simulation 1	172
S2.T1 Bias Estimate, Simulation 2	177
S2.T2 Bias Diff. Between Fourier and Hourly Estimate, Simulation 2	178
S2.T3 M.S.E. Diff. Between Fourier and Hourly Estimate, Simulation 2 ..	179
S2.T4 Ratio of M.S.E. (Hourly / Fourier), Simulation 2	180
S2.T5 Bias and M.S.E. Diff. 5 & 7 Term Fourier, Simulation 2	181
S2.T6 Comparison of 5 & 7 Term Fourier Estimators, Simulation 2	182
S3.T1 Bias Estimate, Simulation 3	185
S3.T2 Bias Diff. Between Fourier and Hourly Estimate, Simulation 3	186

LIST OF TABLES
(Continued)

Number	Page
S3.T3 M.S.E. Diff. Between Fourier and Hourly Estimate, Simulation 3 .	187
S3.T4 Ratio of M.S.E. (Hourly / Fourier), Simulation 3	188
S3.T5 Bias and M.S.E. Diff. 5 & 7 Term Fourier, Simulation 3	189
S3.T6 Comparison of 5 & 7 Term Fourier Estimators, Simulation 3	190
S4.T1 Bias Estimate, Simulation 4	193
S4.T2 Bias Diff. Between Fourier and Hourly Estimate, Simulation 4	194
S4.T3 M.S.E. Diff. Between Fourier and Hourly Estimate, Simulation 4	195
S4.T4 Ratio of M.S.E. (Hourly / Fourier), Simulation 4	196
S4.T5 Bias and M.S.E. Diff. 5 & 7 Term Fourier, Simulation 4	197
S4.T6 Comparison of 5 & 7 Term Fourier Estimators, Simulation 4	198
S5.T1 Bias Estimate, Simulation 5	205
S5.T2 Bias Diff. Between Fourier and Hourly Estimate, Simulation 5	206
S5.T3 M.S.E. Diff. Between Fourier and Hourly Estimate, Simulation 5	207
S5.T4 Ratio of M.S.E. (Hourly / Fourier), Simulation 5	208
S5.T5 Bias and M.S.E. Diff. 5 & 7 Term Fourier, Simulation 5	209
S5.T6 Comparison of 5 & 7 Term Fourier Estimators, Simulation 5	210
CV.T1 Covariance Matrix Used in Simulation211

ACKNOWLEDGMENTS

The author wishes to express sincere appreciation to Professor Lloyd Fisher who made this possible and provided guidance and encouragement. In addition, thanks to Professors Kathryn Davis - Kennedy and William Barlow for their constructive feedback in the preparation of this manuscript.

Introduction

Ambulatory blood pressure monitoring (ABPM) is common in the evaluation of the efficacy of antihypertensive drug therapies. New portable ABPM devices provide a method of measuring the effect of a drug regimen over the total drug response time period away from a physicians office. These devices can be programmed to automatically measure subject blood pressure (diastolic and systolic) and heart rates at predetermined intervals for extended periods of time, typically 24 hours.

The diagnosis and management of elevated blood pressure (hypertension) has traditionally been based on blood pressure readings taken at a physicians office. In-office hypertension has long been considered diagnostic of disease. The degree to which elevated blood pressure has been correlated with target organ disease is well documented [Kannel 1974 , Heptinstall 1974]. Several studies have demonstrated that the presence of and severity of cardiovascular morbidity and mortality are more closely associated with ambulatory measurements than with blood pressure measured in the physicians office [Zachariah et al, 1991]

A number of clinical applications of ABPM have been published utilizing various techniques for analyzing the ABPM data. Typically the length of time between measurements is relatively short (5 minutes to 15 or 30 minutes). Hourly means are commonly computed and used in the analysis due to inconsistencies in time spans between readings and occasional bad and discarded readings. Diurnal patterns (also called circadian rhythm) in blood pressure is well documented (Staessen et al, 1991), and is largely associated with sleep and physical activity patterns. Therefore the analysis of ABPM data separate time dependent changes in blood pressure due to this blood pressure cycle. Typically day time and night time

blood pressure readings are grouped and analyzed separately, with day time readings further divided into two parts during which the subjects are awake or asleep.

Several methods have been reported to model the diurnal variation. Univariate cosinor analysis (Marire et al, 1988) and Fourier analysis (Streffberg et al, 1989) have been used to smooth hourly ABPM hourly means, typically on the treatment group sample average hourly means. Running averages have been used to smooth individual ABPM data (Cramer et al, 1991) which are then averaged across treatment groups to create univariate statistics for comparison of treatment effects.

Some of the clinical trials in which ABPM data are collected to study the effect of antihypertensive drug therapies use randomly allocated placebo controlled crossover designs to increase precision when comparing treatments and thereby reducing the number of study subjects. In these studies a baseline ABPM is taken followed possibly by a washout period. Then a series of on - treatment ABPM's follow to measure the effect of the antihypertensive therapy. Typically the clinical protocol will include 2 or more treatment arms, with one treatment a placebo, to use as the control group. Typically drug treatment and ABPM monitoring are initiated at approximately the same time of day for all patients to minimize variation in blood pressure due to diurnal variation .

Two end points of particular interest in assessing the efficacy of antihypertensive drug therapies is the drug peak effect and the drug trough effect. The peak effect is defined as the maximum change in blood pressure observed in a placebo subtracted dose response curve and the trough is the placebo subtracted change at

the end of the dose response curve. This will be a trough of the drug plasma concentration but may or may not have the smallest effect on blood pressure. It is important to measure an effect at trough to show the drug covers the whole treatment period. Typically the statistic that is reported is the ratio of the trough to peak (denoted as T/P ratio).

In the following discussion, I will develop a classical multivariate model using individual subject hourly ABPM reading averages to model the diurnal blood pressure variation, which is appropriate for a clinical trial with a multiple treatment arm crossover design. A trough to peak estimate is developed using the multivariate approach and simpler univariate models. The T/P estimators are then compared in terms of asymptotic behavior and finally the estimators are compared for various drug response curves for finite sample sizes.

Chapter 1

Curve Fitting of Repeated Measures

In many of the APBM experimental protocols, several APBM's are performed on each study patient . Typically an APBM is taken at baseline prior to treatment, then after randomization and treatment one or more follow-up APBM's are recorded on each individual.

Many of the APBM's carried out on an individual have a duration of approximately 24 hours with readings occurring at regular intervals, such as every 15 minutes. For this development we will assume that we have readings that are equally spaced in time. The APBM readings taken on an individual are correlated, but the model for the correlation structure is unknown and may be complex. However the correlation should be taken into account in the modeling and analysis of the data.

Methods have been developed to model repeated measures data by Potthoff and Roy (1964), Khatri (1966), Rao and Grizzle and Allen (1969). These models come under the general heading of Growth Curve Analysis. Using the notation of Morrison (1976) p 216-218 we can model these data as a full-rank univariate liner model:

$$(1.1) \quad X_i = D\beta + e .$$

Let r be the number of repeated readings, p the number of readings in a single ABPM, X_i the $rp \times 1$ vector of ABPM readings for an individual, β a $q \times 1$

unknown parameter vector, D the known $r_p \times q$ non random (considering the randomized assignment as fixed) design matrix of rank $q \leq r_p$ and the $r_p \times 1$ error vector e . We assume e has the multinormal distribution with zero mean vector and positive definite covariance matrix. That is

$$E(ee') = \Sigma$$

with Σ unknown or possibly with a specified structure.

If we assume we have N independent observations of X_i 's ($i=1, \dots, N$) the generalization of model (1.1) which allows for the imposition of an experimental design on the N sampling units is the following:

$$(1.2) \quad X = D\beta A + e$$

with:

X the $r_p \times N$ matrix of ABPM readings [X_1, X_2, \dots, X_N]

D is a $r_p \times q$ known matrix of rank q

β is a $q \times m$ matrix of unknown regression parameters

A is a $m \times N$ known matrix reflecting the design of experiment,

with rank m

m = the number of treatments.

and:

$$E(X_I) = D\beta A_I \text{ where } A_I \text{ represents the } I \text{ th column of } A$$

$$V(X_I) = \Sigma .$$

As mentioned above, many ABPM study protocols have a baseline ABPM reading prior to treatment, then after randomization and treatment dose one or more follow-up ABPM recordings of length p are taken on each individual, giving a total of r separate ABPM readings for each subject in the study, and a total of rp separate observations on each subject.. In this experimental situation the X_i vectors are composed of r vectors of length p . We also assume we have m treatment groups (including possibly the placebo group) with n_j ($j=1,\dots,m$) subjects in each treatment group and no missing data. Then a general formulation of equation (1.2) is:

X the $rp \times N$ matrix of vectors

(1.3)

$$X = \begin{bmatrix} X_{1,1} & \dots & X_{1,n_1} & X_{1,n_1+n_2} & \dots & X_{1,n_1+n_2+\dots+n_{m-1}} & X_{1,n_1+n_2+\dots+n_{m-1}+n_m} \\ X_{2,1} & \dots & X_{2,n_1} & X_{2,n_1+n_2} & \dots & X_{2,n_1+n_2+\dots+n_{m-1}} & X_{2,n_1+n_2+\dots+n_{m-1}+n_m} \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ X_{r,1} & \dots & X_{r,n_1} & X_{r,n_1+n_2} & \dots & X_{r,n_1+n_2+\dots+n_{m-1}} & X_{r,n_1+n_2+\dots+n_{m-1}+n_m} \end{bmatrix}$$

with $N = \sum_{j=1}^m n_j$

and $X'_{i,j} = [x_{i,j,1} \ x_{i,j,2} \ \dots \ x_{i,j,p}] (1 \times p)$, $i=1, \dots, r$ $j=1, \dots, N$

D is a $rp \times q$ known matrix of rank q , made up of sub matrices D_1, D_2, \dots, D_r such that $D' = [D'_1, D'_2, \dots, D'_r]$ depending on the regression model and parameter formulation.

With ABPM readings one can model the circadian rhythm with a low term Fourier cosine and sine series or other orthogonal transformation (Streffberg et al, 1989). If we use the $(c+s+1)$ term Fourier sine and cosine model, where c is the number of cosine terms and s the number of sine terms for example, and we fit separate Fourier coefficients for each treatment group and follow-up period then D takes the form:

$$D = \begin{bmatrix} D_F & 0 & \dots & 0 \\ 0 & D_F & \dots & 0 \\ \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & D_F \end{bmatrix}$$

with D_F a $p \times (c+s+1)$ matrix with $(c+s+1)$ the number of Fourier terms used in the model for each of the follow-up ABPM curves. D_F has the form

$$D_F = \sqrt{\frac{2}{p}} \begin{bmatrix} 1/\sqrt{2} & \cos(\frac{2\pi}{p}) & \dots & \cos(\frac{2c\pi}{p}) & \sin(\frac{2\pi}{p}) & \dots & \sin(\frac{2s\pi}{p}) \\ \vdots & \vdots & \vdots & \vdots & \vdots & \dots & \vdots \\ 1/\sqrt{2} & \cos(\frac{2\pi p}{p}) & \dots & \cos(\frac{2c\pi p}{p}) & \sin(\frac{2\pi p}{p}) & \dots & \sin(\frac{2s\pi p}{p}) \end{bmatrix}$$

β is then an $r \times (c+s+1) \times m$ matrix of unknown Fourier coefficients with the form:

$$(1.4) \quad \beta = \begin{bmatrix} \beta_{1,1} & \beta_{1,2} & \dots & \beta_{1,m} \\ \beta_{2,1} & \beta_{2,2} & \dots & \beta_{2,m} \\ \vdots & \vdots & \dots & \vdots \\ \beta_{r,1} & \beta_{r,2} & \dots & \beta_{r,m} \end{bmatrix} \quad \text{with } \beta_{i,j} = \begin{bmatrix} \beta_{i,j,1} \\ \beta_{i,j,2} \\ \vdots \\ \beta_{i,j,(c+s+1)} \end{bmatrix}$$

and the $m \times N$ matrix A :

$$(1.5) \quad A = \begin{bmatrix} A_1 & 0 & \dots & 0 \\ 0 & A_2 & \dots & 0 \\ \vdots & \vdots & \dots & \vdots \\ 0 & 0 & \dots & A_m \end{bmatrix}$$

where each A_j is a $1 \times n_j$ matrix of 1's for all $j=1, \dots, m$.

In the following I derive the Maximum Likelihood estimators for the unknown regression parameter β and Σ in model (1.2) above for the situation where r , the number of repeated sequences of ABPM readings on each individual is 2. For notational convenience I assume that each ABPM is a sequence of $p/2$ (with $p/2$ an integer) readings with a total of p readings on each individual. The covariance matrix is unknown, but assumed to have structure:

$$(1.6) \quad \Sigma = \begin{bmatrix} \Sigma_D & \Sigma_O' \\ \Sigma_O & \Sigma_D \end{bmatrix}$$

with Σ_D, Σ_O both $p/2 \times p/2$ and of unspecified structure.

Maximum Likelihood Estimators for β, Σ

Theorem 1.1

Let X be a $p \times N$ matrix of random variables where:

$$X = \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} \quad \text{with } X_1 \text{ and } X_2 \text{ both } p/2 \times N \text{ matrices}$$

Assume:

$$E(X) = D\beta A$$

where:

D is a $p \times q$ known matrix of rank q

β is a $q \times m$ matrix of unknown parameters

A is a $m \times N$ known matrix reflecting the design of experiment,
rank m .

Further assume that X_I are independent multivariate normals such that:

$$E(X_I) = D\beta A_I \quad \text{where } A_I \text{ represents the } I \text{ th column of } A$$

and a design matrix D of the form:

$$D = \begin{pmatrix} D_1 \\ D_2 \end{pmatrix} \text{ with}$$

$$D_1 = [D_{11}, 0] \text{ and } D_2 = [0, D_{11}]$$

D_1, D_2 both with dimension $p/2 \times q$

D_{11} a $p/2 \times q/2$ matrix of rank $q/2$ and 0 a $p/2 \times q/2$ matrix of 0's.

Also the covariance matrix is:

$V(X_I) = \Sigma$ where Σ is of the form:

$$\Sigma = \begin{bmatrix} \Sigma_D & \Sigma'_O \\ \Sigma_O & \Sigma_D \end{bmatrix} \quad \text{each submatrix is } p/2 \text{ by } p/2.$$

that is the diagonal and off diagonal covariance matrices are equal .

Then the M.L.E.'s for β and Σ are:

$$\bar{\beta} = (B_1'S^{-1}B_1)^{-1}B_1'S^{-1})XA'(AA')^{-1}$$

$$\bar{\Sigma} = \frac{1}{2N} \left[(Z_1 - B_1\bar{\beta}A)(Z_1 - B_1\bar{\beta}A)' + (Z_2 - B_2\bar{\beta}A)(Z_2 - B_2\bar{\beta}A)' \right]$$

with $Z_1 = \begin{bmatrix} X_1 \\ X_2 \end{bmatrix}$ and $Z_2 = \begin{bmatrix} X_2 \\ X_1 \end{bmatrix}$

$$B_1 = \begin{bmatrix} D_1 \\ D_2 \end{bmatrix} \quad \text{and} \quad B_2 = \begin{bmatrix} D_2 \\ D_1 \end{bmatrix}$$

Proof:

The M.L.E.'s for β and Σ are derived using an approach similar one used by Khatri (1979) p. 191 use to derive the M.L.E.'s for the generalized growth curve model.

The likelihood function can be written as (Khatri, 1979):

$$(1.7) \quad L(\beta, \Sigma) = (2\pi)^{-\frac{1}{2}pN} |\Sigma|^{-\frac{1}{2}N} \exp\left(-\frac{1}{2}\Sigma^{-1}(X - D\beta A)(X - D\beta A)'\right)$$

We can rewrite X and D as:

$$X = \begin{bmatrix} X_1 \\ X_2 \end{bmatrix}, \quad D = \begin{bmatrix} D_1 \\ D_2 \end{bmatrix}$$

where X_1 is the matrix of the first $p/2$ rows, X_2 the last $p/2$ rows of X . Similarly D_1 is the matrix of the first $p/2$ rows and D_2 the last $p/2$ rows of D .

Then (1.7) can be rewritten as:

(1.8)

$$L(\beta, \Sigma) = (2\pi)^{-\frac{1}{2}pN} |\Sigma|^{-\frac{1}{2}N} \exp\left\{-\frac{1}{2}\text{tr}\left(\Sigma^{-1} \begin{pmatrix} X_1 - D_1\beta A \\ X_2 - D_2\beta A \end{pmatrix} \begin{pmatrix} X_1 - D_1\beta A \\ X_2 - D_2\beta A \end{pmatrix}'\right)\right\}$$

letting $Y_1 = X_1 - D_1\beta A$,

$$Y_2 = X_2 - D_2\beta A$$

(1.8) becomes:

$$(1.9) \quad (2\pi)^{-\frac{1}{2}pN} |\Sigma|^{-\frac{1}{2}N} \exp\left\{-\frac{1}{2}\text{tr}\left(\Sigma^{-1} \begin{pmatrix} Y_1 Y_1' & Y_1 Y_2' \\ Y_2 Y_1' & Y_2 Y_2' \end{pmatrix}\right)\right\}$$

Now with the positive definite covariance matrix with the form:

$$\Sigma = \begin{pmatrix} \Sigma_D & \Sigma_O' \\ \Sigma_O & \Sigma_D \end{pmatrix} \quad \text{with} \quad \Sigma_O = \Sigma_O' \quad \text{then the form of its}$$

inverse is of the form:

$$(1.10) \quad \Sigma^{-1} = \begin{pmatrix} A & B' \\ B & A \end{pmatrix} \quad \text{with} \quad B = B'$$

Using (1.10) and the general form of the inverse of a partitioned matrix from

Rao, 1965 p. 33 we can write the inverse of Σ as:

$$(\Sigma)^{-1} = \begin{pmatrix} \Sigma_D & \Sigma_O' \\ \Sigma_O & \Sigma_D \end{pmatrix}^{-1} = \begin{pmatrix} \Sigma_D^{-1} + FE^{-1}F' & -FE^{-1} \\ -E^{-1}F' & \Sigma_D^{-1} + FE^{-1}F' \end{pmatrix}$$

where:

$$\begin{aligned} E &= \Sigma_D - \Sigma_O \Sigma_D^{-1} \Sigma_O', \\ F &= \Sigma_D^{-1} \Sigma_O' \end{aligned}$$

Multiplying the matrices in the exponent the likelihood equation becomes:

(1.11)

$$\begin{aligned} L(\beta, \Sigma) &= (2\pi)^{-\frac{pN}{2}} |\Sigma|^{-\frac{N}{2}} \exp\left\{-\frac{1}{2}\left[\right. \right. \\ &\quad \text{tr}[(\Sigma_D^{-1} + \Sigma_D^{-1} \Sigma_O (\Sigma_D - \Sigma_O \Sigma_D^{-1} \Sigma_O)^{-1} \Sigma_O \Sigma_D^{-1}) Y_1 Y_1'] + \\ &\quad \text{tr}[(\Sigma_D^{-1} + \Sigma_D^{-1} \Sigma_O (\Sigma_D - \Sigma_O \Sigma_D^{-1} \Sigma_O)^{-1} \Sigma_O \Sigma_D^{-1}) Y_2 Y_2'] - \\ &\quad \left. \left. 2\text{tr}[(\Sigma_D^{-1} \Sigma_O' (\Sigma_D - \Sigma_O \Sigma_D^{-1} \Sigma_O)^{-1}) Y_1 Y_2'] \right] \right\} \end{aligned}$$

For a given β let

$$(1.12) \quad \begin{aligned} \overline{\Sigma_D} &= \frac{1}{2N} [Y_1 Y_1' + Y_2 Y_2'], \\ \overline{\Sigma_O} &= \frac{1}{N} [Y_1 Y_2'] \end{aligned}$$

be the proposed estimates for Σ_D and Σ_O respectively. Substituting into (1.11) get:

(1.13)

$$L(\beta, \Sigma) = (2\pi)^{-\frac{pN}{2}} |\Sigma|^{-\frac{N}{2}} \exp\left\{-\frac{1}{2} \left[\text{tr}\left\{(\overline{\Sigma}_D^{-1} + \overline{\Sigma}_D^{-1} \overline{\Sigma}_O (\overline{\Sigma}_D - \overline{\Sigma}_O' \overline{\Sigma}_D^{-1} \overline{\Sigma}_O)^{-1} \overline{\Sigma}_O' \overline{\Sigma}_D^{-1}) 2N \overline{\Sigma}_D\right\} - 2 \text{tr}\left\{(\overline{\Sigma}_D^{-1} \overline{\Sigma}_O (\overline{\Sigma}_D - \overline{\Sigma}_O' \overline{\Sigma}_D^{-1} \overline{\Sigma}_O)^{-1} N \overline{\Sigma}_O)\right\} \right]\right\}$$

Simplifying (1.13) becomes:

$$(1.14) \quad L(\beta, \overline{\Sigma}) = (2\pi)^{-\frac{pN}{2}} |\overline{\Sigma}|^{-\frac{N}{2}} \exp\left\{-\frac{Np}{2}\right\}$$

with:

$$(1.15) \quad \overline{\Sigma} = \begin{pmatrix} \overline{\Sigma}_D & \overline{\Sigma}_O' \\ \overline{\Sigma}_O & \overline{\Sigma}_D \end{pmatrix}$$

Now let $\overline{\Sigma}_D, \overline{\Sigma}_O$ be any two other estimators with

$$\overline{\Sigma} = \begin{pmatrix} \overline{\Sigma}_D & \overline{\Sigma}_O' \\ \overline{\Sigma}_O & \overline{\Sigma}_D \end{pmatrix} \text{ positive definite.}$$

The likelihood is then:

$$(116) \quad L(\beta, \Sigma) = (2\pi)^{-\frac{pN}{2}} |\bar{\Sigma}|^{-\frac{N}{2}} \exp\left\{-\frac{1}{2} \text{tr}[\bar{\Sigma}^{-1} \begin{pmatrix} Y_1 Y_1' & Y_1 Y_2' \\ Y_2 Y_1' & Y_2 Y_2' \end{pmatrix}]\right\}$$

now since $\bar{\Sigma}^{-1}$ has the form $\begin{pmatrix} A & B' \\ B & A \end{pmatrix}$ it is easy to show that:

$$\text{tr}[\bar{\Sigma}^{-1} \begin{pmatrix} Y_1 Y_1' & Y_1 Y_2' \\ Y_2 Y_1' & Y_2 Y_2' \end{pmatrix}] = \frac{1}{2} \text{tr}[\bar{\Sigma}^{-1} \begin{pmatrix} Y_1 Y_1' + Y_2 Y_2' & 2Y_1 Y_2' \\ 2Y_2 Y_1' & Y_2 Y_2' + Y_1 Y_1' \end{pmatrix}]$$

or

$$\text{tr}[\bar{\Sigma}^{-1} \begin{pmatrix} Y_1 Y_1' & Y_1 Y_2' \\ Y_2 Y_1' & Y_2 Y_2' \end{pmatrix}] = \text{tr}[\bar{\Sigma}^{-1} N \bar{\Sigma}]$$

with $\bar{\Sigma}$ defined in (1.15) above

the likelihood (1.16) is:

$$(1.17) \quad L(\beta, \Sigma) = (2\pi)^{-\frac{pN}{2}} |\bar{\Sigma}|^{-\frac{N}{2}} \exp\left\{-\frac{1}{2} \text{tr}[\bar{\Sigma}^{-1} N \bar{\Sigma}]\right\}$$

Now I will prove that

$$L(\beta, \bar{\Sigma}) \geq L(\beta, \Sigma)$$

for β fixed, that is equation (1.14) \geq (1.17) or equivalently

$$(1.18) \log(L(\beta, \bar{\Sigma})) - \log(L(\beta, \bar{\Sigma})) \geq 0$$

Now (1.18) is:

$$(1.19)$$

$$\begin{aligned} & \left[-\frac{pN}{2} \log(2\pi) - \frac{N}{2} \log(|\bar{\Sigma}|) - \frac{Np}{2} \right] - \\ & \left(-\frac{pN}{2} \log(2\pi) - \frac{N}{2} \log(|\bar{\Sigma}|) - \frac{N}{2} \text{tr}[\bar{\Sigma}^{-1} \bar{\Sigma}] \right) \end{aligned}$$

Rearranging terms get

$$(1.20) \quad \frac{N}{2} \left[-\log\left(\frac{|\bar{\Sigma}|}{|\bar{\Sigma}|}\right) + \text{tr}(\bar{\Sigma}^{-1} \bar{\Sigma}) - p \right]$$

Following the development in Rao (1967) p 531, letting

$\lambda_1, \lambda_2, \dots, \lambda_p$ be the roots of $|\bar{\Sigma} - \lambda \bar{\Sigma}| = 0$. Now all $\lambda_i \geq 0$ since both matrices in the expression are positive definite.

And (1.20) becomes:

$$(1.21)$$

$$\begin{aligned} & \frac{N}{2} [-\log(\lambda_1 \lambda_2 \dots \lambda_p) + (\lambda_1 + \lambda_2 + \dots + \lambda_p) - p] = \\ & \frac{N}{2} \sum_{i=1}^p [-\log(\lambda_i) - 1 + \lambda_i] \end{aligned}$$

Since $\lambda_i > 0$ and $x \leq e^{x-1}$ for $x > 0$ we have:

$$-\log(x) - 1 + x \geq 0$$

Therefore:

$$\frac{N}{2} \sum_{i=1}^p [-\log(\lambda_i) - 1 + \lambda_i] \geq 0$$

Therefore for any fixed β :

$$L(\beta, \bar{\Sigma}) \geq L(\beta, \bar{\bar{\Sigma}}) \text{ with :}$$

$$\bar{\bar{\Sigma}} = \begin{pmatrix} \bar{\Sigma}_D & \bar{\Sigma}'_O \\ \bar{\Sigma}_O & \bar{\Sigma}_D \end{pmatrix}$$

with:

$$\bar{\Sigma}_D = \frac{1}{2N} [Y_1 Y_1' + Y_2 Y_2']$$

$$\bar{\Sigma}_O = \frac{1}{N} [Y_1 Y_2']$$

Now we will find $\bar{\beta}$ such that:

$$L(\bar{\beta}, \bar{\Sigma}) \geq L(\beta, \bar{\Sigma})$$

Let

$$\begin{aligned} Z_1 &= \begin{matrix} X_1 \\ X_2 \end{matrix}, & Z_2 &= \begin{matrix} X_2 \\ X_1 \end{matrix} \\ B_1 &= \begin{matrix} D_1 \\ D_2 \end{matrix}, & B_2 &= \begin{matrix} D_2 \\ D_1 \end{matrix} \end{aligned}$$

then

$$\bar{\Sigma} = \frac{1}{2N} [(Z_1 - B_1\beta A)(Z_1 - B_1\beta A)' + (Z_2 - B_2\beta A)(Z_2 - B_2\beta A)']$$

and from equation (1.14) the likelihood is:

$$L(\beta, \bar{\Sigma}) = (2\pi)^{-\frac{Np}{2}} |\bar{\Sigma}|^{-\frac{N}{2}} \exp\left\{-\frac{Np}{2}\right\}$$

To maximize the likelihood with respect to β therefore we have to maximize:

$$|\bar{\Sigma}|^{-\frac{N}{2}}.$$

or minimize:

$$|\bar{\Sigma}|$$

Now using a method similar to that used by Khatri 1979, p. 24

$$\bar{\Sigma} = \frac{1}{2N} [(Z_1 - B_1\beta A)(Z_1 - B_1\beta A)' + (Z_2 - B_2\beta A)(Z_2 - B_2\beta A)']$$

is equal to:

(1.22)

$$\begin{aligned} & \frac{1}{2N} [(Z_1 - B_1\beta A)(I - A'(AA')^{-1}A)(Z_1 - B_1\beta A) \\ & + (Z_1 - B_1\beta A)A'(AA')^{-1}A(Z_1 - B_1\beta A)' \\ & + (Z_2 - B_2\beta A)(I - A'(AA')^{-1}A)(Z_2 - B_2\beta A)' \\ & + (Z_1 - B_1\beta A)A'(AA')^{-1}A(Z_1 - B_1\beta A)'] \end{aligned}$$

with

$$\begin{aligned} & (Z_i - B_i\beta A)(I - A'(AA')^{-1}A)(Z_i - B_i\beta A)' \\ & = Z_i Z_i' - Z_i A'(AA')^{-1} A Z_i' \end{aligned}$$

Let

$$\begin{aligned} Y_1 &= Z_1 A'(AA')^{-1} \\ S_1 &= Z_1 Z_1' - Z_1 A'(AA')^{-1} A Z_1' \\ Y_2 &= Z_2 A'(AA')^{-1} \\ S_2 &= Z_2 Z_2' - Z_2 A'(AA')^{-1} A Z_2' \\ T &= \begin{bmatrix} 0 & I \\ I & 0 \end{bmatrix} \end{aligned}$$

where Y_1 is $p \times m$, S_1 is $p \times p$, T is $p \times p$ consisting of submatrices

0 a zero matrix of dimension $\frac{p}{2} \times \frac{p}{2}$ and I the identity matrix with dimensions

also $\frac{p}{2} \times \frac{p}{2}$.

Now

$$Y_2 = Z_2 A' (A A')^{-1} = T Y_1$$

$$S_2 = Z_2 Z_2' - Z_2 A' (A A')^{-1} A Z_2' = T S_1 T'$$

and (1.22) is equal to:

$$\frac{1}{2N} [S_1 + S_2 + (Y_1 - B_1 \beta) A A' (Y_1 - B_1 \beta)' + (Y_2 - B_2 \beta) A A' (Y_2 - B_2 \beta)']$$

which is equal to:

$$\frac{1}{2N} [S_1 + T S_1 T' + (Y_1 - B_1 \beta) A A' (Y_1 - B_1 \beta)' + T (Y_1 - B_1 \beta) A A' (Y_1 - B_1 \beta)' T']$$

or

$$(1.23) \quad \bar{\Sigma} = \frac{1}{2N} [S_1 + T S_1 T' + P G']$$

with P a $p \times 2m$ matrix and D a $p \times 2m$ matrix where:

$$P = [(Y_1 - B_1 \beta), T(Y_1 - B_1 \beta)]$$

$$G' = \begin{bmatrix} A A' (Y_1 - B_1 \beta) \\ A A' (Y_1 - B_1 \beta)' T' \end{bmatrix}$$

Therefore we want to minimize:

$$|\bar{\Sigma}| = \left| \frac{1}{2N} [S_1 + TS_1T' + PG'] \right| \text{ or}$$

$$(1.24) \quad |[S_1 + TS_1T' + PG']|$$

with respect to β

Now $S_1 + TS_1T'$ is positive definite with probability 1 if $N \geq p/2$, therefore,

$(S_1 + TS_1T')^{-1}$ exists and

(1.24) is equal to

$$|(S_1 + TS_1T')| \left| I + (S_1 + TS_1T')^{-1} PG' \right|$$

Using Khatri's Corollary 1.3.3, 1979 p. 5 the above equation can be rewritten as:

$$= |(S_1 + TS_1T')| \left| I + G'(S_1 + TS_1T')^{-1} P \right|$$

Now $G'(S_1 + TS_1T')^{-1} P$ in the original variables is equal to:

(1.25)

$$\begin{bmatrix} AA' & 0 \\ 0 & AA' \end{bmatrix} \begin{bmatrix} (Y_1 - B_1\beta)' S^{-1} (Y_1 - B_1\beta) & (Y_1 - B_1\beta)' S^{-1} T (Y_1 - B_1\beta) \\ (Y_1 - B_1\beta)' T' S^{-1} (Y_1 - B_1\beta) & (Y_1 - B_1\beta)' S^{-1} (Y_1 - B_1\beta) \end{bmatrix}$$

with $S = (S_1 + TS_1T')$

Following Khatri's outline for proving Theorem 1.10.3 ,1979 p 24

and using:

$$S^{-1} = (S^{-1} - S^{-1}B_1(B_1'S^{-1}B_1)^{-1}B_1'S^{-1}) + S^{-1}B_1(B_1'S^{-1}B_1)^{-1}B_1'S^{-1}$$

and $(TS)^{-1} = S^{-1}T = TS^{-1}$ with S defined above.

Then

$$(Y_1 - B_1\beta)'S^{-1}(Y_1 - B_1\beta) = H + \eta'(B_1'S^{-1}B_1)\eta$$

$$(Y_1 - B_1\beta)'T'S^{-1}(Y_1 - B_1\beta) = J + \upsilon'(B_1'T'S^{-1}B_1)\upsilon$$

with

$$H = Y_1'(S^{-1} - S^{-1}B_1(B_1'S^{-1}B_1)^{-1}B_1'S^{-1})Y_1$$

$$\eta = ((B_1'S^{-1}B_1)^{-1}B_1'S^{-1})Y_1 - \beta$$

$$J = Y_1'(T'S^{-1} - T'S^{-1}B_1(B_1'T'S^{-1}B_1)^{-1}B_1'T'S^{-1})Y_1$$

$$\upsilon = (B_1'T'S^{-1}B_1)^{-1}B_1'T'S^{-1})Y_1 - \beta$$

We will now show that with the structure of the design matrix assumed in the initial setup that $\eta = \upsilon$.

Since $S = (S_1 + TS_1T')$ it is easy to show that S has the structure that can be re expressed as the following partitioned matrix:

$$S = \begin{bmatrix} X & R \\ R & X \end{bmatrix} \text{ where } X \text{ and } R \text{ are } p/2 \times p/2.$$

and therefore S^{-1} has a similar form, that is:

$$S^{-1} = \begin{bmatrix} K & L \\ L & K \end{bmatrix} \text{ where } K \text{ and } L \text{ are } p/2 \times p/2.$$

Also by assumption:

$$B = \begin{bmatrix} D_1 \\ D_2 \end{bmatrix} = \begin{bmatrix} D_{11} & 0 \\ 0 & D_{11} \end{bmatrix}$$

Therefore:

$$B_1'S^{-1}B_1 = \begin{bmatrix} D_{11}'KD_{11} & D_{11}'LD_{11} \\ D_{11}'LD_{11} & D_{11}'KD_{11} \end{bmatrix}$$

Notice that $B_1'S^{-1}B_1$ is symmetric so we can write its inverse as:

$$(B_1'S^{-1}B_1)^{-1} = \begin{bmatrix} T & U \\ U & T \end{bmatrix} \text{ with } T \text{ and } U \text{ } q/2 \times q/2.$$

Therefore

$$(1.26) \quad (B_1'S^{-1}B_1)^{-1}B_1'S^{-1} = \begin{bmatrix} TD_{11}'K + UD_{11}'L & UD_{11}'K + TD_{11}'L \\ UD_{11}'K + TD_{11}'L & TD_{11}'K + UD_{11}'L \end{bmatrix}$$

Now

$$TS^{-1} = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} K & L \\ L & K \end{bmatrix} = \begin{bmatrix} L & K \\ K & L \end{bmatrix}.$$

Therefore

$$B_1' TS^{-1} B_1 = \begin{bmatrix} D_{11}' L D_{11} & D_{11}' K D_{11} \\ D_{11}' K D_{11} & D_{11}' L D_{11} \end{bmatrix}$$

consequently:

$$(B_1' TS^{-1} B_1)^{-1} = \begin{bmatrix} U & T \\ T & U \end{bmatrix} \text{ using the above notation.}$$

And:

$$(1.27) \quad (B_1' TS^{-1} B_1)^{-1} B_1' TS^{-1} = \begin{bmatrix} U D_{11}' L + T D_{11}' K & T D_{11}' L + U D_{11}' K \\ T D_{11}' L + U D_{11}' K & U D_{11}' L + T D_{11}' K \end{bmatrix}$$

Now examining the right side of equations (1.26) and (1.27) we see they are identical, therefore:

$$(B_1' TS^{-1} B_1)^{-1} B_1' TS^{-1} = (B_1' S^{-1} B_1)^{-1} B_1' S^{-1}$$

thus: $\eta = \upsilon$.

Therefore noting that $\eta = \upsilon$ (1.25) becomes:

$$\begin{bmatrix} AA' & 0 \\ 0 & AA' \end{bmatrix} \begin{bmatrix} H + \eta'(B_1'S^{-1}B_1)\eta & J + \eta'(B_1'T'S^{-1}B_1)\eta \\ J + \eta'(B_1'T'S^{-1}B_1)\eta & H + \eta'(B_1'S^{-1}B_1)\eta \end{bmatrix}$$

which is equal to:

$$\begin{bmatrix} AA' & 0 \\ 0 & AA' \end{bmatrix} \left(\begin{bmatrix} H & J \\ J & H \end{bmatrix} + \begin{bmatrix} \eta'(B_1'S^{-1}B_1)\eta & \eta'(B_1'T'S^{-1}B_1)\eta \\ \eta'(B_1'T'S^{-1}B_1)\eta & \eta'(B_1'S^{-1}B_1)\eta \end{bmatrix} \right)$$

Therefore (1.24) $|[S_1 + TS_1T' + PD']|$ is equal to

$$|S|x|I + \begin{bmatrix} AA' & 0 \\ 0 & AA' \end{bmatrix} \left(\begin{bmatrix} H & J \\ J & H \end{bmatrix} + \begin{bmatrix} \eta'(B_1'S^{-1}B_1)\eta & \eta'(B_1'T'S^{-1}B_1)\eta \\ \eta'(B_1'T'S^{-1}B_1)\eta & \eta'(B_1'S^{-1}B_1)\eta \end{bmatrix} \right)|$$

Letting:

$$\mathcal{H} = \begin{bmatrix} H & J \\ J & H \end{bmatrix}, \quad \mathcal{A} = \begin{bmatrix} A & 0 \\ 0 & A \end{bmatrix} \text{ the above equation}$$

becomes:

$$|S|x|I + \mathcal{A}'\mathcal{H}\mathcal{A} + \mathcal{A}' \begin{bmatrix} \eta'(B_1'S^{-1}B_1)\eta & \eta'(B_1'T'S^{-1}B_1)\eta \\ \eta'(B_1'T'S^{-1}B_1)\eta & \eta'(B_1'S^{-1}B_1)\eta \end{bmatrix} \mathcal{A}$$

Using Khattri's corollary 1.3.3 this becomes:

$$|S|x|I + \mathcal{A}'\mathcal{H}\mathcal{A} + \mathcal{A}' \begin{bmatrix} \eta'(B_1'S^{-1}B_1)\eta & \eta'(B_1'T'S^{-1}B_1)\eta \\ \eta'(B_1'T'S^{-1}B_1)\eta & \eta'(B_1'S^{-1}B_1)\eta \end{bmatrix} \mathcal{A}$$

Now \mathcal{H} positive semi-definite, hence $I + A\mathcal{H}A'$ is positive definite.

Let the characteristic roots of

$$(I + A\mathcal{H}A')^{-1} A' \begin{bmatrix} \eta'(B_1'S^{-1}B_1)\eta & \eta'(B_1'T'S^{-1}B_1)\eta \\ \eta'(B_1'T'S^{-1}B_1)\eta & \eta'(B_1'S^{-1}B_1)\eta \end{bmatrix} A$$

be λ_i ($i = 1, 2, \dots, N$),

which gives $\lambda_i \geq 0$ for all i and

$$| [S_1 + TS_1T' + PD'] | = |S|x|I + A\mathcal{H}A'|x \prod_{i=1}^N (1 + \lambda_i).$$

The minimum value of $\prod_{i=1}^N (1 + \lambda_i)$ varying η is 1, and it can only

be attained iff $\lambda_1 = \lambda_2 = \dots = \lambda_N = 0$, that is

$$A' \begin{bmatrix} \eta'(B_1'S^{-1}B_1)\eta & \eta'(B_1'T'S^{-1}B_1)\eta \\ \eta'(B_1'T'S^{-1}B_1)\eta & \eta'(B_1'S^{-1}B_1)\eta \end{bmatrix} A = 0$$

which means $B_1\eta A = 0$ or

$$(1.28) \quad B_1\beta A = B_1(B_1'S^{-1}B_1)^{-1}B_1'S^{-1}Y_1A$$

Since B with dimension $p \times q$ has rank q and A with dimension $m \times N$ has rank m then $B_1' B_1$ with dimension $q \times q$ has rank q and AA' with dimension $m \times m$ has rank m . Therefore $(B_1' B_1)^{-1}$ and $(AA')^{-1}$ exists and (1.28) becomes:

$$(1.29) \quad \beta = (B_1' S^{-1} B_1)^{-1} B_1' S^{-1} Y_1$$

We have shown that if

$$\bar{\Sigma} = \frac{1}{2N} [(Z_1 - B_1 \beta A)(Z_1 - B_1 \beta A)' + (Z_2 - B_2 \beta A)(Z_2 - B_2 \beta A)']$$

then

$$L(\beta, \bar{\Sigma}) \geq L(\beta, \Sigma) \quad \text{for any } \beta \quad \text{and}$$

$$L(\bar{\beta}, \bar{\Sigma}) \geq L(\beta, \bar{\Sigma}) \quad \text{iff } \bar{\beta} = \beta = (B_1' S^{-1} B_1)^{-1} B_1' S^{-1} Y_1$$

therefore $\bar{\Sigma}, \bar{\beta}$ are the maximum likelihood estimators of Σ, β proving the theorem.

Asymptotic Properties of M.L.E. for β

To derive the asymptotic properties of the M.L. estimator for β , I must first look at the properties of S introduced in the above theorem, specifically we are interested in S_M which is S divided by $2(N-m)$, that is:

$$(1.30) \quad S_M = (S_1 + TS_1T') / 2(N - m)$$

with

$$\sum_{j=1}^m n_j = N$$

$$(1.31) \quad S_1 = X(I - A'(AA')^{-1}A)X$$

$$S_1 = \begin{pmatrix} X_1 \\ X_2 \end{pmatrix} (I - A'(AA')^{-1}A) \begin{pmatrix} X_1' & X_2' \end{pmatrix} \quad \text{and}$$

$$T = \begin{bmatrix} 0 & I \\ I & 0 \end{bmatrix} \quad \text{and} \quad X = \begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \quad \text{with } X_1 \text{ and } X_2 \text{ } p/2 \times N \text{ submatrices of}$$

X .

Lemma 1.1

Given the assumptions of Theorem 1.1 then S_M as defined in (1.30) converges in probability as all n_1, n_2, \dots, n_k approach infinity to Σ .

That is:

$$S_M = \frac{(S_1 + TS_1T')}{2(N-m)} \xrightarrow{P} \Sigma$$

Proof:

We denote the elements of S_1 as

$$(1.32) \quad S_1 = \begin{bmatrix} s_{1,1} & s_{1,2} & \dots & s_{1,p-1} & s_{1,p} \\ s_{2,1} & s_{2,2} & \dots & s_{2,p-1} & s_{2,p} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ s_{p-1,1} & s_{p-1,2} & \dots & s_{p-1,p-1} & s_{p-1,p} \\ s_{p,1} & s_{p,2} & \dots & s_{p,p-1} & s_{p,p} \end{bmatrix}$$

We can rewrite S_1 as:

$$(1.33) \quad (Z + D\beta A)P(Z + D\beta A)$$

with

$$Z = X - D\beta A$$

$$P = I - A'(AA')^{-1}A$$

Now expanding (1.33) we get:

$$\begin{aligned}
 & (Z + D\beta A)P(Z + D\beta A)' = \\
 & (Z + D\beta A)(Z' + A'\beta'D' - A'(AA')^{-1}AZ' - A'(AA')^{-1}AA'\beta'D') \\
 & = Z(I - A'(AA')^{-1}A)Z'
 \end{aligned}$$

Therefore

$$(1.34) \quad S_1 = Z(I - A'(AA')^{-1}A)Z'$$

where Z is a $p \times N$ matrix with columns which are

independently distributed as p dimensional multivariate normal random

variables with mean 0 and covariance Σ .

That is

$$Z = (Z_1 \quad Z_2 \quad \dots \quad Z_N)$$

$$Z_j \sim N_p(0, \Sigma) \quad j=1, \dots, N$$

$$\text{COV}(Z_i, Z_j) = 0 \quad \text{for all } i \neq j$$

Now letting $P = I - A'(AA')^{-1}A$, then the trace of P is:

$$\text{tr}(P) = \text{tr}(I) - \text{tr}(A'(AA')^{-1}A)$$

Since I is $N \times N$, $\text{tr}(I) = N$

Now

$$A = \begin{bmatrix} 1_1 & \dots & 1_{n_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1_{n_1+1} & \dots & 1_{n_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ [: & : & : & : & : & : & : & : & : & : & : & : & : & : & :] \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1_{n_{m-2}+1} & \dots & 1_{n_{m-1}} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1_{n_{m-1}+1} & \dots & 1_{n_m} \end{bmatrix}$$

with $\sum_{j=1}^m n_j = N$

Therefore if we denote:

$${}_n 1_m = \begin{bmatrix} 1 & \dots & 1 \\ : & & : \\ 1 & \dots & 1 \end{bmatrix} \text{ a } n \times m \text{ matrix of 1's}$$

$${}_n 0_m = \begin{bmatrix} 0 & \dots & 0 \\ : & & : \\ 0 & \dots & 0 \end{bmatrix} \text{ a } n \times m \text{ matrix of 0's}$$

Then

$$A'(AA')^{-1}A = \begin{bmatrix} 1/n_1(1_{n_1}) & 0_{n_2} & \dots & 0_{n_m} \\ 0_{n_1} & 1/n_2(1_{n_2}) & \dots & 0_{n_m} \\ \vdots & \vdots & \ddots & \vdots \\ 0_{n_1} & 0_{n_2} & \dots & 1/n_m(1_{n_m}) \end{bmatrix}$$

and therefore

$$\text{tr}(A'(AA')^{-1}A) = m$$

Consequently:

$$\text{tr}(P) = \text{tr}(I) - \text{tr}(A'(AA')^{-1}A) = N - m$$

From above:

$$(1.35) \quad S_1 = ZPZ'$$

with $P = I - A'(AA')^{-1}A$ and $Z = \begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix}$, Z a $p \times N$ matrix with

columns which are independently distributed as p dimensional multivariate

normal random variables with mean 0 and covariance Σ .

Using a similar argument as in Johnson & Wichern (1988) p. 285 and the fact that

$P = I - A'(AA')^{-1}A$ is idempotent and symmetric, we can write P

as:

$$P = \lambda_1 e_1 e_1' + \lambda_2 e_2 e_2' + \dots + \lambda_{N-m} e_{N-m} e_{N-m}' \text{ where } (\lambda_i, e_i) \text{ are the}$$

eigenvalue and normalized eigenvector pairs of P. Note that all N-m

eigenvalues λ_i are equal to 1 since P is idempotent, so

$$P = e_1 e_1' + e_2 e_2' + \dots + e_{N-m} e_{N-m}' \text{ and therefore from (1.35) above}$$

$$S_1 = \sum_{k=1}^{N-m} Z e_k e_k' Z'$$

Letting $V_k = Z e_k$ we have that the V_k are Normally distributed and

$$E(V_k) = E(Z e_k) = 0 \quad \text{and}$$

$$\text{COV}(V_k, V_l) = e_l e_k' \Sigma = \begin{cases} 0 & l \neq k \\ \Sigma & l = k \end{cases}$$

Therefore

$$S_1 = \sum_{k=1}^{N-m} V_k V_k' \text{ has a central}$$

Wishart distribution $W_{N-m}(\cdot | \Sigma)$ with N-m degrees of freedom.

From the properties of the Wishart distribution each element of S , which we have labeled $s_{i,j}$ (see 1.32) is a sum of N-m independent random variables,

that is
$$s_{i,j} = \sum_{r=1}^{N-m} v_{i,j,r} v'_{i,j,r} \quad \text{with}$$

$E(v_{i,j,r} v'_{i,j,r}) = \sigma_{i,j}$ where $\sigma_{i,j}$ is the i,j element of Σ

$\text{VAR}(v_{i,j,r} v'_{i,j,r}) = c_{i,j} < \infty$ for

all $i, j=1,2,\dots,p$ and $r=1 \dots N-m$.

Also $\text{Cov}(v_{i,j,r} v'_{i,j,r}, v_{i,j,s} v'_{i,j,s}) = 0$ for all $r \neq s$.

Therefore using the results of Chebyshev's Theorem (Rao p. 112) as $N-m$ increases to infinity:

$$\frac{s_{i,j}}{(N-m)} = \frac{1}{(N-m)} \sum_{r=1}^{N-m} v_{i,j,r} v'_{i,j,r} \xrightarrow{P} \sigma_{i,j}$$

And consequently as $N-m$ increases to infinity:

$$\frac{S_1}{(N-m)} = \frac{1}{(N-m)} \sum_{k=1}^{N-m} V_k V_k' \xrightarrow{P} \Sigma$$

Similarly, as $N-m$ increases to infinity:

$$\frac{TS_1T'}{(N-m)} = \frac{1}{(N-m)} \sum_{k=1}^{N-m} TV_k V_k' T' \xrightarrow{P} T\Sigma T' = \Sigma$$

since by assumption $\Sigma = \begin{matrix} \Sigma_D & \Sigma'_O \\ \Sigma_O & \Sigma_D \end{matrix}$.

Therefore as $N-m$ increases to infinity:

$$S_M = \frac{(S_1 + TS_1\Gamma)}{2(N-m)} \xrightarrow{P} \Sigma.$$

We showed that the maximum likelihood estimator of β denoted as $\bar{\beta}$ is

$$(1.36) \quad \bar{\beta} = (D'S^{-1}D)^{-1}D'S^{-1}XA'(AA')^{-1} \quad \text{with}$$

$$S = (S_1 + TS_1\Gamma)$$

$$S_1 = X(I - A'(AA')^{-1}A)X$$

or equivalently:

$$(1.37) \quad \bar{\beta} = (D'S_M^{-1}D)^{-1}D'S_M^{-1}XA'(AA')^{-1}$$

with S_M defined in (1.30).

I will now show that $\bar{\beta}$ defined above converges to β as n goes to infinity.

Lemma 2.2

Given the assumptions of Theorem 1.1 then $\bar{\beta}$ as defined in (1.36 or 1.37) converges in probability to β as all n_1, n_2, \dots, n_k approach infinity. That is:

$$\bar{\beta} = (D'S_M^{-1}D)^{-1}D'S_M^{-1}XA'(AA')^{-1} \xrightarrow{P} \beta.$$

Proof:

$$\bar{\beta} = ((D'S_M^{-1}[\Sigma\Sigma^{-1}]D)^{-1}D'S_M^{-1}[\Sigma\Sigma^{-1}])(XA'(AA')^{-1} - D\beta + D\beta)$$

$$(1.38) \quad = ((D'[S_M^{-1}\Sigma]\Sigma^{-1}D)^{-1}D'[S_M^{-1}\Sigma]\Sigma^{-1})(XA'(AA')^{-1} - D\beta)$$

$$+ (D'[S_M^{-1}\Sigma]\Sigma^{-1}D)^{-1}D'[S_M^{-1}\Sigma]\Sigma^{-1}D\beta$$

In the previous section we proved that as $(N - m)$ goes to infinity

$$S_M = \frac{(S_1 + TS_1T')}{2(N - m)} \xrightarrow{P} \Sigma$$

Therefore

$$[S_M]^{-1} = \left[\frac{(S_1 + TS_1T')}{2(N - m)} \right]^{-1} \xrightarrow{P} \Sigma^{-1}$$

Applying the results from Rao (1973) p. 122 we have as (N-m)

goes to infinity

$$[S_M]^{-1}\Sigma \xrightarrow{P} \Sigma\Sigma^{-1} = I$$

The second term in (1.38) is

$$(D'[S_M^{-1}\Sigma]\Sigma^{-1}D)^{-1}D'[S_M^{-1}\Sigma]\Sigma^{-1}D\beta \quad \text{therefore}$$

as (N-m) goes to infinity

$$(D'[S_M^{-1}\Sigma]\Sigma^{-1}D)^{-1}D'[S_M^{-1}\Sigma]\Sigma^{-1}D\beta \xrightarrow{P}$$

$$(D'\Sigma^{-1}D)^{-1}D'\Sigma^{-1}D\beta$$

$$= \beta$$

That is the second term of (1.38) converges in probability to β .

ie (1.39) $(D'[S_M^{-1}\Sigma]\Sigma^{-1}D)^{-1}D'[S_M^{-1}\Sigma]\Sigma^{-1}D\beta \xrightarrow{P} \beta$

Now the first term of (1.38) is

$$= ((D'[S_M^{-1}\Sigma]\Sigma^{-1}D)^{-1}D'[S_M^{-1}\Sigma]\Sigma^{-1})(XA'(AA')^{-1} - D\beta)$$

Now

$$(1.40) \quad E(XA'(AA')^{-1}) = D\beta AA'(AA')^{-1} = D\beta$$

Also given the structure of A given in (1.5) in the previous section we can see that

$$A'(AA')^{-1} = \begin{bmatrix} 1/n_1 & 0 & \dots & 0 \\ : & 0 & \dots & 0 \\ 1/n_1 & 0 & \dots & 0 \\ 0 & 1/n_2 & \dots & 0 \\ 0 & : & \dots & 0 \\ 0 & 1/n_2 & \dots & 0 \\ 0 & 0 & \dots & 1/n_m \\ 0 & 0 & & : \\ 0 & 0 & & 1/n_m \end{bmatrix}$$

and

$$XA'(AA')^{-1} = \begin{bmatrix} \sum_{j=1}^{n_1} x_{1,j} / n_1 & \sum_{j=n_1+1}^{n_1+n_2} x_{1,j} / n_2 & \dots & \sum_{j=n_1+\dots+n_{m-1}+1}^{n_1+\dots+n_m} x_{1,j} / n_m \\ \sum_{j=1}^{n_1} x_{2,j} / n_1 & \sum_{j=n_1+1}^{n_1+n_2} x_{2,j} / n_2 & \dots & \sum_{j=n_1+\dots+n_{m-1}+1}^{n_1+\dots+n_m} x_{2,j} / n_m \\ : & : & \dots & : \\ \sum_{j=1}^{n_1} x_{p,j} / n_1 & \sum_{j=n_1+1}^{n_1+n_2} x_{p,j} / n_2 & \dots & \sum_{j=n_1+\dots+n_{m-1}+1}^{n_1+\dots+n_m} x_{p,j} / n_m \end{bmatrix}$$

Denoting the row vectors of D as

$$D = \begin{pmatrix} d_1 \\ d_2 \\ \vdots \\ d_p \end{pmatrix} \text{ and the columns of } \beta \text{ as } \beta = (\beta_1, \dots, \beta_m) \text{ have}$$

taking expectations:

$$E(XA'(AA')^{-1}) = E\left(\begin{bmatrix} \sum_{j=1}^{n_1} x_{1,j} / n_1 & \sum_{j=n_1+1}^{n_1+n_2} x_{1,j} / n_2 & \dots & \sum_{j=n_1+\dots+n_{m-1}+1}^{n_1+\dots+n_m} x_{1,j} / n_m \\ \sum_{j=1}^{n_1} x_{2,j} / n_1 & \sum_{j=n_1+1}^{n_1+n_2} x_{2,j} / n_2 & \dots & \sum_{j=n_1+\dots+n_{m-1}+1}^{n_1+\dots+n_m} x_{2,j} / n_m \\ \vdots & \vdots & \dots & \vdots \\ \sum_{j=1}^{n_1} x_{p,j} / n_1 & \sum_{j=n_1+1}^{n_1+n_2} x_{p,j} / n_2 & \dots & \sum_{j=n_1+\dots+n_{m-1}+1}^{n_1+\dots+n_m} x_{p,j} / n_m \end{bmatrix} \right)$$

from (1.40) above

$$= \begin{bmatrix} d_1\beta_1 & d_1\beta_2 & \dots & d_1\beta_m \\ d_2\beta_1 & d_2\beta_2 & \dots & d_2\beta_m \\ \vdots & \vdots & \vdots & \vdots \\ d_p\beta_1 & d_p\beta_2 & \dots & d_p\beta_m \end{bmatrix}$$

So

$$E(\sum_G x_{i,j} / n_G) = d_i\beta_G$$

and

$$\text{VAR}(\sum_{\mathbf{G}} x_{i,j} / n_{\mathbf{G}}) = \frac{1}{n_{\mathbf{G}}} E(x_{i,j}) = \frac{\sigma_{i,i}}{n_{\mathbf{G}}}$$

and each $x_{i,j}$ are i.i.d. random variables for any i and $j=1, \dots, N$.

So by the Weak Law of Large Numbers (W.L.L.N) Rao (1973) p. 112

$$\lim_{N \rightarrow \infty} [(\sum_{\mathbf{G}} x_{i,j} / n_{\mathbf{G}}) - d_i \beta_{\mathbf{G}}] = 0 \quad \text{ie.}$$

$$(\sum_{\mathbf{G}} x_{i,j} / n_{\mathbf{G}}) - d_i \beta_{\mathbf{G}} \xrightarrow{\mathbf{P}} 0 \quad \text{as } N \rightarrow \infty$$

Therefore

$$XA'(AA')^{-1} - D\beta \xrightarrow{\mathbf{P}} 0$$

also

$$((D'[S_M^{-1}\Sigma]\Sigma^{-1}D)^{-1}D'[S_M^{-1}\Sigma]\Sigma^{-1}) \xrightarrow{\mathbf{P}} (D'\Sigma^{-1}D)^{-1}D'\Sigma^{-1}$$

Therefore the first term of (2.12)

$$((D'[S_M^{-1}\Sigma]\Sigma^{-1}D)^{-1}D'[S_M^{-1}\Sigma]\Sigma^{-1})(XA'(AA')^{-1} - D\beta) \xrightarrow{\mathbf{P}} 0$$

In conclusion as N goes to infinity

$$\bar{\beta} = (D'S_M^{-1}D)^{-1}D'S_M^{-1}XA'(AA')^{-1} \xrightarrow{P} \beta.$$

Now I will derive the asymptotic distribution of $\bar{\beta}$.

Theorem 1.2

Given the same set up and assumptions of Theorem 1.1, when m and p are fixed, and all n_1, n_2, \dots, n_k approach infinity:

$$\text{vec} \left[(\bar{\beta} - \beta)(AA')^{1/2} \right]' \xrightarrow{L} N_{mp}(0, I \otimes (D'\Sigma^{-1}D)^{-1})$$

Proof:

We will look at the statistic:

$$(1.41) \quad U = (X - D\beta A)A'(AA')^{-1/2}$$

We can rewrite (1.41) as

$$(1.42) \quad U = [U_1, U_2, \dots, U_m]$$

$$= [(X_1 - D\beta_1 A_1)A_1'(A_1 A_1')^{-1/2} \quad \dots \quad (X_m - D\beta_m A_m)A_m'(A_m A_m')^{-1/2}]$$

Now

$$E(X_i - D\beta_i A_i) = 0 \quad \text{for all } i=1, \dots, m.$$

So $E[(X_i - D\beta_i A_i)A_i(A_i A_i')^{-1/2}] = 0$ for all $i=1, \dots, m$.

Also $A_i A_i' = n_i$ and $A_i'(A_i A_i')^{-1/2} = \begin{bmatrix} 1/n_i \\ : \\ 1/n_i \end{bmatrix}^{1/2}$

so $(X_i - D\beta_i A_i)A_i(A_i A_i')^{-1/2} = \left[\frac{1}{n_i}\right]^{1/2} \left(\sum_{k=1}^{n_i} (x_{i,k} - D\beta_i)\right)$ where

the $x_{i,k}$ $k=1, \dots, n_i$ are $p \times 1$ vectors that are the columns of X_i .

Now $\text{VAR}(x_{i,k}) = \Sigma = \begin{bmatrix} \Sigma_D & \Sigma_O' \\ \Sigma_O & \Sigma_D \end{bmatrix}$

and $\text{COV}(x_{i,k}, x_{i,r}) = 0$ for $k \neq r$.

Therefore

$$\text{VAR}[(X_i - D\beta_i A_i)A_i(A_i A_i')^{-1/2}] = \frac{1}{n_i} \text{VAR}\left(\sum_{k=1}^{n_i} (x_{i,k} - D\beta_i)\right) = \Sigma$$

Consequently U' , the transpose of U is distributed as a $m \times p$

multivariate normal matrix with mean zero and covariance $I \otimes \Sigma$ where

\otimes is the direct or Kronecker product.

Now from above:

$$\bar{\beta} = [\bar{\beta}_1 \quad \bar{\beta}_2 \quad \dots \quad \bar{\beta}_m] = (D'S_M^{-1}D)^{-1}DS_M^{-1}XA'(AA')^{-1}$$

with $S_M = (S_1 + TS_1T') / 2(N - m)$ and

$$S_1 = X(I - A'(AA')^{-1}A)X$$

Now

$$\begin{aligned} \bar{\beta} &= (D'S_M^{-1}D)^{-1}D'S_M^{-1}(X - D\beta A + D\beta A)A'(AA')^{-1} \\ &= (D'S_M^{-1}D)^{-1}D'S_M^{-1}(X - D\beta A)A'(AA')^{-1} \\ &\quad + (D'S_M^{-1}D)^{-1}D'S_M^{-1}D\beta AA'(AA')^{-1} \\ &= (D'S_M^{-1}D)^{-1}D'S_M^{-1}U(AA')^{-1/2} + \beta \text{ with } U \text{ defined above.} \end{aligned}$$

Therefore

$$(1.43) \quad (\bar{\beta} - \beta)(AA')^{1/2} = (D'S_M^{-1}D)^{-1}D'S_M^{-1}U$$

Now

$$(\bar{\beta} - \beta)(AA')^{1/2} = [n_1^{1/2}(\bar{\beta}_1 - \beta_1) \quad n_2^{1/2}(\bar{\beta}_2 - \beta_2) \quad \dots \quad n_m^{1/2}(\bar{\beta}_m - \beta_m)]$$

and

$$(D'S_M^{-1}D)^{-1}D'S_M^{-1}U = [P_1 \quad P_2 \quad \dots \quad P_m] \text{ with}$$

$$P_i = (D'S_M^{-1}D)^{-1}D'S_M^{-1}U_i$$

with $U_i = (X_i - D\beta_i A_i)A_i'(A_i A_i')^{-1/2}$

As $N-m$ increases to infinity, that is, as $N = \sum_{i=1}^m n_i - m \longrightarrow \infty$ with each

$n_i \longrightarrow \infty$ we know from above that $S_M^{-1} \xrightarrow{P} \Sigma^{-1}$. Therefore

$$(D'S_M^{-1}D)^{-1}D'S_M^{-1} \xrightarrow{P} (D'\Sigma^{-1}D)^{-1}D'\Sigma^{-1}$$

Also as each n_i increases to infinity, U_i converges in distribution to a random variable, say Ψ_i that is p -dimensional multivariate Normal with mean 0 and covariance Σ (the same distribution as U_i , that is, as each n_i increases to infinity):

$$U_i \xrightarrow{L} \Psi_i$$

Therefore from Rao (1973) pp. 122 the sequence of random variables in (1.43) converges in distribution to a p -dimensional Normal random variable, that is:

$$\lim_{\substack{n_1 \rightarrow \infty \\ \vdots \\ n_m \rightarrow \infty}} (D'S_M^{-1}D)^{-1}D'S_M^{-1}U_i \xrightarrow{L} N(0, \Sigma_{\bar{\beta}})$$

with $\Sigma_{\bar{\beta}} = (D'\Sigma^{-1}D)^{-1}D'\Sigma^{-1}\Sigma\Sigma^{-1}D(D'\Sigma^{-1}D)^{-1}$

$$\Sigma_{\bar{\beta}} = (D'\Sigma^{-1}D)^{-1}$$

To rewrite

As $n_i \rightarrow \infty$, for all $i=1,2,\dots,m$

$$n_i^{1/2}(\bar{\beta}_i - \beta_i) \xrightarrow{L} N(0, \Sigma_{\bar{\beta}}) \quad \text{with}$$

$$\Sigma_{\bar{\beta}} = (D' \Sigma^{-1} D)^{-1}$$

Therefore

$$\text{vec} \left[(\bar{\beta} - \beta)(AA')^{1/2} \right]' \xrightarrow{L} N_{mp}(0, I \otimes (D' \Sigma^{-1} D)^{-1})$$

Chapter 2

Trough to Peak Ratio

Examination of the diurnal variation in a 24 hour ABPM profile can be helpful in assessing the characteristics and duration of the antihypertensive effect of a drug under investigation. In a placebo controlled study, the net change in systolic or diastolic pressure elicited by an antihypertensive agent is compared to placebo across time from dosing, typically by creating and analyzing a placebo subtracted curve. In the United States, it has been necessary to estimate the peak and trough effect of new drugs in order to gain approval for marketing, with the peak defined at the maximum measured effect of the drug and the trough as the effect of the drug at the end of the normal treatment cycle time. The statistic which is usually reported is the trough to peak ratio (T/P), or $100 \times T/P$ which is the ratio of the effect of the drug at the end of the treatment cycle and the "peak" or greatest effect throughout the treatment cycle.

In this chapter we will discuss and compare three methods to estimate the trough to peak ratio, the first method is a univariate method based on time of day averages of the actual ABPM data, a second method using a fitted Fourier curve with the multivariate statistical models and methods described in chapter 1 and a third simple univariate Fourier model.

We will assume an experimental design which has two treatment arms, placebo or drug, each with the same number of individuals assigned (n). We have two sets of ambulatory hourly readings for each individual in each treatment arm, the first set

of ambulatory readings representing a baseline reading and the second the on treatment reading (placebo or drug). We also assume p ambulatory readings at equally spaced (hourly) intervals spanning the full expected drug effect cycle time (usually 24 hours, $p=24$).

Using the notation of chapter 1, the ABPM measurements can be denoted as a $2p \times 2n$ data matrix:

$$(2.1) \quad X = \begin{bmatrix} X_{1,1} & \dots & X_{1,n} & X_{1,n+1} & \dots & X_{1,2n} \\ X_{2,1} & \dots & X_{2,n} & X_{2,n+1} & \dots & X_{2,2n} \end{bmatrix}$$

with

$$X'_{i,j} = [x_{i,j,1} \quad x_{i,j,2} \quad \dots \quad x_{i,j,p}], \text{ a } (1 \times p) \text{ vector}$$

$$\text{with } i=1,2, j=1, \dots, 2n$$

and

$X_{1,j}$ the baseline readings and $X_{2,j}$ the on treatment readings for the j th individual with the first n columns of the matrix representing the ambulatory data from the placebo treatment group and the last n columns ambulatory data from the drug treatment group. With this experimental design we will compute a baseline adjusted, placebo subtracted trough to peak ratio.

To calculate the baseline adjusted, placebo subtracted T/P ratio based on time of day averages, we first subtract the hourly baseline values from the on treatment hourly values to get the difference from baseline readings for each individual:

$$X'_{D,j} = X'_{2,j} - X'_{1,j} = (x_{D,j,1}, x_{D,j,2}, \dots, x_{D,j,p})$$

Next we compute averages for each of the p time periods across all n individuals within each treatment arm:

$$\bar{X}'_{D,PL} = (\bar{x}_{D,PL,1}, \bar{x}_{D,PL,2}, \dots, \bar{x}_{D,PL,p}) = \left(\sum_{j=1}^n x_{D,j,1}, \sum_{j=1}^n x_{D,j,2}, \dots, \sum_{j=1}^n x_{D,j,p} \right)$$

for the placebo treatment arm and

$$\bar{X}'_{D,DG} = (\bar{x}_{D,DG,1}, \bar{x}_{D,DG,2}, \dots, \bar{x}_{D,DG,p}) = \left(\sum_{j=n+1}^{2n} x_{D,j,1}, \sum_{j=n+1}^{2n} x_{D,j,2}, \dots, \sum_{j=n+1}^{2n} x_{D,j,p} \right)$$

for the drug therapy arm.

The mean drug effect difference is:

(2.2)

$$\begin{aligned} \bar{X}'_M &= (\bar{x}_{D,PL,1} - \bar{x}_{D,DG,1}, \bar{x}_{D,PL,2} - \bar{x}_{D,DG,2}, \dots, \bar{x}_{D,PL,p} - \bar{x}_{D,DG,p}) \\ &= (\bar{x}_{M,1}, \bar{x}_{M,2}, \dots, \bar{x}_{M,p}) \end{aligned}$$

Assuming $X_{i,j}$ above are random variables with mean:

$$(2.3) \quad \mu_{B,PL} = (\mu_{B,PL,1} \dots \mu_{B,PL,p}) \text{ for } i=1 \text{ and } j=1, \dots, n$$

$$\mu_{T,PL} = (\mu_{T,PL,1} \dots \mu_{T,PL,p}) \text{ for } i=2 \text{ and } j=1, \dots, n$$

$$\mu_{B,DG} = (\mu_{B,DG,1} \dots \mu_{B,DG,p}) \text{ for } i=1 \text{ and } j=n+1, \dots, 2n$$

$$\mu_{T,DG} = (\mu_{T,DG,1} \dots \mu_{T,DG,p}) \text{ for } i=2 \text{ and } j=n+1, \dots, 2n$$

then $\bar{X}_M = (\bar{x}_{M,1}, \bar{x}_{M,2}, \dots, \bar{x}_{M,p})$ has mean vector θ with elements:

$$(2.4) \quad \theta_i = (\mu_{T,DG,i} - \mu_{B,DG,i}) - (\mu_{T,PL,i} - \mu_{B,PL,i}) \quad i=1, \dots, p$$

The baseline adjusted, placebo subtracted trough to peak ratio estimate (T/P) based on sample averages is then defined as:

$$(2.5) \quad \overline{T/P}_M \equiv \bar{x}_{M,p} / \max(\bar{x}_{M,1}, \bar{x}_{M,2}, \dots, \bar{x}_{M,p})$$

where max denotes the maximum of the p sample means. In case of a tie we will always use the observation at the earliest time of the observed maximum value.

The second type of trough to peak statistic we will consider is constructed using estimates of measurements assuming a parametric model for the dose response curves. If we assume the ambulatory hourly readings over the period p can be represented at a time t by a (c+s+1)- term Fourier function (for example), where c is the number of cosine terms and s the number of sine terms ($c+s+1 < p$) of the form:

$$(2.6) \quad x_{i,j,t} = \sqrt{\frac{2}{p}} \left[a_{i,m} + \sum_{g=1}^c b_{i,m,g} \cos\left(\frac{2g\pi t}{p}\right) + \sum_{g=1}^s c_{i,m,g} \sin\left(\frac{2g\pi t}{p}\right) \right] + e_{i,j,t}$$

with $t = 1, \dots, p$ and $i = 1$ for the baseline ABPM, $i = 2$ for the on treatment ABPM and $m = 1$ if in Placebo treatment group and $m = 2$ if in drug treatment group.

Defining $\beta_{i,m} = (a_{i,m}, b_{i,m,1}, b_{i,m,2}, \dots, b_{i,m,c}, c_{i,m,1}, \dots, c_{i,m,s})$

to be the vectors of the unknown Fourier coefficients for each of the four groups

and β the $2 \times (c+s+1)$ matrix :

$$(2.7) \quad \beta = \begin{bmatrix} \beta_{1,1} & \beta_{1,2} \\ \beta_{2,1} & \beta_{2,2} \end{bmatrix}$$

and

$$D = \begin{bmatrix} D_F & 0 \\ 0 & D_F \end{bmatrix}$$

with D_F a $p \times (c+s+1)$ matrix with $(c+s+1)$ the number of Fourier terms used in the model for each of the ABPM curves.

D_F has the form:

$$D_F = \sqrt{\frac{2}{p}} \begin{bmatrix} 1/\sqrt{2} & \cos(\frac{2\pi}{p}) & \dots & \cos(\frac{2c\pi}{p}) & \sin(\frac{2\pi}{p}) & \dots & \sin(\frac{2s\pi}{p}) \\ \vdots & \vdots & \vdots & \vdots & \vdots & \dots & \vdots \\ 1/\sqrt{2} & \cos(\frac{2\pi p}{p}) & \dots & \cos(\frac{2c\pi p}{p}) & \sin(\frac{2\pi p}{p}) & \dots & \sin(\frac{2s\pi p}{p}) \end{bmatrix}$$

and the $2 \times N$ matrix A :

$$(2.8) \quad A = \begin{bmatrix} A_1 & 0 \\ 0 & A_2 \end{bmatrix}$$

where each A_j is a $1 \times n$ matrix of 1's for each $j=1,2$ then the model for the ABPM data in matrix form is equation 1.2 in chapter 1:

$$(2.9) \quad X = D\beta A + e.$$

Defining $\bar{\beta}_{i,m}$ to be estimates of the unknown Fourier coefficients, then an estimate of the expected value at a time period h for each treatment group is:

$$\bar{f}_{i,m,h} = d'_h \bar{\beta}_{i,m}$$

with

$$d'_h = \sqrt{\frac{2}{p}} \left(1, \cos\left(\frac{2\pi h}{p}\right), \cos\left(\frac{4\pi h}{p}\right), \dots, \cos\left(\frac{2c\pi h}{p}\right), \sin\left(\frac{2\pi h}{p}\right), \dots, \sin\left(\frac{2s\pi h}{p}\right) \right)$$

The estimated baseline adjusted, placebo subtracted drug effect for each time period h is:

$$(2.10) \quad \bar{f}_h = d'_h \bar{\beta}_D$$

where $\bar{\beta}_D$ is the estimate of the difference in fourier coefficients ,that is $\bar{\beta}_D$ estimates

$$(2.11) \quad \beta_D = [(\beta_{2,1} - \beta_{1,1}) - (\beta_{2,2} - \beta_{1,2})]$$

with:

$\beta_{1,1}$ the fourier coefficients for the baseline placebo data

$\beta_{2,1}$ the fourier coefficients for the on treatment placebo data

$\beta_{1,2}$ the fourier coefficients for the baseline drug data

$\beta_{2,2}$ the fourier coefficients for the on treatment drug data

Then we define the trough to peak ratio based on the above fourier fit as:

$$(2.12) \quad \overline{T/P}_F = \bar{f}_p / \max(\bar{f}_1, \bar{f}_2, \dots, \bar{f}_p)$$

Asymptotic Distribution of T/P statistics

We will now determine the asymptotic distribution of the above statistics represented in equations (2.5) and (2.12) with the help of the following results.

Lemma 2.1.

Let $X_{1,n}, X_{2,n}, \dots, X_{p,n}$ be m random variables such that each converges in probability to a constant θ_i , $i=1, \dots, p$, i.e.

$$\lim_{n \rightarrow \infty} P(|X_{i,n} - \theta_i| > \varepsilon) = 0 \quad \text{denoted as } X_{i,n} \xrightarrow{P} \theta_i$$

then $\max(X_{1,n}, X_{2,n}, \dots, X_{p,n}) \xrightarrow{P} \max(\theta_1, \theta_2, \dots, \theta_p)$.

Proof:

Denoting n_i as the sample size of $X_{i,n}$, choose n_i so large that:

$$\mathbf{X}_p = [X_{1,n}, X_{2,n}, \dots, X_{p,n}]' \quad \text{for a given } \delta \geq 0 .$$

Then for $n \geq N = \max(n_1, n_2, \dots, n_m)$:

$$P(|\max(X_{1,n}, X_{2,n}, \dots, X_{p,n}) - \max(\theta_1, \theta_2, \dots, \theta_p)| > \varepsilon)$$

$$\leq P\left(\bigcup_{i=1}^p |X_{i,n_i} - \theta_i| > \varepsilon\right) \leq \sum_{i=1}^p P(|X_{i,n_i} - \theta_i| > \varepsilon) \leq \frac{p \cdot \delta}{p} = \delta$$

Since δ is arbitrary it can be made as small as desired, establishing the desired result.

Next we will derive the asymptotic distribution of

$$\sqrt{n}(\max(X_{1,n}, X_{2,n}, \dots, X_{p,n}) - \theta_j).$$

Lemma 2.2

Let $X_{1,n}, X_{2,n}, \dots, X_{p,n}$ be m random variables such that each converges in probability to a constant θ_i , $i=1, \dots, p$. And further assume that there is one θ_j such that $\theta_i < \theta_j$ for all $i \neq j$.

Then

$$\lim_{n \rightarrow \infty} P(\sqrt{n}[\max(X_{1,n}, \dots, X_{p,n}) - \theta_j] \leq z) = P(\sqrt{n}(X_{j,n} - \theta_j) \leq z).$$

Proof:

Its enough to show:

$$\lim_{n \rightarrow \infty} P(\max(X_{1,n}, \dots, X_{p,n}) = X_{j,n}) = 1$$

Let $0 < \varepsilon \leq \frac{\theta_j - \theta_r}{2}$ where θ_r is the next largest constant, that is:

$$\theta_i \leq \theta_r < \theta_j \text{ for all } i = 1, 2, \dots, j-1, j+1, \dots, r-1, r+1, \dots, p.$$

denote n_i as the sample size of $X_{i,n}$, choose n_i so large that:

$$P(|X_{i,n_i} - \theta_i| > \varepsilon) \leq \frac{\delta}{2(p-1)} \text{ for a given } \delta \geq 0.$$

Then for $n \geq N = \max(n_1, n_2, \dots, n_p)$:

$$P(\max(X_{1,n}, \dots, X_{p,n}) = X_{j,n}) = 1 - P(\max(X_{1,n}, \dots, X_{p,n}) \neq X_{j,n})$$

$$= 1 - \sum_{i \neq j} P(\max(X_{1,n}, \dots, X_{p,n}) = X_{i,n}) \geq 1 - \sum_{i \neq j} P(X_{i,n} > X_{j,n})$$

Now:

$$\begin{aligned}
& \sum_{i \neq j} P(X_{i,n} > X_{j,n}) = \\
& \sum_{i \neq j} [P(X_{i,n} > X_{j,n} \cap |X_{j,n} - \theta_j| > \varepsilon) + P(X_{i,n} > X_{j,n} \cap |X_{j,n} - \theta_j| \leq \varepsilon)] \\
& \frac{\sqrt{n}(X_{p,n} - \theta_p)}{\theta_j} - \frac{\sqrt{n}\theta_p(X_{j,n} - \theta_j)}{\theta_j^2} \\
& \leq \sum_{i \neq j} [P(|X_{j,n} - \theta_j| > \varepsilon) + P(X_{i,n} > \theta_j - \varepsilon)] \\
& \leq \sum_{i \neq j} [P(|X_{j,n} - \theta_j| > \varepsilon) + P(|X_{i,n} - \theta_i| > \theta_j - \theta_i - \varepsilon)]
\end{aligned}$$

now $\theta_i \leq \theta_r < \theta_j$ for all $i = 1, 2, \dots, j-1, j+1, \dots, r-1, r+1, \dots, p$. therefore:

$$\leq \sum_{i \neq j} [P(|X_{j,n} - \theta_j| > \varepsilon) + P(|X_{i,n} - \theta_i| > \theta_j - \theta_r - \varepsilon)]$$

and since $0 < \varepsilon \leq \frac{\theta_j - \theta_r}{2}$

$$\leq \sum_{i \neq j} [P(|X_{j,n} - \theta_j| > \varepsilon) + P(|X_{i,n} - \theta_i| > \varepsilon)] = \frac{2(p-1)}{2(p-1)} \delta = \delta$$

Therefore:

$$= 1 - \sum_{i \neq j} P(\max(X_{1,n}, \dots, X_{p,n}) = X_{i,n}) \geq 1 - \delta$$

Since ϵ, δ are arbitrary and can be made as small as desired, the result is established.

With lemma 1 and lemma 2 we can now derive the asymptotic distribution of the trough to peak ratio.

Theorem 2.1.

Let $X_{1,n}, X_{2,n}, \dots, X_{p,n}$ be m random variables such that each converges in probability to a constant θ_i , $i=1, \dots, p$. And further assume that there is one θ_j such that .

$$\theta_i < \theta_j \text{ for all } i = 1, 2, \dots, j-1, j+1, \dots, p .$$

Further assume:

$\sqrt{n}(X_{i,n} - \theta_i)$ converges in law to a distribution for all $i=1, 2, \dots, p$

and $\frac{\sqrt{n}(X_{p,n} - \theta_p)}{\theta_j} - \frac{\sqrt{n}\theta_p(X_{j,n} - \theta_j)}{\theta_j^2}$ converges to a distribution as

n increases to infinity.

Defining the trough to peak ratio statistic to be:

$$\overline{T/P}_n = X_{p,n} / \max(X_{i,n})$$

where $\max(X_{i,n})$ is the maximum of $X_{1,n}, X_{2,n}, \dots, X_{p,n}$

Then as the sample size n goes to infinity $\sqrt{n}(\overline{T/P_n} - \frac{\theta_p}{\theta_j})$ converges in law to

the same distribution as does

$$\frac{\sqrt{n}(X_{p,n} - \theta_p)}{\theta_j} - \frac{\sqrt{n}\theta_p(X_{j,n} - \theta_j)}{\theta_j^2} . \text{ That is}$$

$$\lim_{n \rightarrow \infty} \sqrt{n}(\overline{T/P_n} - \frac{\theta_p}{\theta_j}) \xrightarrow{L} \lim_{n \rightarrow \infty} \left[\frac{\sqrt{n}(X_{p,n} - \theta_p)}{\theta_j} - \frac{\sqrt{n}\theta_p(X_{j,n} - \theta_j)}{\theta_j^2} \right]$$

Proof:

$$\sqrt{n}(\overline{T/P_n} - \frac{\theta_p}{\theta_j}) = \sqrt{n} \left(\frac{X_{p,n}}{\max(X_{i,n})} - \frac{\theta_p}{\theta_j} \right) = \sqrt{n} \left(\frac{X_{p,n}\theta_j - \max(X_{i,n})\theta_p}{\max(X_{i,n})\theta_j} \right) =$$

$$(2.13) \quad \sqrt{n} \left(\frac{X_{p,n} - \theta_p}{\max(X_{i,n})} \right) - \sqrt{n}\theta_p \left(\frac{\max(X_{i,n}) - \theta_j}{\max(X_{i,n})\theta_j} \right) .$$

Now

$$\sqrt{n} \left(\frac{X_{p,n} - \theta_p}{\max(X_{i,n})} \right) = \sqrt{n} \left(\frac{X_{p,n} - \theta_p}{\max(X_{i,n})} \right) + \sqrt{n} \left(\frac{X_{p,n} - \theta_p}{\theta_j} \right) - \sqrt{n} \left(\frac{X_{p,n} - \theta_p}{\theta_j} \right) =$$

$$(2.14) \quad \sqrt{n} \frac{(X_{p,n} - \theta_p)[\theta_j - \max(X_{i,n})]}{\max(X_{i,n})\theta_j} + \sqrt{n} \left(\frac{X_{p,n} - \theta_p}{\theta_j} \right)$$

Now as n goes to infinity

$$\begin{aligned}\sqrt{n}(X_{p,n} - \theta_p) &\xrightarrow{L} Z \\ [\theta_j - \max(X_{i,n})] &\xrightarrow{P} 0 \text{ by assumption and lemma 2.1.,} \\ \max(X_{i,n}) &\xrightarrow{P} \theta_j\end{aligned}$$

Now from Rao p. 122 if:

$$\begin{array}{ccc} X_n \xrightarrow{L} Z & & \\ C_n \xrightarrow{P} 0 & \text{then} & C_n X_n \xrightarrow{P} 0 \end{array}$$

Therefore:

$$\sqrt{n} \frac{(X_{p,n} - \theta_p)[\theta_j - \max(X_{i,n})]}{\max(X_{i,n})\theta_j} \xrightarrow{P} 0$$

Therefore (2.14) converges to the same distribution as

$$(2.15) \quad \sqrt{n} \left(\frac{X_{p,n} - \theta_p}{\theta_j} \right)$$

Now

$$\begin{aligned}\sqrt{n}\theta_p \left(\frac{\max(X_{i,n}) - \theta_j}{\max(X_{i,n})\theta_j} \right) &= \sqrt{n}\theta_p \left(\frac{\max(X_{i,n}) - \theta_j}{\max(X_{i,n})\theta_j} \right) + \\ \sqrt{n}\theta_p \left(\frac{\max(X_{i,n}) - \theta_j}{\theta_j^2} \right) &- \sqrt{n}\theta_p \left(\frac{\max(X_{i,n}) - \theta_j}{\theta_j^2} \right)\end{aligned}$$

Rearranging we get (2.16)

$$\sqrt{n}\theta_p \left(\frac{\max(X_{i,n}) - \theta_j}{\max(X_{i,n})\theta_j} \right) = \sqrt{n}\theta_p \left(\frac{(\max(X_{i,n}) - \theta_j)[\theta_j - \max(X_{i,n})]}{\max(X_{i,n})\theta_j^2} \right) +$$

$$\sqrt{n}\theta_p \left(\frac{\max(X_{i,n}) - \theta_j}{\theta_j^2} \right)$$

Now as n goes to infinity

$$\sqrt{n}[\max(X_{i,n}) - \theta_j] \xrightarrow{L} \sqrt{n}(X_{j,n} - \theta_j)$$

$$[\theta_j - \max(X_{i,n})] \xrightarrow{P} 0$$

$$\max(X_{i,n}) \xrightarrow{P} \theta_j$$

by assumption and lemma 2.2..

Therefore

$$\sqrt{n}\theta_p \left(\frac{(\max(X_{i,n}) - \theta_j)[\theta_j - \max(X_{i,n})]}{\max(X_{i,n})\theta_j^2} \right) \xrightarrow{P} 0 \text{ and}$$

the right hand side of (2.16) converges to the same distribution as:

$$(2.17) \quad \sqrt{n}\theta_p \left(\frac{X_{j,n} - \theta_j}{\theta_j^2} \right)$$

Using equation (2.13) and (2.15) and (2.17) we see that as the sample

size n goes to infinity $\sqrt{n}(\overline{T/P_n} - \frac{\theta_p}{\theta_j})$ converges in law to the same distribution

as does

$$(2.18) \frac{\sqrt{n}(X_{p,n} - \theta_p)}{\theta_j} - \frac{\sqrt{n}\theta_p(X_{j,n} - \theta_j)}{\theta_j^2}$$

Thus completes the proof.

In our case the $X_{1,n}, X_{2,n}, \dots, X_{p,n}$ are sample averages or estimates based on

Fourier Regression. If we denote $X_p = [X_{1,n}, X_{2,n}, \dots, X_{p,n}]'$ and

$\theta = (\theta_1, \theta_2, \dots, \theta_p)$ and we assume that asymptotically $\sqrt{n}(X_m - \theta)$ is a

Multivariate Normal with mean 0 and covariance matrix Σ whose structure is dependent on the covariance structure of the ambulatory data and the process used

to estimate the effect, the asymptotic distribution of $\sqrt{n}(\overline{T/P_n} - \frac{\theta_p}{\theta_j})$ is Normal

with mean 0 and variance σ^2 which we will prove in the following corollary.

Corollary 2.1.

Let $X_p = [X_{1,n}, X_{2,n}, \dots, X_{p,n}]'$ be a vector of m random variables and

$\theta = (\theta_1, \theta_2, \dots, \theta_p)$ a vector of p constants with $\theta_i < \theta_j$ for all

$i = 1, 2, \dots, j-1, j+1, \dots, p$ such that as the sample size n increases to infinity

that $\sqrt{n}(X_p - \theta)$ converges in law to a p dimensional Multivariate Normal

distribution with mean 0 and covariance Σ then

$\sqrt{n}(\overline{T/P_n} - \frac{\theta_p}{\theta_j})$ converges in law to a Normal random variable with mean 0 and

variance

$$(2.19) \sigma^2 = \frac{\theta_j^2 \sigma_p^2 + \theta_p^2 \sigma_j^2 - 2\theta_j \theta_p \rho_{j,p} \sigma_p \sigma_j}{\theta_j^4}$$

with σ_p^2 the asymptotic variance of the p^{th} variable $X_{p,n}$ -the trough

σ_j^2 the asymptotic variance of the j^{th} variable $X_{j,n}$ - the peak

$\rho_{j,p} \sigma_p \sigma_j$ the covariance between the j^{th} and the p^{th} variables

θ_j is the peak value that $X_{j,n}$ converges to asymptotically and

θ_p is the trough value that $X_{p,n}$ converges to asymptotically.

Proof:

From theorem 2.1 $\sqrt{n}(\overline{T/P_n} - \frac{\theta_p}{\theta_j})$ converges in law to a random variable that is

the same as the asymptotic distribution of :

$$(2.20) \frac{\sqrt{n}(X_{p,n} - \theta_p)}{\theta_j} - \frac{\sqrt{n}\theta_p(X_{j,n} - \theta_j)}{\theta_j^2}$$

We can rewrite (2.20) as: $a'X_n$

with

$$a' = \left(\frac{\sigma_p}{\theta_j}, \frac{-\theta_p \sigma_j}{\theta_j^2} \right) \quad \text{and} \quad X_n = \begin{bmatrix} \frac{\sqrt{n}(X_{p,n} - \theta_p)}{\sigma_p} \\ \frac{\sqrt{n}(X_{j,n} - \theta_j)}{\sigma_j} \end{bmatrix}$$

By assumption

$$\begin{bmatrix} \frac{\sqrt{n}(X_{p,n} - \theta_p)}{\sigma_p} \\ \frac{\sqrt{n}(X_{j,n} - \theta_j)}{\sigma_j} \end{bmatrix} \xrightarrow{L} N(0, \Sigma)$$

with $\Sigma = \begin{bmatrix} 1 & \rho_{j,p} \\ \rho_{j,p} & 1 \end{bmatrix}$ the asymptotic covariance matrix

Therefore:

$$a' \begin{bmatrix} \frac{\sqrt{n}(X_{p,n} - \theta_p)}{\sigma_p} \\ \frac{\sqrt{n}(X_{j,n} - \theta_j)}{\sigma_j} \end{bmatrix} \xrightarrow{L} N(0, a' \Sigma a)$$

$$\text{and} \quad a' \Sigma a = \frac{\theta_j^2 \sigma_p^2 + \theta_p^2 \sigma_j^2 - 2\theta_j \theta_p \rho_{j,p} \sigma_p \sigma_j}{\theta_j^4}$$

proving the corollary.

We now will derive the asymptotic distributions of the two types estimators of the trough to peak ratio we described in equations (2.5) and (2.12) above.

The mean drug effect difference \bar{X}_M in equation (2.2) above can be expressed as:

$$(2.20) \quad \bar{X}_M = LXA'(AA')^{-1}c$$

with X and A defined in (2.1) and (2.8) above,

with $c = \begin{bmatrix} -1 \\ 1 \end{bmatrix}$ (2 x 1 vector) and L a p x 2p matrix with each row i of L denoted at l_i having all zero's and a -1 in position i and a 1 in position p+i, that is

$$l_i = [0, \dots, -1, 0, \dots, 1, 0, \dots] = [-\ell_i, \ell_i]$$

with $\ell_i = (0, \dots, 1, 0, \dots, 0)$ all zeros and a 1 at position i.

If we assume that X_j are 2 p multivariate normal random variables with mean (2.3a) and covariance matrix :

$$(2.21) \quad \Sigma_X = \begin{bmatrix} \Sigma_D & \Sigma_O \\ \Sigma_O & \Sigma_D \end{bmatrix}$$

then

$$E(\bar{X}_M) = \Theta \quad \text{with} \quad \Theta' = [\theta_1, \theta_2, \dots, \theta_p] \quad \text{with } \theta_i \text{ defined in (2.4) and}$$

$\sqrt{n}(\bar{X}_M - \Theta)$ is distributed as an p-dimensional multivariate normal random variable with mean zero and covariance matrix

$$\Sigma_M = L(\Sigma_X + \Sigma_X)L'$$

If we assume that $\theta_i < \theta_j$ for all $i = 1, 2, \dots, j-1, j+1, \dots, p$ then the trough to peak ratio based on the means (equation 2.2), using the results from theorem 2.1, has the following properties:

$$\text{If } \overline{T/P}_M = \bar{x}_{M,p} / \max(\bar{x}_{M,1}, \bar{x}_{M,2}, \dots, \bar{x}_{M,p})$$

then

$$\sqrt{n}(\overline{T/P}_M - \frac{\theta_p}{\theta_j}) \xrightarrow{L} N(0, \sigma_{T/P,M}^2)$$

with θ_p, θ_j defined in equation (2.14).

If we denote the elements of the asymptotic covariance matrix of the averages as

$$\Sigma_M = \begin{bmatrix} \sigma_{M,1,1} & \sigma_{M,1,2} & \dots & \sigma_{M,1,p} \\ \sigma_{M,2,1} & \sigma_{M,2,2} & \dots & \sigma_{M,2,p} \\ \vdots & \vdots & \dots & \vdots \\ \sigma_{M,p,1} & \sigma_{M,p,1} & \dots & \sigma_{M,p,p} \end{bmatrix}$$

then (2.19) becomes:

$$(2.22) \quad \sigma_{T/P,M}^2 = \frac{\theta_j^2 \sigma_{M,p,p} + \theta_p^2 \sigma_{M,j,j} - 2\theta_j \theta_p \sigma_{M,p,j}}{\theta_j^4}$$

with $\sigma_{M,p,p}$ the asymptotic variance of the p^{th} mean $\bar{x}_{M,p}$ -the trough

$$\sigma_{M,p,p} = [-l_p', l_p'](\Sigma_X + \Sigma_X) \begin{bmatrix} -l_p \\ l_p \end{bmatrix}$$

$\sigma_{M,j,j}$ the asymptotic variance of the j^{th} mean $\bar{x}_{M,j}$ - the peak

$$\sigma_{M,j,j} = [-l_j', l_j'](\Sigma_X + \Sigma_X) \begin{bmatrix} -l_j \\ l_j \end{bmatrix}$$

$\sigma_{M,p,j}$ the covariance between the j^{th} and the p^{th} means

$$\sigma_{M,p,j} = [-l_p', l_p'](\Sigma_X + \Sigma_X) \begin{bmatrix} -l_j \\ l_j \end{bmatrix}$$

θ_j is the peak value that $\bar{x}_{M,j}$ converges to asymptotically and

θ_m is the trough value that $\bar{x}_{M,p}$ converges to asymptotically .

In terms of the elements of the covariance matrix Σ_X , if we denote the elements of the covariance matrix as $\sigma_{X,i,j}$, and with the covariance matrix having the form (2.21) then:

$$\sigma_{M,p,p} = 4\sigma_{X,p,p}$$

$$\sigma_{M,j,j} = 4\sigma_{X,j,j}$$

$$\sigma_{M,p,j} = 4\sigma_{X,p,j}$$

To calculate the T/P ratio based on the Fourier model, we first estimate the different regression coefficients (equation 2.9), calculate the estimate of the baseline adjusted placebo subtracted drug effect for each ABPM reading (equation 2.10), then compute the T/P ratio (2.12). The problem of estimating the T/P ratio, therefore reduces to the problem of estimating equation (2.11) which is:

$$\beta_D = [(\beta_{2,1} - \beta_{1,1}) - (\beta_{2,2} - \beta_{1,2})]$$

with:

$\beta_{1,1}$ the fourier coefficients for the baseline placebo data

$\beta_{2,1}$ the fourier coefficients for the on treatment placebo data

$\beta_{1,2}$ the fourier coefficients for the baseline drug data

$\beta_{2,2}$ the fourier coefficients for the on treatment drug data

Two estimates for β_D will be examined, the first based on the M.L.E. for β developed in chapter 1 and another based on a simple estimate for β .

From chapter 1 the M.L.E. estimate for β is:

$$\bar{\beta}_{(MLE)} = \begin{bmatrix} \bar{\beta}_{(MLE),1,1} & \bar{\beta}_{(MLE),1,2} \\ \bar{\beta}_{(MLE),2,1} & \bar{\beta}_{(MLE),2,2} \end{bmatrix} = (D'S_M^{-1}D)^{-1}D'S_M^{-1}XA'(AA')^{-1}$$

we also define the simple estimate for β as:

$$\bar{\beta}_{(S)} = \begin{bmatrix} \bar{\beta}_{(S),1,1} & \bar{\beta}_{(S),1,2} \\ \bar{\beta}_{(S),2,1} & \bar{\beta}_{(S),2,2} \end{bmatrix} = (D'D)^{-1}D'XA'(AA')^{-1}$$

Now:

$$E(\bar{\beta}_{(S)}) = E[(D'D)^{-1}D'XA'(AA')^{-1}] = (D'D)^{-1}D'D\beta AA'(AA')^{-1} = \beta$$

so $\bar{\beta}_{(S)}$ is an unbiased estimate of β .

The estimate of the baseline adjusted placebo subtracted drug effect for each time period t is:

$$\bar{f}_{(MLE),t} = d_t'[(\bar{\beta}_{(MLE),2,1} - \bar{\beta}_{(MLE),1,1}) - (\bar{\beta}_{(MLE),2,2} - \bar{\beta}_{(MLE),1,2})]$$

$$\bar{f}_{(S),t} = d_t'[(\bar{\beta}_{(S),2,1} - \bar{\beta}_{(S),1,1}) - (\bar{\beta}_{(S),2,2} - \bar{\beta}_{(S),1,2})]$$

with:

$$d_t' = \sqrt{\frac{2}{p}}(1, \cos(\frac{2\pi t}{p}), \cos(\frac{4\pi t}{p}), \dots, \cos(\frac{2c\pi t}{p}), \sin(\frac{2\pi t}{p}), \dots, \sin(\frac{2s\pi t}{p}))$$

Now using results from chapter 1:

$$\text{vec} [(\bar{\beta}_{(MLE)} - \beta)(AA')^{1/2}]' \xrightarrow{L} N_{4(c+s+1)}(0, I \otimes (D'\Sigma_X^{-1}D)^{-1})$$

and using similar methods as employed in theorem 1.2, it is easy to show that:

$$\text{vec}[(\bar{\beta}_{(S)} - \beta)(AA')^{1/2}]' \xrightarrow{L} N_{4(c+s+1)}(0, I \otimes (D'D)^{-1}(D'\Sigma_X D)(D'D)^{-1})$$

and since $D'D = I$ (in our case):

$$\text{vec}[(\bar{\beta}_{(S)} - \beta)(AA')^{1/2}]' \xrightarrow{L} N_{4(c+s+1)}(0, I \otimes (D' \Sigma_X D))$$

Now:

$$\sqrt{n}(\bar{f}_{(MLE),t} - f_t) = (-d_t' \quad d_t' \quad d_t' \quad -d_t') \text{vec}[(\bar{\beta}_{(MLE)} - \beta)(AA')^{1/2}]'$$

$$\sqrt{n}(\bar{f}_{(S),t} - f_t) = (-d_t' \quad d_t' \quad d_t' \quad -d_t') \text{vec}[(\bar{\beta}_{(S)} - \beta)(AA')^{1/2}]'$$

Therefore:

$$\sqrt{n}(\bar{f}_{(MLE),t} - f_t) \xrightarrow{L} N(0, \sigma_{MLE,t}^2)$$

$$\sqrt{n}(\bar{f}_{(S),t} - f_t) \xrightarrow{L} N(0, \sigma_{S,t}^2)$$

with

$$\sigma_{MLE,t}^2 = (-d_t' \quad d_t' \quad d_t' \quad -d_t') I \otimes (D' \Sigma_X^{-1} D)^{-1} \begin{pmatrix} -d_t \\ d_t \\ d_t \\ -d_t \end{pmatrix}$$

$$\sigma_{S,t}^2 = (-d_t' \quad d_t' \quad d_t' \quad -d_t') I \otimes (D' \Sigma_X D) \begin{pmatrix} -d_t \\ d_t \\ d_t \\ -d_t \end{pmatrix}$$

$$\text{Now } \begin{pmatrix} -d_t & & & \\ & d_t & & \\ & & d_t & \\ & & & -d_t \end{pmatrix} I \otimes A \begin{pmatrix} d_t \\ d_t \\ d_t \\ -d_t \end{pmatrix} = 4 * d_t' A d_t$$

Therefore:

$$\sigma_{MLE}^2 = 4 * d_t' (D' \Sigma_X^{-1} D)^{-1} d_t$$

$$\sigma_S^2 = 4 * d_t' (D' \Sigma_X D) d_t$$

If we denote $\bar{f}'_{(MLE)} = [\bar{f}_{(MLE),1}, \bar{f}_{(MLE),2}, \dots, \bar{f}_{(MLE),p}]$ as the vector of M.L.E. Fourier estimates and $\bar{f}'_{(S)} = [\bar{f}_{(S),1}, \bar{f}_{(S),2}, \dots, \bar{f}_{(S),p}]$ and $f' = [f_1, f_2, \dots, f_p]$ as the actual values of the Fourier transform at times 1,2,...,p.

Then as n goes to infinity:

$$(2.23) \quad \sqrt{n}(\bar{f}_{(MLE)} - f) \xrightarrow{L} N_p(0, \Sigma_{(MLE)})$$

$$\sqrt{n}(\bar{f}_{(S)} - f) \xrightarrow{L} N_p(0, \Sigma_{(S)})$$

with the elements of $\Sigma_{(MLE)}$ and $\Sigma_{(S)}$ the following:

$$(2.24) \quad \sigma_{(MLE),i,j} = 4 * d_i' (D' \Sigma_X^{-1} D)^{-1} d_j$$

$$\sigma_{(S),i,j} = 4 * d'_i (D' \Sigma_X D) d_j$$

Using corollary 1 we can conclude determine the asymptotic properties of the trough to peak estimate based on the above Fourier estimates, specifically:

Letting (2.25)

$$\overline{T/P}_{(MLE)} = \bar{f}_{(MLE)} / \max(\bar{f}_{(MLE),1}, \bar{f}_{(MLE),2}, \dots, \bar{f}_{(MLE),p})$$

$$\overline{T/P}_{(S)} = \bar{f}_{(S)} / \max(\bar{f}_{(S),1}, \bar{f}_{(S),2}, \dots, \bar{f}_{(S),p})$$

and we assume that $f_j > f_k$ for some j, k between 1 and m then:

$$(2.26) \quad \sqrt{n}(\overline{T/P}_{(MLE)} - \frac{f_p}{f_j}) \xrightarrow{L} N(0, \sigma_{T/P,MLE}^2)$$

$$\sqrt{n}(\overline{T/P}_{(S)} - \frac{f_p}{f_j}) \xrightarrow{L} N(0, \sigma_{T/P,S}^2)$$

with

$$(2.27) \quad \sigma_{T/P,MLE}^2 = \frac{f_j^2 \sigma_{(MLE),p,p} + f_p^2 \sigma_{(MLE),j,j} - 2f_j f_p \sigma_{(MLE),p,j}}{f_j^4}$$

$$\sigma_{T/P,S}^2 = \frac{f_j^2 \sigma_{(S),p,p} + f_p^2 \sigma_{(S),j,j} - 2f_j f_p \sigma_{(S),p,j}}{f_j^4}$$

as above with

$$\sigma_{(MLE),i,j} = 4 * d'_i (D' \Sigma_X^{-1} D)^{-1} d_j$$

$$\sigma_{(S),i,j} = 4 * d'_i (D' \Sigma_X D) d_j$$

With the above results we can directly compare the three trough to peak estimators outlined above in terms of their asymptotic properties.

The trough to peak estimator based on time of day averages converges to the ratio of the baseline adjusted placebo subtracted mean trough and peak under all conditions in which a trough and peak exist, and is therefore asymptotically unbiased in practical situations. The trough to peak estimator based on the Fourier (or other orthogonal) expansion converges to the ratio of the estimate of the baseline adjusted placebo subtracted mean trough and peak, and therefore may be asymptotically biased.

On the other hand if we can assume that a low term Fourier (or other) orthogonal expansion adequately models the drug effect over time and thus provides an asymptotically unbiased estimate, the T/P ratio based on the Fourier transform will have a variance smaller than the variance of the T/P estimate based on the time of day averages, since $D(D'S_M^{-1}D)^{-1}DS_M^{-1}$ (or $D(D'D)^{-1}D$) is an orthogonal projector into the subspace spanned by the $(1+c+s)$ columns of D_F where c is the number of cosine terms and s the number of sin terms in the Fourier expansion. The effect of adding terms to the Fourier expansion are illustrated in table 2.1. The asymptotic variances for each of the above T/P statistics were computed for a specific known covariance structure (table CV.T1), which is the combined estimate of the covariance matrix calculated from 4 ambulatory studies. The peak

value was set at 130, the trough at 135. The 23 potential variances were computed for each of the T/P estimators assuming the peak effect occurred at each of the first 23 hour periods (total of 24 readings). The table has listed the minimum and maximum ratio of asymptotic variances across the 23 readings between the MLE Fourier versus the Averages T/P estimate, of the Simple Fourier T/P versus the Averages T/P estimate and the ratio of the Simple Fourier versus the MLE Fourier T/P estimate.

The results in Table 2.1 demonstrates the significant increase in variance of the T/P estimator based on the time of day averages when a few term Fourier series adequately models the dose response curve. The table illustrates also that asymptotically the Fourier T/P estimator based on the MLE has significantly smaller variance than the Simple Fourier T/P estimator.

For finite samples the situation is not as clear since since the exact moments for each of the above statistics for various drug response curves are not known. Each of the above estimates are biased since all involve the maximum of either the time of day average drug effect or the Fourier estimate of the time of day drug effect. The nature of the bias will be related to the underlying response curve and sample size. Although the variance of the T/P estimates based on the Fourier estimators will be less than the T/P estimate based on the time of day averages, the bias may be significantly larger for the T/P estimators based on the Fourier expansion. Further it is not known how the MLE Fourier estimate will compare to the Simple Fourier estimate for finite samples.

In the next chapter the above three estimators will be compared for finite sample sizes and various dose response curves using Monte-Carlo methods.

Table 2.1
Comparison of Asymptotic Variances of the Three Trough to Peak Estimators

Number of cosine terms	Number of sin terms		Ratio of variances: Fourier MLE / Average	Ratio of variances: Fourier Simple / Average	Ratio of variances: Fourier Simple / MLE
1	1	max	0.209	0.309	1.814
		min	0.004	0.007	1.467
2	2	max	0.292	0.399	1.523
		min	0.016	0.022	1.352
3	3	max	0.338	0.445	1.532
		min	0.046	0.056	1.171
4	4	max	0.465	0.593	1.404
		min	0.079	0.091	1.153
5	5	max	0.577	0.687	1.375
		min	0.112	0.128	1.127
6	6	max	0.644	0.744	1.360
		min	0.186	0.227	1.135
7	7	max	0.758	0.865	1.359
		min	0.282	0.331	1.075
8	8	max	0.851	0.929	1.256
		min	0.397	0.437	1.043
9	9	max	0.906	0.957	1.169
		min	0.520	0.555	1.011
10	10	max	0.944	0.985	1.185
		min	0.580	0.656	1.025
11	11	max	0.999	1.000	1.124
		min	0.809	0.863	1.000
12	11	max	1.000	1.000	1.000
		min	1.000	1.000	1.000

Chapter 3

T/P Estimator Monte - Carlo Simulation

The performance of the T/P estimate based on the time of day averages and the T/P estimates based on the Fourier fits described in the previous chapter are compared using Monte Carlo methods for selected finite sample sizes and a variety of hypothetical drug response placebo subtracted curves.

The plan of the simulation was to replicate an experimental design in which we have ambulatory data consisting of 24 equally spaced data points representing a placebo effect from baseline for each subject in a placebo group and similar ambulatory data representing a treatment effect from baseline for a treatment group. I chose the time period between each observation to always be 1 unit, with a total of 24 of these equally spaced observations for each patient for both the baseline ABPM and the on treatment ABPM, since many of the actual studies involving ambulatory data are over a 24 hour period and the data is summarized at 1 hour intervals.

Pseudo-random data is generated for the placebo and treatment groups of specified sample size and the baseline adjusted Placebo adjusted T/P ratios are computed based on either the time of day (hourly) averages or the simple or M.L.E. Fourier estimates discussed in the previous section. This procedure is repeated multiple times, each time drawing new pseudo-random samples with the same underlying placebo and drug effect and recomputing the T/P statistics. Then the resulting sampling distributions of the various T/P estimates are compared to the known

simulation values to determine the sample bias, variance and mean square error for each of the estimates.

For this study, the 24 hour ambulatory data is generated as pseudo-random 24-dimensional multivariate normal data with known mean $\theta_{P,B}$ for the placebo ABPM baseline data, $\theta_{P,T}$ for the placebo on treatment ABPM data, $\theta_{D,B}$ for the drug ABPM baseline data and $\theta_{D,T}$ for the drug on treatment ABPM data, with the combined baseline and on treatment data vector (length 48) with a known covariance structure Σ . The covariance matrix has a structure equal to the covariance matrix in table CV.T1 described in the previous chapter.

The simulations were programmed in S and executed on the University of Washington Department of Biostatistics computer system. The plan of the study required that the vectors $\theta_{P,B}$ and $\theta_{P,T}$, each consisting of 24 hourly means be specified for the placebo effect and the vectors $\theta_{D,B}$ and $\theta_{D,T}$ of hourly means specified for the drug baseline and on treatment effects. In this simulation the hourly difference between placebo on treatment and baselines (elements of $\theta_{P,T} - \theta_{P,B}$) were always set to 0 with the elements of $(\theta_{D,T} - \theta_{D,B})$ set to values to simulate various types of hypothetical placebo subtracted drug response curves. Then two 48 (24 x 2) element vectors, e_P, e_D , of pseudo-normal random variates are generated using the standard normal random number generator, `rnorm`, supplied with the S software. Each of the pseudo-normal random vectors e_P, e_D , are then pre multiplied by the 48 x 48 matrix B calculated from the matrix multiplication of the matrix V, of unit orthogonal columns and the square root of the diagonal matrix S, of singular values calculated from the singular value decomposition of the specified covariance matrix Σ . This transforms the vectors

e_P, e_D , into new vectors of length 48 each, say η_P, η_D , each a pseudo-random normal vector of length 48 with mean 0 and covariance matrix Σ . Next the known placebo and drug effect hourly means (baseline and on treatment) are added to η_P, η_D respectively to produce two pseudo-random 24 hour ABPM data vectors (baseline and on treatment) for one placebo and one drug response study patient, with known hourly mean and covariance structure. That is, if we denote the vector of pseudo-random placebo and drug response data as η_P, η_D respectively then:

$$\begin{array}{ll}
 B = VS & \text{with: } VSS' V = \Sigma \\
 \eta_P = Be_P & \eta_D = Be_D \\
 x_P = \eta_P + \theta_P & x_D = \eta_D + \theta_D \\
 \theta_P = \begin{bmatrix} \theta_{P,B} \\ \theta_{P,T} \end{bmatrix} & \theta_D = \begin{bmatrix} \theta_{D,B} \\ \theta_{D,T} \end{bmatrix}
 \end{array}$$

The above process is repeated N times to get a complete sample of size of $2 \times N$ for each run of the simulation. Each of the N pseudo-random vector pairs x_P, x_T generated become columns of the pseudo-random matrices X_P, X_T .

With the appropriate sample generated each of T/P estimators included in the study were calculated using the same sample and saved along with the sample size, actual T/P value, the actual hourly mean drug response, the sample bias and square error for each of the estimates.

The T/P estimators computed include:

1. T/P ratio computed from between subject time of day averages referred in this text as the Hourly Mean T/P estimator.

Calculation:

$$\overline{T/P}_M = \overline{y}_m / \max(\overline{y}_1, \overline{y}_2, \dots, \overline{y}_m) \text{ with}$$

$$\overline{y}_i = l_i' X A' (A A')^{-1} c \text{ with } X = [X_T X_P] \text{ and}$$

$$l_i' = [0, \dots, 1, 0, \dots, -1, 0, \dots] = [-\ell_i, \ell_i] \text{ with}$$

$$\ell_i = (0, \dots, 1, 0, \dots, 0) \text{ all zeros and a 1 at position } i$$

$$\text{and } c = \begin{bmatrix} -1 \\ 1 \end{bmatrix}.$$

2. The 3,5,7 and 9 term Simple Fourier estimate are referred to in the text as the Simple Fourier T/P estimator or just Simple estimator.

Calculation:

$$\overline{T/P}_{(S)} = \overline{f}_{(S)} / \max(\overline{f}_{(S),1}, \overline{f}_{(S),2}, \dots, \overline{f}_{(S),m})$$

with:

$$\overline{f}_{(S),t} = d_t' [(\overline{\beta}_{(S),2,1} - \overline{\beta}_{(S),1,1}) - (\overline{\beta}_{(S),2,2} - \overline{\beta}_{(S),1,2})] \text{ for } i=1,2,\dots,24$$

$$\overline{\beta}_{(S)} = \begin{bmatrix} \overline{\beta}_{(S),1,1} & \overline{\beta}_{(S),1,2} \\ \overline{\beta}_{(S),2,1} & \overline{\beta}_{(S),2,2} \end{bmatrix} = (D'D)^{-1} D' X A' (A A')^{-1}$$

$$D = \begin{bmatrix} D_F & 0 \\ 0 & D_F \end{bmatrix} \text{ with:}$$

$$D_F = \sqrt{\frac{2}{24}} \begin{bmatrix} 1/\sqrt{2} & \cos(\frac{2\pi}{24}) & \dots & \cos(\frac{2q\pi}{24}) & \sin(\frac{2\pi}{24}) & \dots & \sin(\frac{2q\pi}{24}) \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1/\sqrt{2} & \cos(\frac{2\pi 24}{24}) & \dots & \cos(\frac{2q\pi 24}{24}) & \sin(\frac{2\pi 24}{24}) & \dots & \sin(\frac{2q\pi 24}{24}) \end{bmatrix}$$

with $q=1,2,3$ or 4 for the $3,5,7,9$ term Simple Fourier T/P estimator respectively.

3. The $3,5,7$ and 9 term M.L.E. Fourier estimates derived in the previous section assuming equality of covariance matrix, and referred to in this text as M.L.E.

Fourier T/P estimator or just M.L.E. estimator.

These estimates are only included for samples sizes larger than or equal to 30 , since the inverse covariance matrix S_M^{-1} is required for these statistics.

Calculation:

$$\overline{T/P}_{(MLE)} = \bar{f}_{(MLE),24} / \max(\bar{f}_{(MLE),1}, \bar{f}_{(MLE),2}, \dots, \bar{f}_{(MLE),24})$$

$$\bar{f}_{(MLE),t} = d'_t [(\bar{\beta}_{(MLE),2,1} - \bar{\beta}_{(MLE),1,1}) - (\bar{\beta}_{(MLE),2,2} - \bar{\beta}_{(MLE),1,2})]$$

for $i=1,2,\dots,24$

$$\bar{\beta}_{(MLE)} = \begin{bmatrix} \bar{\beta}_{(MLE),1,1} & \bar{\beta}_{(MLE),1,2} \\ \bar{\beta}_{(MLE),2,1} & \bar{\beta}_{(MLE),2,2} \end{bmatrix} = (D'S_M^{-1}D)^{-1} D'S_M^{-1}XA'(AA')^{-1}$$

In each of the simulations 400 replicates were generated and analyzed comparing each of the estimators' characteristics.

In the simulation study, the behavior of each of the T/P statistics were examined for different study sample sizes, placebo subtracted drug response curve shapes and T/P ratios. Sample sizes for the placebo and drug response groups were kept equal and were set at $10,20,30$ and 50 which created a total study sample size of $(2 \times N)$ $20,40,60$ and 100 respectively. For each of the above sample sizes 42 different placebo subtracted drug effect curve types and T/P ratio combinations were simulated.

Each of the 42 curves have two characteristic in common. Each of the response curves has a value at the beginning of the time period (hour 1) which is the same as the value of the response curve at the end of the time period (24 hours). This cyclical characteristic would be expected in an ongoing drug treatment program in which the dosage is repeated every 24 hours. The second characteristic in common is that the drug responses lower the value of the end point of interest. So the "peak" in our case is the peak reduction in the value of the end point, such as the peak reduction in systolic and/or diastolic blood pressure attributed to an antihypertensive drug.

The 42 curves are variations of 5 main types, which potentially mimic placebo adjusted antihypertensive drug response curves .

The first main type of response curves (simulation 1) is pictured in figure S1. The end point decreases in value at a constant rate until the peak hour (peak), then immediately increases at a constant rate back to the initial value at 24 hours (trough). In total 30 curves of this type are included in the simulation and are made up of all combinations of initial and ending values of -3 and -6, peak effect hours of 2,3,4,6 and 8 and T/P ratios of 0.75, 0.50 and 0.25.

The second set of response curves (simulation 2) are pictured in figure S2. The end point decreases to 1/2 of the peak decrease within the first hour, then gradually decreases to a peak decrease at 8 hours, then increases gradually until hour 12, then increases constantly to the initial value at 24 hours. A total of 6 curves are simulated made up of all combinations of 2 initial and ending values of -3 and -6, and T/P ratios of .75, 0.5 and 0.25.

The third set of response curves (simulation 3) are pictured in figure S3. The end point decreases at a constant rate to the peak decrease after 2 hours, maintains the peak decrease over the next 20 hours, then increases at a constant rate to the initial value. A total of 3 curves are simulated each with an ending value of -3 and T/P ratios of .75, 0.5 and 0.25.

The fourth set of response curves (simulation 4) are pictured in figure S4. The end point is at a constant value throughout the 24 hours giving a T/P ratio of 1. Two curves are simulated, the first with a constant value of -4 and the second with a constant value of -12.

The fifth set of response curves (simulation 5) are pictured in figure 5. There are 3 curves which are Fourier curve fits to 3 different actual ambulatory data sets. The first curve (case 1) is a three term Fourier curve, the second curve (cases 2) is a 5 term Fourier series and the third curve (case 3) is a 7 term Fourier series. The T/P ratios are 0.40, 0.91 and 0.49 respectively.

After the 400 simulation replicates are generated and the above T/P statistics computed the sample average, median, variance, 25 th. and 75 th. percentiles, minimum value, maximum value, mean squared error (MSE) and average bias were calculated from the resultant sample distribution for each of the T/P estimates. In addition, since each of the T/P statistics are computed from the same samples, various paired difference statistics were also computed and p-values calculated for the comparisons of interest; specifically differences in bias and squared error. Further ratios of sample mean squared errors (MSER) for specific T/P statistics along with asymptotic 95 % confidence limits were computed to estimate and compare the relative estimation efficiency (as defined in Anderson

1971) of the T/P estimates of interest. Tables and figures were generated for representative subsets of the simulation results and are discussed in the paragraphs that follow to highlight various simulation experiment results .

In the discussions of the results of the simulation for each of the Curve Sets described above, the characteristics of the T/P estimator based on the Simple Fourier estimator are first compared to the estimator based on the M.L.E. Fourier estimator and then compared to the T/P estimator based on the Hourly Mean.

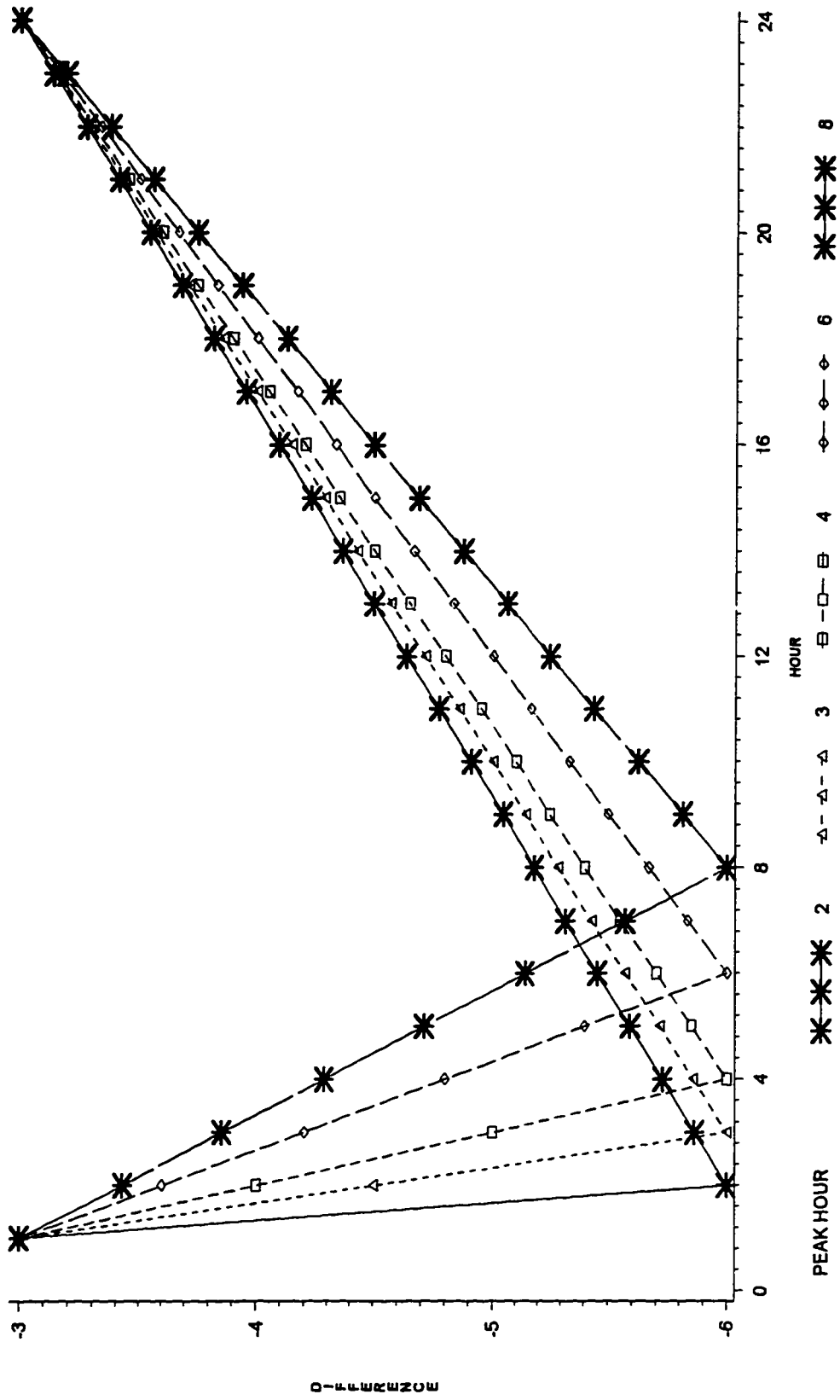


FIGURE S1: PLOT OF SIMULATED DRUG EFFECT CURVES - SIMULATION 1

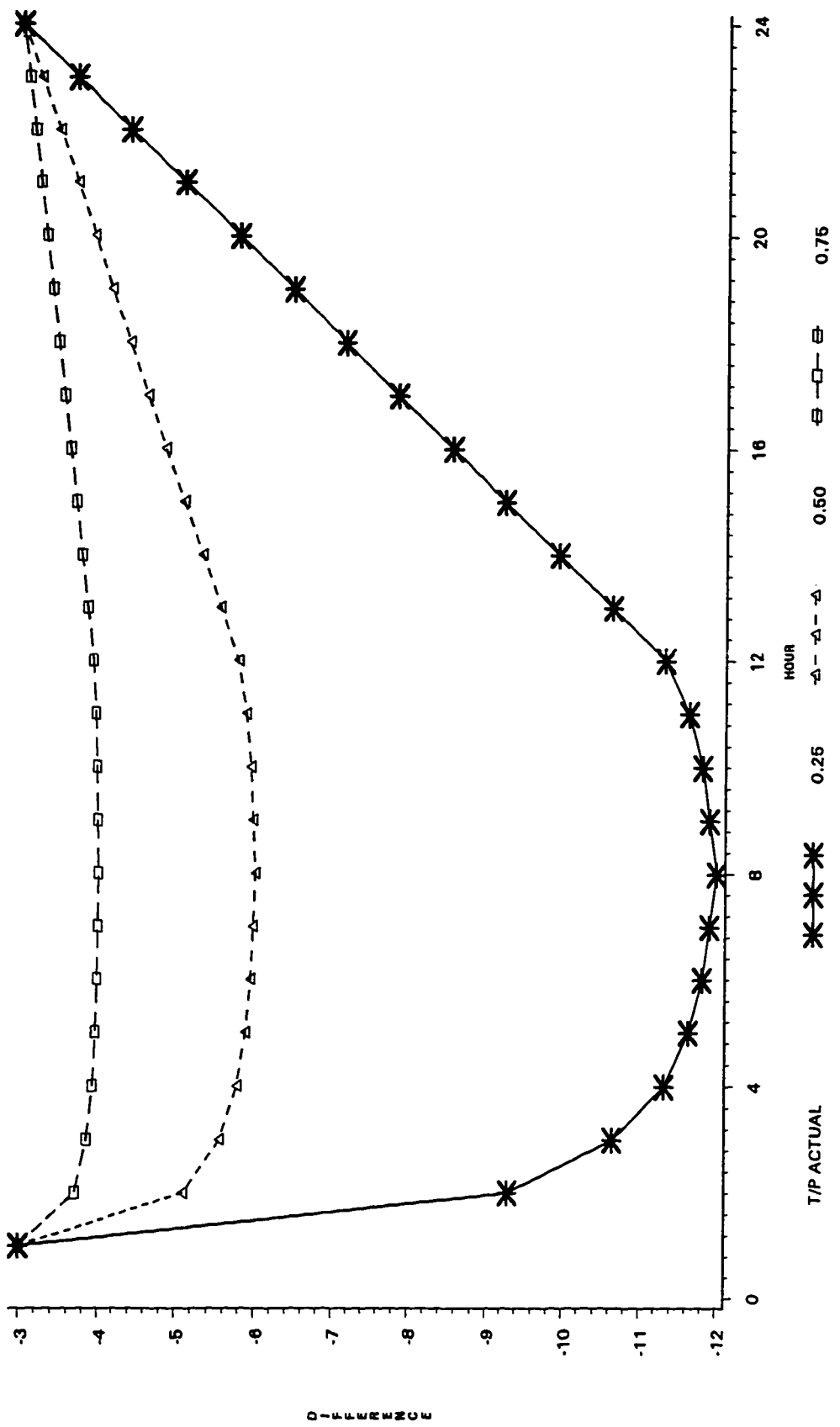


FIGURE S2: PLOT OF SIMULATED DRUG EFFECT CURVES - SIMULATION 2

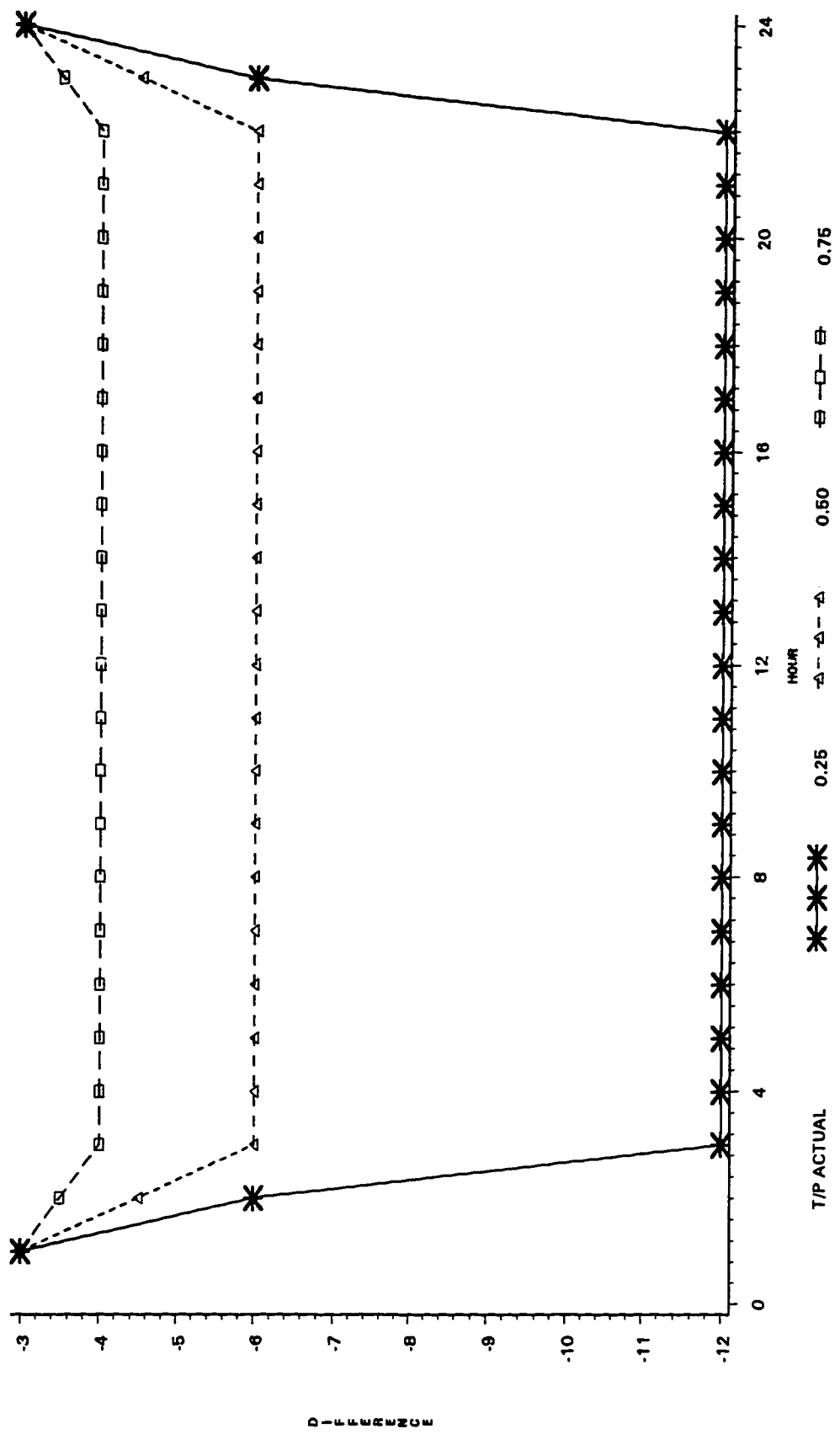


FIGURE S3: PLOT OF SIMULATED DRUG EFFECT CURVES - SIMULATION 3

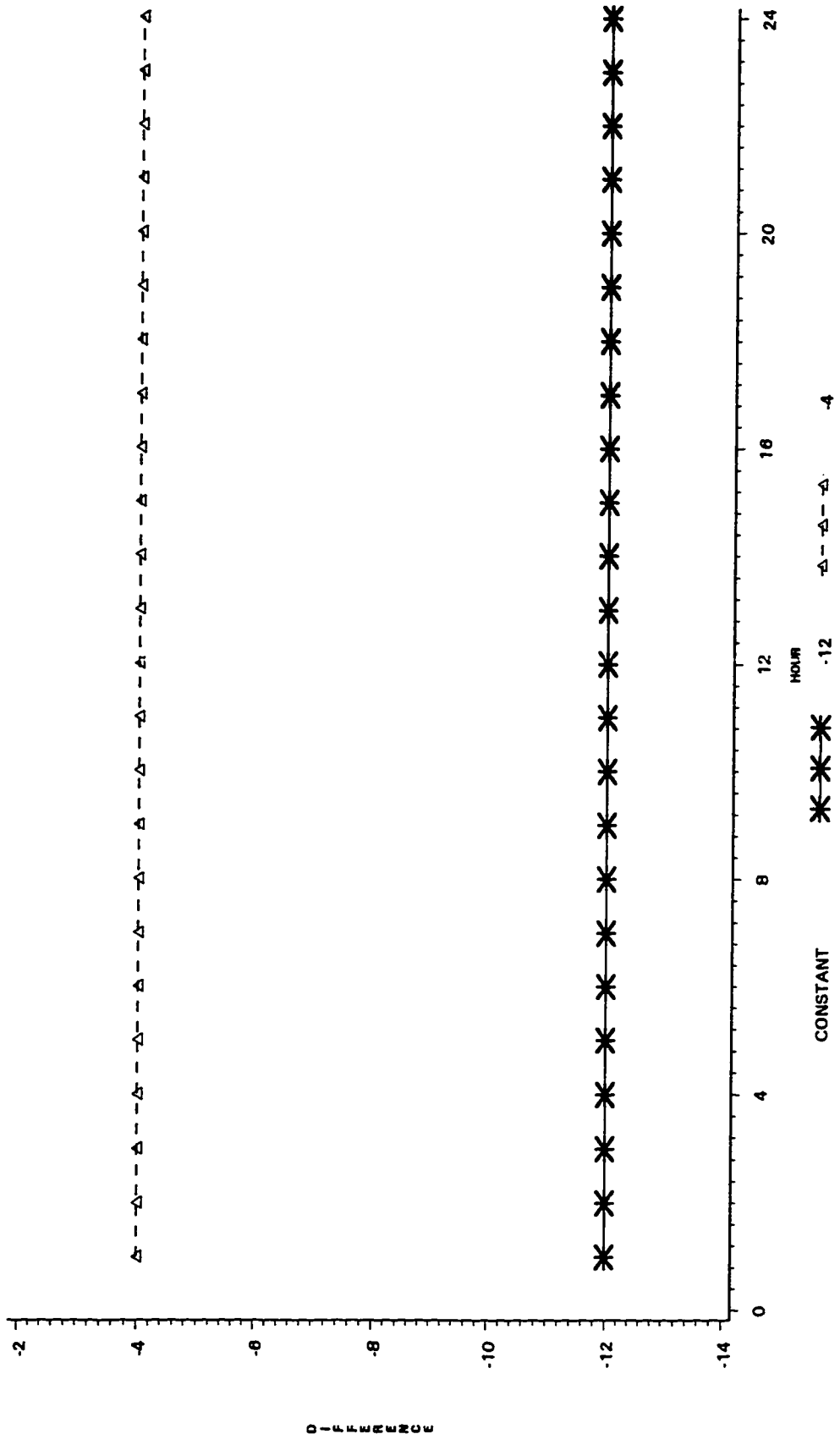


FIGURE S4: PLOT OF SIMULATED DRUG EFFECT CURVES - SIMULATION 4

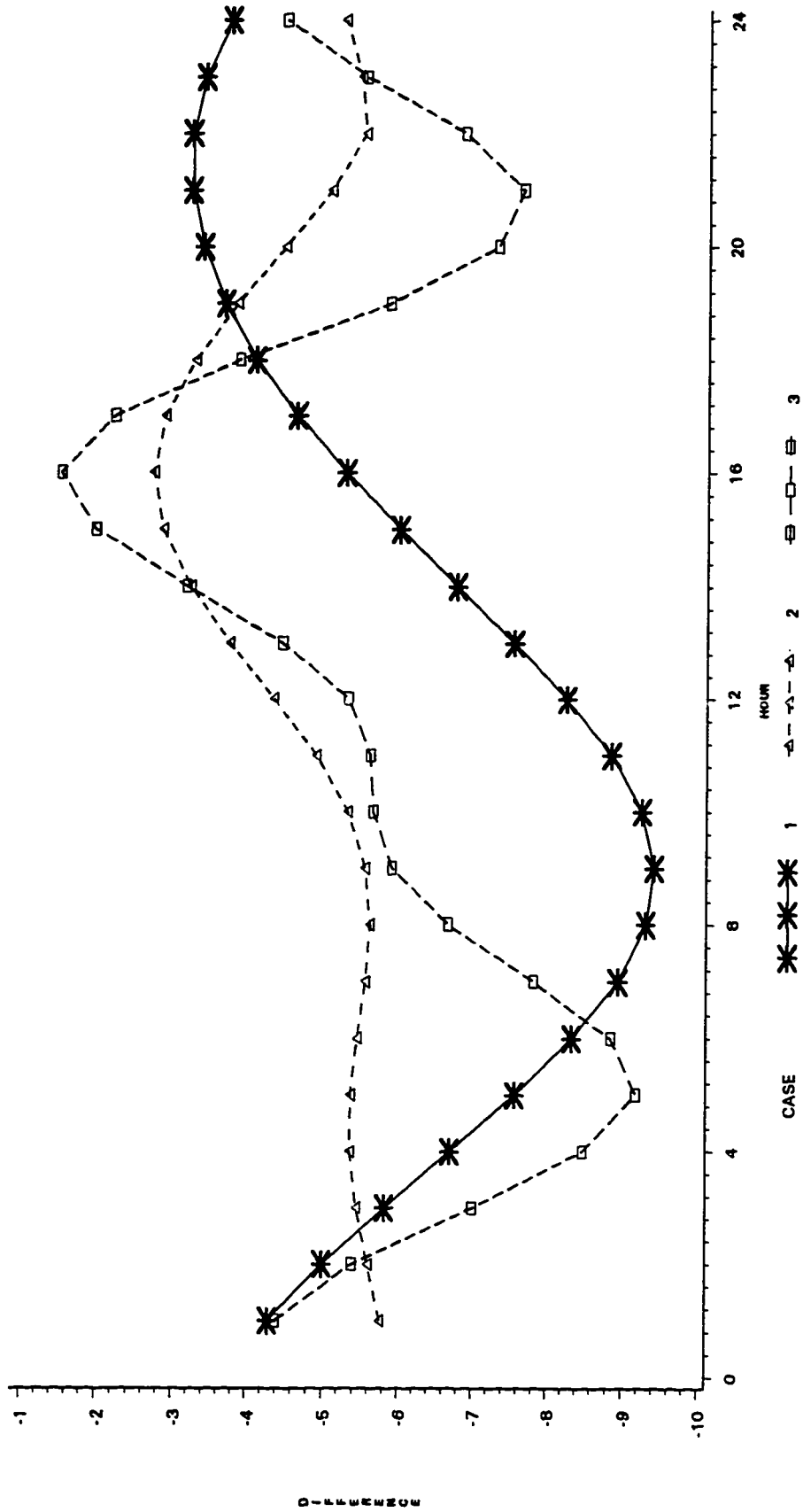


FIGURE S5: PLOT OF SIMULATED DRUG EFFECT CURVES - SIMULATION 5

Simulation Results Simple versus M.L.E. Fourier T/P Estimators

The simulation sample mean, variance, bias, and asymptotic bias 95% C.I. for the Simple Fourier T/P estimates and the M.L.E. Fourier T/P estimates for simulation 1, sample sizes 30 and 50 are found in table S1.C1 in the appendix . These are the only two sample sizes used in the simulation where both the Simple Fourier T/P estimate and the M.L.E. Fourier T/P estimate were computed. A section of table S1.C1 for initial value -6 and dose response peak hour of 6 is found in the accompanying table S1.C1.R. The type of estimator are identified in the table in column 4 as either 'M.L.E.' or 'Simple' followed by a number indicating the number of terms included in the Fourier estimate. Examining table S1.C1.R we find that the degree of bias changes depending on the actual T/P ratio and the number of terms used in either the Simple or M.L.E. Fourier estimate.

With the high T/P ratio 0.75 the estimators based on 3 Fourier terms seem to have a smaller bias than those with more terms; with T/P ratio of 0.5 the 5 term Fourier T/P estimators have the smallest bias and with T/P ratio of 0.25 the T/P estimator based on the 7 or 9 term Fourier fit have the least bias. All of the Fourier estimators tend to be biased toward giving lower values than actual for the high T/P ratio (0.75) and are biased to give higher values than actual for low T/P ratio (0.25). Using the span of the 95% confidence interval associated with the bias term as an indicator whether the true bias of the statistic is possibly zero, we find that for T/P ratio 0.75, N=30 the 3 term Simple Fourier estimator confidence interval span zero and for T/P=0.75, N=50 the 3 term M.L.E. Fourier estimator confidence interval span zero, are consistent with the hypothesis of zero bias.

For T/P=0.5, N=30 and N=50 both the 5 term Simple and M.L.E. Fourier estimators confidence intervals span zero, and for T/P=0.25, N=30 the 7 and 9

term Simple and M.L.E. Fourier estimators confidence intervals span zero and for $N=50$ the Simple 7 and 9 term Fourier estimators confidence intervals span zero and the confidence interval for the 7 and 9 term M.L.E. has a lower limit very close to zero. The above suggests, at least for the set of curves represented in curve set 1, as the actual T/P ratio decreases one needs to add more Fourier terms to the curve fits to produce T/P ratio estimators with optimal bias characteristics.

The tables of sample means, variances, biases for simulations 2 and 3 are found in tables S2.C1 and S3.C1 respectively. The same bias pattern is found with these curves also, the 3 term Fourier estimators have least bias for curves with high T/P ratios, the 5 term Fourier estimators have least bias for curves with T/P ratio of 0.5 and the 7 or 9 term Fourier estimators show least bias for T/P ratio 0.25. The sample statistics for curve set 4 are found in table S4.C1. Both curves in this set are constants (at -4 and -12) across time, both with T/P ratio of 1. In this case the 3 term Fourier estimators consistently have the least bias. The sample statistics for curves in set 5 are found in table S5.C1. For case 1 in this curve set, which is a three term Fourier function, the 3 term estimators have minimum bias, for case 2, a 5 term Fourier function, the 3 term estimators also demonstrate minimum bias and with case 3, a 7 term Fourier function, the 7 term estimators have minimum bias. These results suggest that the T/P estimator based on the appropriate Fourier fit for the actual function may produce a T/P estimator with minimum or close to minimum bias.

The sample variance of the estimators are also listed in these tables, based on the 400 replications in each simulation. Notice that the variance of the estimators decrease in curve sets 1, 2 and 3 as the actual trough to peak ratio decreases. This is consistent with the asymptotic distribution results developed in the previous section.

In tables S1.C2, S1.C3, S2.C2, S2.C3, S3.C2, S3.C3, S4.C2, S4.C3, S5.C2 and S5.C3 the T/P estimators based on the Simple Fourier series fit and the M.L.E. Fourier fit are compared. In the Sx.C2 ($x=1,2,3,4,5$ for each of the 5 simulations) tables the sample bias differences between the two estimators are compared for the 3, 5, 7 and 9 term estimators (labeled F3, F5, F7 and F9 respectively). Included in these tables, in columns labeled 'prob. diff=0', are the p-value associated with the paired Wilcoxon signed rank test (Hollander, Wolfe pp 27) to test the null hypothesis of no difference in bias between the two types of Fourier T/P estimators. In the Sx.C3 tables the sample mean square error (MSE) differences between the two Fourier estimators are tabled along with their Wilcoxon signed rank p - values . A summary of the bias, variance and m.s.e. comparisons between the Simple and M.L.E. Fourier estimators are found in the Sx.C4 tables. The Sx.C4 tables summarize in an easy to visualize format which T/P ratio estimator had the smaller bias, variance and MSE, and whether the difference was found significant at to 0.01 p - value level.

Examining the S1.C4 table, the bias for actual T/P = 0.5 and 0.25 is less and in many cases significant at the 0.01 p - value level for the 3 term M.L.E. estimator versus the 3 term Simple estimator and also found for the T/P = 0.25 5 term Fourier estimators, but the Simple estimator often show significantly less bias when comparing the 7 and 9 term Simple and M.L.E. Fourier estimators.

The variance associated with the Simple estimator is almost always smaller than for the M.L.E.. The means square error, which is the combination of the bias and variance is typically dominated by the bias component and therefore has a pattern similar to the bias term, with the 3 term estimators based on the M.L.E. often smaller, but for the 5,7 and 9 term Fourier estimators most of the mean square errors are smaller for the Simple estimator, with a few significant at the 0.01 p - value level, particularly for the 7 and 9 term Fourier estimators with actual

T/P=0.25. Out of the 176 comparisons of MSEs involving the 5,7 and 9 term estimators, 156 were smaller with the Simple estimator, compared to only 8 smaller for the M.L.E. estimator with 12 ties.

The summary of findings for the second simulation is found in S2.C4. The bias is typically less for the Simple Fourier estimator for T/P ratio = 0.75, but with T/P=0.25 the 3,5 and 7 term Fourier T/P estimators the bias is less for the M.L.E., and for the 9 term Fourier T/P estimators the bias associated with the Simple estimate is typically smaller. The variance was always smaller for the Simple estimator (except one occasion with both equal), and the MSE is smaller for the Simple estimator except with the 3 term estimators which has half smaller for the Simple estimator and half for the M.L.E.. This pattern is essentially repeated in table S3.C4 the summary for simulation 3. In simulation 4 the pattern is different. Significantly smaller bias is found for the Simple estimator in the -12 curve, sample size = 30, and 13 out of the 16 comparisons of variances (both the -4 and -12) are also smaller for the Simple estimator, and 12 of the 16 MSEs are smaller for the Simple estimator. The results of the comparison between the Simple and M.L.E. T/P estimator for curve set 5, summarized in S5.C4 is similar to results found in simulations 1,2 and 3.

One can conclude from these simulation the Simple estimator typically fairs better in terms of variance and MSE than the M.L.E. for this covariance structure, set of curves and sample sizes .

Table S1.C1R
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 1

T/P	Initial	Peak	Estimator	N	Sample	Sample	Sample	Lower	Upper
ratio	value	Hour			Mean	Variance	Bias	95%	95%
								C.I.	C.I.
-6	0.75	6	M.L.E. 3	30	0.708	.039	-.042	-.061	-.023
-6	0.75	6	Fourier 3	30	0.741	.032	-.009	-.027	.009
-6	0.75	6	M.L.E. 5	30	0.627	.040	-.123	-.143	-.103
-6	0.75	6	Fourier 5	30	0.643	.034	-.107	-.125	-.089
-6	0.75	6	M.L.E. 7	30	0.584	.044	-.166	-.187	-.145
-6	0.75	6	Fourier 7	30	0.602	.038	-.148	-.167	-.129
-6	0.75	6	M.L.E. 9	30	0.564	.049	-.186	-.208	-.164
-6	0.75	6	Fourier 9	30	0.576	.041	-.174	-.194	-.154
-6	0.75	6	M.L.E. 3	50	0.757	.023	.007	-.008	.022
-6	0.75	6	Fourier 3	50	0.768	.023	.018	.003	.033
-6	0.75	6	M.L.E. 5	50	0.685	.022	-.065	-.080	-.050
-6	0.75	6	Fourier 5	50	0.68	.022	-.070	-.085	-.055
-6	0.75	6	M.L.E. 7	50	0.636	.028	-.114	-.130	-.098
-6	0.75	6	Fourier 7	50	0.632	.027	-.118	-.134	-.102
-6	0.75	6	M.L.E. 9	50	0.618	.032	-.132	-.150	-.114
-6	0.75	6	Fourier 9	50	0.615	.031	-.135	-.152	-.118
-6	0.5	6	M.L.E. 3	30	0.574	.031	.074	.057	.091
-6	0.5	6	Simple 3	30	0.619	.024	.119	.104	.134
-6	0.5	6	M.L.E. 5	30	0.486	.028	-.014	-.030	.002
-6	0.5	6	Simple 5	30	0.496	.020	-.004	-.018	.010
-6	0.5	6	M.L.E. 7	30	0.455	.028	-.045	-.061	-.029
-6	0.5	6	Simple 7	30	0.465	.022	-.035	-.050	-.020
-6	0.5	6	M.L.E. 9	30	0.451	.031	-.049	-.066	-.032
-6	0.5	6	Simple 9	30	0.461	.027	-.039	-.055	-.023
-6	0.5	6	M.L.E. 3	50	0.576	.018	.076	.063	.089
-6	0.5	6	Simple 3	50	0.62	.015	.120	.108	.132
-6	0.5	6	M.L.E. 5	50	0.507	.016	.007	-.005	.019
-6	0.5	6	Simple 5	50	0.507	.016	.007	-.005	.019
-6	0.5	6	M.L.E. 7	50	0.484	.017	-.016	-.029	-.003
-6	0.5	6	Simple 7	50	0.483	.017	-.017	-.030	-.004
-6	0.5	6	M.L.E. 9	50	0.478	.020	-.022	-.036	-.008
-6	0.5	6	Simple 9	50	0.482	.017	-.018	-.031	-.005
-6	0.25	6	M.L.E. 3	30	0.361	.011	.111	.101	.121
-6	0.25	6	Fourier 3	30	0.422	.007	.172	.164	.180
-6	0.25	6	M.L.E. 5	30	0.273	.009	.023	.014	.032
-6	0.25	6	Fourier 5	30	0.273	.006	.023	.015	.031
-6	0.25	6	M.L.E. 7	30	0.251	.009	.001	-.008	.010
-6	0.25	6	Fourier 7	30	0.247	.007	-.003	-.011	.005
-6	0.25	6	M.L.E. 9	30	0.258	.009	.008	-.001	.017

Table S1.C1R
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 1

T/P ratio	Initial value	Peak Hour	Estimator	N	Sample Mean	Sample Variance	Sample Bias	Lower 95% C.I.	Upper 95% C.I.
-6	0.25	6	Fourier 9	30	0.253	.007	.003	-.005	.011
-6	0.25	6	M.L.E. 3	50	0.361	.005	.111	.104	.118
-6	0.25	6	Fourier 3	50	0.422	.004	.172	.166	.178
-6	0.25	6	M.L.E. 5	50	0.278	.004	.028	.022	.034
-6	0.25	6	Fourier 5	50	0.278	.004	.028	.022	.034
-6	0.25	6	M.L.E. 7	50	0.257	.005	.007	.000	.014
-6	0.25	6	Fourier 7	50	0.254	.004	.004	-.002	.010
-6	0.25	6	M.L.E. 9	50	0.26	.005	.010	.003	.017
-6	0.25	6	Fourier 9	50	0.256	.005	.006	-.001	.013

Table S2.C1
COMPARISON OF FOURIER ESTIMATORS

SIMULATION 2

T/P ratio	Initial value	Estimator	N	Sample Mean	Sample Variance	Sample Bias	Lower 95% C.I.	Upper 95% C.I.
-3	0.75	M.L.E. 3	30	.614	.088	-.136	-.165	-.107
-3	0.75	Simple 3	30	.625	.078	-.125	-.152	-.098
-3	0.75	M.L.E. 5	30	.531	.085	-.219	-.248	-.190
-3	0.75	Simple 5	30	.529	.072	-.221	-.247	-.195
-3	0.75	M.L.E. 7	30	.482	.080	-.268	-.296	-.240
-3	0.75	Simple 7	30	.477	.073	-.273	-.299	-.247
-3	0.75	M.L.E. 9	30	.451	.084	-.299	-.327	-.271
-3	0.75	Simple 9	30	.441	.071	-.309	-.335	-.283
-3	0.5	M.L.E. 3	30	.540	.075	.040	.013	.067
-3	0.5	Simple 3	30	.590	.067	.090	.065	.115
-3	0.5	M.L.E. 5	30	.445	.063	-.055	-.080	-.030
-3	0.5	Simple 5	30	.480	.058	-.020	-.044	.004
-3	0.5	M.L.E. 7	30	.395	.059	-.105	-.129	-.081
-3	0.5	Simple 7	30	.419	.057	-.081	-.104	-.058
-3	0.5	M.L.E. 9	30	.357	.057	-.143	-.166	-.120
-3	0.5	Simple 9	30	.375	.054	-.125	-.148	-.102
-3	0.25	M.L.E. 3	30	.381	.024	.131	.116	.146
-3	0.25	Simple 3	30	.443	.020	.193	.179	.207
-3	0.25	M.L.E. 5	30	.315	.024	.065	.050	.080
-3	0.25	Simple 5	30	.337	.019	.087	.073	.101
-3	0.25	M.L.E. 7	30	.258	.023	.008	-.007	.023
-3	0.25	Simple 7	30	.266	.021	.016	.002	.030
-3	0.25	M.L.E. 9	30	.214	.024	-.036	-.051	-.021
-3	0.25	Simple 9	30	.225	.021	-.025	-.039	-.011
-3	0.75	M.L.E. 3	50	.651	.068	-.099	-.125	-.073
-3	0.75	Simple 3	50	.680	.060	-.070	-.094	-.046
-3	0.75	M.L.E. 5	50	.563	.062	-.187	-.211	-.163
-3	0.75	Simple 5	50	.576	.054	-.174	-.197	-.151
-3	0.75	M.L.E. 7	50	.506	.067	-.244	-.269	-.219
-3	0.75	Simple 7	50	.516	.059	-.234	-.258	-.210
-3	0.75	M.L.E. 9	50	.465	.070	-.285	-.311	-.259
-3	0.75	Simple 9	50	.477	.064	-.273	-.298	-.248
-3	0.5	M.L.E. 3	50	.572	.050	.072	.050	.094
-3	0.5	Simple 3	50	.604	.047	.104	.083	.125
-3	0.5	M.L.E. 5	50	.506	.047	.006	-.015	.027
-3	0.5	Simple 5	50	.514	.044	.014	-.007	.035
-3	0.5	M.L.E. 7	50	.439	.050	-.061	-.083	-.039
-3	0.5	Simple 7	50	.445	.045	-.055	-.076	-.034
-3	0.5	M.L.E. 9	50	.400	.048	-.100	-.121	-.079
-3	0.5	Simple 9	50	.407	.048	-.093	-.114	-.072

Table S2.C1
COMPARISON OF FOURIER ESTIMATORS

SIMULATION 2

T/P ratio	Initial value	Estimator	N	Sample Mean	Sample Variance	Sample Bias	Lower 95% C.I.	Upper 95% C.I.
-3	0.25	M.L.E. 3	50	.390	.014	.140	.128	.152
-3	0.25	Simple 3	50	.451	.012	.201	.190	.212
-3	0.25	M.L.E. 5	50	.341	.014	.091	.079	.103
-3	0.25	Simple 5	50	.353	.011	.103	.093	.113
-3	0.25	M.L.E. 7	50	.268	.014	.018	.006	.030
-3	0.25	Simple 7	50	.273	.012	.023	.012	.034
-3	0.25	M.L.E. 9	50	.219	.014	-.031	-.043	-.019
-3	0.25	Simple 9	50	.228	.013	-.022	-.033	-.011
-6	0.75	M.L.E. 3	30	.710	.042	-.040	-.060	-.020
-6	0.75	Simple 3	30	.732	.031	-.018	-.035	-.001
-6	0.75	M.L.E. 5	30	.634	.042	-.116	-.136	-.096
-6	0.75	Simple 5	30	.649	.033	-.101	-.119	-.083
-6	0.75	M.L.E. 7	30	.578	.043	-.172	-.192	-.152
-6	0.75	Simple 7	30	.592	.037	-.158	-.177	-.139
-6	0.75	M.L.E. 9	30	.541	.048	-.209	-.230	-.188
-6	0.75	Simple 9	30	.552	.040	-.198	-.218	-.178
-6	0.25	M.L.E. 3	30	.389	.008	.139	.130	.148
-6	0.25	Simple 3	30	.451	.005	.201	.194	.208
-6	0.25	M.L.E. 5	30	.347	.008	.097	.088	.106
-6	0.25	Simple 5	30	.358	.005	.108	.101	.115
-6	0.25	M.L.E. 7	30	.285	.010	.035	.025	.045
-6	0.25	Simple 7	30	.287	.007	.037	.029	.045
-6	0.25	M.L.E. 9	30	.234	.010	-.016	-.026	-.006
-6	0.25	Simple 9	30	.244	.008	-.006	-.015	.003
-6	0.75	M.L.E. 3	50	.757	.024	.007	-.008	.022
-6	0.75	Simple 3	50	.773	.023	.023	.008	.038
-6	0.75	M.L.E. 5	50	.690	.024	-.060	-.075	-.045
-6	0.75	Simple 5	50	.697	.023	-.053	-.068	-.038
-6	0.75	M.L.E. 7	50	.642	.026	-.108	-.124	-.092
-6	0.75	Simple 7	50	.648	.025	-.102	-.117	-.087
-6	0.75	M.L.E. 9	50	.598	.032	-.152	-.170	-.134
-6	0.75	Simple 9	50	.609	.030	-.141	-.158	-.124
-6	0.25	M.L.E. 3	50	.394	.004	.144	.138	.150
-6	0.25	Simple 3	50	.449	.003	.199	.194	.204
-6	0.25	M.L.E. 5	50	.356	.004	.106	.100	.112
-6	0.25	Simple 5	50	.366	.003	.116	.111	.121
-6	0.25	M.L.E. 7	50	.291	.005	.041	.034	.048
-6	0.25	Simple 7	50	.296	.004	.046	.040	.052
-6	0.25	M.L.E. 9	50	.237	.005	-.013	-.020	-.006
-6	0.25	Simple 9	50	.251	.005	.001	-.006	.008

Table S3.C1
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 3

T/P	Initial	Estimator	N	Sample	Sample	Sample	Lower	Upper
ratio	value			Mean	Variance	Bias	95%C.I.	95%C.I.
-3	0.75	M.L.E. 3	30	.602	.090	-.148	-.177	-.119
-3	0.75	Simple 3	30	.663	.071	-.087	-.113	-.061
-3	0.75	M.L.E. 5	30	.504	.084	-.246	-.274	-.218
-3	0.75	Simple 5	30	.525	.070	-.225	-.251	-.199
-3	0.75	M.L.E. 7	30	.431	.082	-.319	-.347	-.291
-3	0.75	Simple 7	30	.450	.070	-.300	-.326	-.274
-3	0.75	M.L.E. 9	30	.395	.077	-.355	-.382	-.328
-3	0.75	Simple 9	30	.407	.072	-.343	-.369	-.317
-3	0.5	M.L.E. 3	30	.622	.065	.122	.097	.147
-3	0.5	Simple 3	30	.682	.049	.182	.160	.204
-3	0.5	M.L.E. 5	30	.501	.059	.001	-.023	.025
-3	0.5	Simple 5	30	.514	.048	.014	-.007	.035
-3	0.5	M.L.E. 7	30	.423	.060	-.077	-.101	-.053
-3	0.5	Simple 7	30	.421	.053	-.079	-.102	-.056
-3	0.5	M.L.E. 9	30	.360	.060	-.140	-.164	-.116
-3	0.5	Simple 9	30	.357	.055	-.143	-.166	-.120
-3	0.25	M.L.E. 3	30	.551	.031	.301	.284	.318
-3	0.25	Simple 3	30	.630	.020	.380	.366	.394
-3	0.25	M.L.E. 5	30	.426	.025	.176	.161	.191
-3	0.25	Simple 5	30	.429	.016	.179	.167	.191
-3	0.25	M.L.E. 7	30	.306	.022	.056	.041	.071
-3	0.25	Simple 7	30	.306	.019	.056	.042	.070
-3	0.25	M.L.E. 9	30	.237	.022	-.013	-.028	.002
-3	0.25	Simple 9	30	.227	.019	-.023	-.037	-.009
-3	0.75	M.L.E. 3	50	.716	.055	-.034	-.057	-.011
-3	0.75	Simple 3	50	.725	.054	-.025	-.048	-.002
-3	0.75	M.L.E. 5	50	.619	.052	-.131	-.153	-.109
-3	0.75	Simple 5	50	.618	.051	-.132	-.154	-.110
-3	0.75	M.L.E. 7	50	.554	.054	-.196	-.219	-.173
-3	0.75	Simple 7	50	.549	.053	-.201	-.224	-.178
-3	0.75	M.L.E. 9	50	.493	.061	-.257	-.281	-.233
-3	0.75	Simple 9	50	.502	.060	-.248	-.272	-.224
-3	0.5	M.L.E. 3	50	.654	.040	.154	.134	.174
-3	0.5	Simple 3	50	.701	.034	.201	.183	.219
-3	0.5	M.L.E. 5	50	.543	.036	.043	.024	.062
-3	0.5	Simple 5	50	.537	.035	.037	.019	.055
-3	0.5	M.L.E. 7	50	.445	.035	-.055	-.073	-.037
-3	0.5	Simple 7	50	.440	.037	-.060	-.079	-.041
-3	0.5	M.L.E. 9	50	.384	.041	-.116	-.136	-.096
-3	0.5	Simple 9	50	.381	.040	-.119	-.139	-.099

Table S3.C1
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 3

T/P ratio	Initial value	Estimator	N	Sample Mean	Sample Variance	Sample Bias	Lower 95% C.L	Upper 95% C.L
-3	0.25	M.L.E. 3	50	.553	.018	.303	.290	.316
-3	0.25	Simple 3	50	.633	.011	.383	.373	.393
-3	0.25	M.L.E. 5	50	.444	.012	.194	.183	.205
-3	0.25	Simple 5	50	.441	.009	.191	.182	.200
-3	0.25	M.L.E. 7	50	.330	.014	.080	.068	.092
-3	0.25	Simple 7	50	.320	.012	.070	.059	.081
-3	0.25	M.L.E. 9	50	.255	.014	.005	-.007	.017

Table S4.C1
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 4

Initial value	Estimator	N	Sample Mean	Sample Variance	Sample Bias	Lower 95% C.I.	Upper 95% C.I.
-12	M.L.E. 3	30	0.874	.012	-.126	-.137	-.115
-12	Simple 3	30	0.896	.009	-.104	-.113	-.095
-12	M.L.E. 5	30	0.822	.015	-.178	-.190	-.166
-12	Simple 5	30	0.848	.011	-.152	-.162	-.142
-12	M.L.E. 7	30	0.786	.020	-.214	-.228	-.200
-12	Simple 7	30	0.811	.016	-.189	-.201	-.177
-12	M.L.E. 9	30	0.762	.022	-.238	-.253	-.223
-12	Simple 9	30	0.784	.018	-.216	-.229	-.203
-12	M.L.E. 3	50	0.916	.006	-.084	-.092	-.076
-12	Simple 3	50	0.915	.005	-.085	-.092	-.078
-12	M.L.E. 5	50	0.876	.008	-.124	-.133	-.115
-12	Simple 5	50	0.876	.008	-.124	-.133	-.115
-12	M.L.E. 7	50	0.851	.010	-.149	-.159	-.139
-12	Simple 7	50	0.85	.010	-.150	-.160	-.140
-12	M.L.E. 9	50	0.826	.013	-.174	-.185	-.163
-12	Simple 9	50	0.826	.012	-.174	-.185	-.163
-4	M.L.E. 3	30	0.697	.079	-.303	-.331	-.275
-4	Simple 3	30	0.715	.076	-.285	-.312	-.258
-4	M.L.E. 5	30	0.617	.080	-.383	-.411	-.355
-4	Simple 5	30	0.636	.065	-.364	-.389	-.339
-4	M.L.E. 7	30	0.575	.077	-.425	-.452	-.398
-4	Simple 7	30	0.597	.069	-.403	-.429	-.377
-4	M.L.E. 9	30	0.541	.082	-.459	-.487	-.431
-4	Simple 9	30	0.555	.076	-.445	-.472	-.418
-4	M.L.E. 3	50	0.784	.042	-.216	-.236	-.196
-4	Simple 3	50	0.777	.044	-.223	-.244	-.202
-4	M.L.E. 5	50	0.695	.048	-.305	-.326	-.284
-4	Simple 5	50	0.692	.047	-.308	-.329	-.287
-4	M.L.E. 7	50	0.66	.055	-.340	-.363	-.317
-4	Simple 7	50	0.654	.054	-.346	-.369	-.323
-4	M.L.E. 9	50	0.619	.064	-.381	-.406	-.356
-4	Simple 9	50	0.626	.062	-.374	-.398	-.350

Table S5.C1
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 5

Case	Fourier Terms	T/P ratio	Estimator	N	Sample Mean	Sample Variance	Sample Bias	Lower 95% C.I	Upper 95% C.I
1	3	0.4	M.L.E. 3	30	.399	.051	-.001	-.023	.021
1	3	0.4	Simple 3	30	.415	.038	.015	-.004	.034
1	3	0.4	M.L.E. 5	30	.362	.041	-.038	-.058	-.018
1	3	0.4	Simple 5	30	.376	.036	-.024	-.043	-.005
1	3	0.4	M.L.E. 7	30	.352	.042	-.048	-.068	-.028
1	3	0.4	Simple 7	30	.355	.037	-.045	-.064	-.026
1	3	0.4	M.L.E. 9	30	.343	.044	-.057	-.078	-.036
1	3	0.4	Simple 9	30	.344	.041	-.056	-.076	-.036
1	3	0.4	M.L.E. 3	50	.395	.023	-.005	-.020	.010
1	3	0.4	Simple 3	50	.410	.023	.010	-.005	.025
1	3	0.4	M.L.E. 5	50	.370	.022	-.030	-.045	-.015
1	3	0.4	Simple 5	50	.374	.020	-.026	-.040	-.012
1	3	0.4	M.L.E. 7	50	.365	.025	-.035	-.050	-.020
1	3	0.4	Simple 7	50	.368	.023	-.032	-.047	-.017
1	3	0.4	M.L.E. 9	50	.361	.027	-.039	-.055	-.023
1	3	0.4	Simple 9	50	.362	.024	-.038	-.053	-.023
2	5	0.911	M.L.E. 3	30	0.803	.047	-.108	-.129	-.087
2	5	0.911	Simple 3	30	0.825	.032	-.086	-.104	-.068
2	5	0.911	M.L.E. 5	30	0.762	.051	-.149	-.171	-.127
2	5	0.911	Simple 5	30	0.789	.040	-.122	-.142	-.102
2	5	0.911	M.L.E. 7	30	0.696	.058	-.215	-.239	-.191
2	5	0.911	Simple 7	30	0.725	.047	-.186	-.207	-.165
2	5	0.911	M.L.E. 9	30	0.646	.067	-.265	-.290	-.240
2	5	0.911	Simple 9	30	0.68	.057	-.231	-.254	-.208
2	5	0.911	M.L.E. 3	50	0.871	.020	-.040	-.054	-.026
2	5	0.911	Simple 3	50	0.845	.023	-.066	-.081	-.051
2	5	0.911	M.L.E. 5	50	0.836	.022	-.075	-.090	-.060
2	5	0.911	Simple 5	50	0.827	.023	-.084	-.099	-.069
2	5	0.911	M.L.E. 7	50	0.779	.032	-.132	-.150	-.114
2	5	0.911	Simple 7	50	0.775	.031	-.136	-.153	-.119
2	5	0.911	M.L.E. 9	50	0.739	.039	-.172	-.191	-.153
2	5	0.911	Simple 9	50	0.739	.036	-.172	-.191	-.153
3	7	0.489	M.L.E. 3	30	.783	.037	.294	.275	.313
3	7	0.489	Simple 3	30	.824	.018	.335	.322	.348
3	7	0.489	M.L.E. 5	30	.649	.044	.160	.139	.181
3	7	0.489	Simple 5	30	.673	.034	.184	.166	.202
3	7	0.489	M.L.E. 7	30	.445	.045	-.044	-.065	-.023
3	7	0.489	Simple 7	30	.474	.039	-.015	-.034	.004
3	7	0.489	M.L.E. 9	30	.439	.044	-.050	-.071	-.029

Table S5.C1
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 5

Case	Fourier Terms	T/P ratio	Estimator	N	Sample Mean	Sample Variance	Sample Bias	Lower 95% C.I.	Upper 95% C.I.
3	7	0.489	Simple 9	30	.460	.037	-.029	-.048	-.010
3	7	0.489	M.L.E. 3	50	.811	.020	.322	.308	.336
3	7	0.489	Simple 3	50	.835	.013	.346	.335	.357
3	7	0.489	M.L.E. 5	50	.681	.031	.192	.175	.209
3	7	0.489	Simple 5	50	.679	.026	.190	.174	.206
3	7	0.489	M.L.E. 7	50	.457	.031	-.032	-.049	-.015
3	7	0.489	Simple 7	50	.457	.028	-.032	-.048	-.016
3	7	0.489	M.L.E. 9	50	.443	.033	-.046	-.064	-.028
3	7	0.489	Simple 9	50	.441	.030	-.048	-.065	-.031

Table S1.C2
BIAS DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 1

T/P ratio	Initial value	Peak Hour	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.75	-6	2	30	0.036	0.000	0.025	0.004	0.014	0.095	0.016	0.122
0.75	-6	2	50	0.009	0.064	-.003	0.359	-.007	0.169	0.004	0.356
0.75	-6	3	30	0.048	0.000	0.037	0.000	0.033	0.000	0.027	0.000
0.75	-6	3	50	0.016	0.007	0.003	0.586	0.001	0.872	0.006	0.307
0.75	-6	4	30	0.032	0.000	0.009	0.164	0.005	0.322	0.007	0.293
0.75	-6	4	50	0.016	0.002	0.004	0.471	0.004	0.230	0.004	0.295
0.75	-6	6	30	0.034	0.000	0.016	0.024	0.017	0.016	0.012	0.051
0.75	-6	6	50	0.011	0.033	-.004	0.500	-.004	0.383	-.003	0.573
0.75	-6	8	30	0.024	0.007	0.013	0.076	0.015	0.113	0.010	0.204
0.75	-6	8	50	0.012	0.046	0.008	0.174	0.009	0.210	0.005	0.533
0.50	-6	2	30	0.039	0.000	0.007	0.195	0.006	0.710	0.023	0.000
0.50	-6	2	50	0.041	0.000	0.000	0.739	-.001	0.835	0.010	0.007
0.50	-6	3	30	0.056	0.000	0.015	0.007	0.015	0.020	0.019	0.000
0.50	-6	3	50	0.053	0.000	-.000	0.907	0.005	0.123	0.010	0.035
0.50	-6	4	30	0.057	0.000	0.014	0.012	0.017	0.000	0.022	0.000
0.50	-6	4	50	0.054	0.000	0.011	0.005	0.011	0.007	0.010	0.003

Table S1.C2
BIAS DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 1

T/P ratio	Initial value	Peak Hour	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.50	-6	6	30	0.045	0.000	0.010	0.071	0.010	0.100	0.010	0.025
0.50	-6	6	50	0.044	0.000	-0.000	0.968	-0.000	0.914	0.004	0.162
0.50	-6	8	30	0.039	0.000	0.020	0.003	0.022	0.000	0.012	0.070
0.50	-6	8	50	0.045	0.000	0.011	0.000	0.008	0.026	0.014	0.000
0.25	-6	2	30	0.052	0.000	-0.012	0.003	-0.016	0.000	0.003	0.590
0.25	-6	2	50	0.059	0.000	-0.011	0.001	-0.013	0.000	0.004	0.181
0.25	-6	3	30	0.079	0.000	0.009	0.022	0.004	0.193	0.008	0.013
0.25	-6	3	50	0.076	0.000	0.012	0.000	0.005	0.070	0.011	0.000
0.25	-6	4	30	0.086	0.000	0.011	0.000	0.010	0.001	0.015	0.000
0.25	-6	4	50	0.085	0.000	0.012	0.000	0.013	0.000	0.014	0.000
0.25	-6	6	30	0.061	0.000	-0.000	0.913	-0.003	0.094	-0.004	0.030
0.25	-6	6	50	0.062	0.000	0.000	0.778	-0.003	0.016	-0.004	0.000
0.25	-6	8	30	0.054	0.000	0.002	0.457
0.25	-6	8	50	0.060	0.000	0.006	0.007
0.75	-3	2	30	0.034	0.006	0.027	0.017	0.012	0.248	0.013	0.119
0.75	-3	2	50	0.022	0.091	0.012	0.326	0.007	0.528	0.005	0.471

Table S1.C2
BIAS DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 1

T/P ratio	Initial value	Peak Hour	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.75	-3	3	30	0.022	0.213	0.019	0.308	0.013	0.409	0.019	0.129
0.75	-3	3	50	0.007	0.415	0.000	0.634	-0.014	0.053	-0.012	0.115
0.75	-3	4	30	0.036	0.006	0.031	0.006	0.030	0.014	0.015	0.119
0.75	-3	4	50	0.013	0.216	0.006	0.511	0.020	0.047	0.016	0.056
0.75	-3	6	30	0.014	0.296	0.003	0.827	-0.003	0.682	-0.012	0.308
0.75	-3	6	50	0.003	0.895	0.002	0.758	0.008	0.524	-0.005	0.698
0.75	-3	8	30	-0.001	0.732	0.010	0.380	-0.002	0.630	-0.003	0.612
0.75	-3	8	50	0.007	0.260	-0.003	0.905	-0.005	0.400	-0.003	0.531
0.50	-3	2	30	0.045	0.000	0.030	0.025	0.029	0.018	0.018	0.030
0.50	-3	2	50	0.050	0.000	0.003	0.920	-0.010	0.134	0.022	0.001
0.50	-3	3	30	0.046	0.000	0.024	0.010	0.017	0.103	0.011	0.121
0.50	-3	3	50	0.047	0.000	0.017	0.021	0.014	0.024	0.013	0.074
0.50	-3	4	30	0.043	0.001	0.016	0.157	0.008	0.264	0.006	0.115
0.50	-3	4	50	0.035	0.000	0.014	0.215	0.012	0.045	0.008	0.127
0.50	-3	6	30	0.024	0.030	-0.002	0.990	0.002	0.437	0.000	0.852
0.50	-3	6	50	0.037	0.000	-0.013	0.142	-0.002	0.969	0.003	0.805

Table S1.C2
BIAS DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 1

T/P ratio	Initial value	Peak Hour	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.50	-3	8	30	0.042	0.000	0.006	0.731	0.008	0.280	0.014	0.077
0.50	-3	8	50	0.040	0.000	0.008	0.321	0.010	0.183	0.003	0.719
0.25	-3	2	30	0.062	0.000	0.011	0.357	0.002	0.802	0.015	0.014
0.25	-3	2	50	0.053	0.000	-0.009	0.069	-0.015	0.004	0.005	0.225
0.25	-3	3	30	0.072	0.000	0.008	0.184	0.004	0.258	-0.001	0.876
0.25	-3	3	50	0.083	0.000	0.014	0.001	0.010	0.007	0.015	0.000
0.25	-3	4	30	0.089	0.000	0.010	0.095	0.013	0.029	0.018	0.000
0.25	-3	4	50	0.078	0.000	0.011	0.005	0.011	0.003	0.012	0.001
0.25	-3	6	30	0.070	0.000	-0.008	0.146	-0.011	0.059	-0.002	0.844
0.25	-3	6	50	0.067	0.000	-0.002	0.663	-0.006	0.060	-0.002	0.533
0.25	-3	8	30	0.054	0.000	0.011	0.013	0.015	0.002	-0.000	0.953
0.25	-3	8	50	0.064	0.000	0.003	0.371	0.001	0.776	0.009	0.006

Table: S1.C3
MEAN SQUARE ERROR DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 1

T/P ratio	Initial value	Peak Hour	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.75	-6	2	30	-.009	.0488	-.011	.0124	-.009	.0635	-.010	.0091
0.75	-6	2	50	0.000	.7997	-.003	.0467	0.001	.6111	-.002	.7128
0.75	-6	3	30	-.013	.0608	-.019	.0000	-.019	.0000	-.018	.0000
0.75	-6	3	50	-.002	.3742	-.001	.3490	-.001	.9589	-.004	.1440
0.75	-6	4	30	-.006	.2628	-.007	.0357	-.006	.0289	-.006	.2422
0.75	-6	4	50	0.001	.1585	-.001	.4951	-.002	.3750	-.004	.6065
0.75	-6	6	30	-.009	.0035	-.010	.0004	-.011	.0008	-.012	.0006
0.75	-6	6	50	0.000	.8435	0.001	.5083	0.000	.9192	-.001	.6511
0.75	-6	8	30	-.005	.2295	-.003	.5814	-.009	.0732	-.008	.3422
0.75	-6	8	50	-.002	.4645	-.002	.0183	-.002	.0793	-.002	.2476
0.50	-6	2	30	0.008	.0026	-.008	.0403	-.006	.0174	-.004	.0111
0.50	-6	2	50	0.015	.0000	-.002	.5707	-.001	.5358	-.002	.1928
0.50	-6	3	30	0.010	.0000	-.003	.3828	-.002	.2555	-.012	.0000
0.50	-6	3	50	0.016	.0000	-.002	.5077	-.001	.7410	-.002	.7620
0.50	-6	4	30	0.006	.0005	-.006	.0307	-.010	.0000	-.011	.0000
0.50	-6	4	50	0.014	.0000	-.003	.2908	-.003	.2191	-.002	.1270

Table: S1.C3
MEAN SQUARE ERROR DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 1

T/P ratio	Initial value	Peak Hour	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.50	-6	6	30	0.002	.2490	-.008	.0002	-.006	.0018	-.005	.0093
0.50	-6	6	50	0.006	.0001	0.000	.5267	0.000	.8739	-.003	.0008
0.50	-6	8	30	-.001	.3634	-.006	.0048	-.004	.2224	-.007	.0023
0.50	-6	8	50	0.004	.0088	-.002	.0109	-.002	.0007	-.003	.0094
0.25	-6	2	30	0.025	.0000	-.013	.0000	-.010	.0000	-.006	.0000
0.25	-6	2	50	0.034	.0000	-.008	.0000	-.006	.0000	-.002	.0066
0.25	-6	3	30	0.035	.0000	-.002	.9773	-.003	.0198	-.003	.0000
0.25	-6	3	50	0.037	.0000	0.001	.0027	-.001	.0061	-.001	.0005
0.25	-6	4	30	0.030	.0000	-.002	.2138	-.003	.0001	-.003	.0000
0.25	-6	4	50	0.034	.0000	0.001	.0373	-.001	.2164	-.001	.0001
0.25	-6	6	30	0.013	.0000	-.003	.0000	-.002	.0000	-.002	.0001
0.25	-6	6	50	0.016	.0000	-.000	.0838	-.000	.2400	-.000	.1739
0.25	-6	8	30	0.006	.0000	-.003	.0000
0.25	-6	8	50	0.009	.0000	-.000	.1348
0.75	-3	2	30	-.021	.0145	-.020	.0483	-.013	.2663	-.016	.0625
0.75	-3	2	50	-.010	.3642	-.008	.3180	-.006	.5911	-.003	.3889

Table: S1.C3
MEAN SQUARE ERROR DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 1

T/P ratio	Initial value	Peak Hour	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.75	-3	3	30	-.018	.1438	-.024	.0148	-.015	.3182	-.020	.0074
0.75	-3	3	50	-.005	.3152	-.009	.1636	0.003	.3768	0.005	.5205
0.75	-3	4	30	-.033	.0020	-.026	.0066	-.024	.0349	-.018	.0261
0.75	-3	4	50	-.007	.7297	-.008	.2016	-.012	.2063	-.012	.1259
0.75	-3	6	30	-.020	.0099	-.022	.0015	-.013	.1303	-.006	.3511
0.75	-3	6	50	-.002	.8727	-.001	.6624	-.004	.6654	-.000	.6060
0.75	-3	8	30	-.015	.0656	-.014	.3991	-.004	.6915	-.008	.5701
0.75	-3	8	50	-.006	.1549	-.005	.5058	-.002	.8345	-.002	.4557
0.50	-3	2	30	-.010	.1121	-.009	.1693	-.008	.0319	-.009	.0285
0.50	-3	2	50	0.010	.0132	-.006	.0063	-.003	.1613	-.008	.0116
0.50	-3	3	30	-.006	.1348	-.013	.0152	-.006	.1399	-.013	.0032
0.50	-3	3	50	0.006	.1895	-.007	.0313	-.006	.0318	-.002	.6946
0.50	-3	4	30	-.011	.0208	-.013	.0090	-.012	.0080	-.007	.0199
0.50	-3	4	50	0.005	.0896	-.008	.0054	-.004	.1644	-.003	.2047
0.50	-3	6	30	-.006	.4166	-.005	.1083	-.006	.1594	-.007	.0302
0.50	-3	6	50	0.002	.3749	-.001	.2843	-.002	.2776	-.003	.9690

Table: S1.C3
MEAN SQUARE ERROR DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 1

T/P ratio	Initial value	Peak Hour	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.50	-3	8	30	-.013	.0074	-.006	.2590	-.009	.0173	-.006	.3048
0.50	-3	8	50	-.002	.8604	-.003	.4795	-.001	.7759	0.001	.4557
0.25	-3	2	30	0.028	.0000	-.011	.0054	-.010	.0012	-.003	.0454
0.25	-3	2	50	0.029	.0000	-.010	.0003	-.008	.0000	-.001	.3853
0.25	-3	3	30	0.021	.0000	-.008	.0059	-.005	.0229	-.004	.0373
0.25	-3	3	50	0.037	.0000	-.000	.8464	0.000	.7070	-.001	.2733
0.25	-3	4	30	0.024	.0000	-.005	.0042	-.002	.1140	-.003	.0194
0.25	-3	4	50	0.030	.0000	0.001	.4453	0.000	.8363	-.000	.9877
0.25	-3	6	30	0.010	.0012	-.007	.0000	-.005	.0091	-.001	.2794
0.25	-3	6	50	0.016	.0000	-.001	.2349	0.000	.8291	-.002	.0276
0.25	-3	8	30	0.004	.0405	-.007	.0038	-.004	.0348	-.001	.4928
0.25	-3	8	50	0.010	.0000	-.000	.7496	0.000	.2931	-.001	.2229

Table S2.C2
BIAS DIFFERENCE
(SIMPLE - M.L.E.)

BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.

SIMULATION 2

T/P ratio	Initial value	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.75	-3	30	0.012	0.473	-0.002	0.823	-0.005	0.789	-0.010	0.517
0.75	-3	50	0.029	0.001	0.012	0.079	0.010	0.251	0.012	0.181
0.75	-6	30	0.022	0.000	0.015	0.002	0.014	0.013	0.012	0.025
0.75	-6	50	0.016	0.000	0.007	0.032	0.006	0.082	0.011	0.001
0.50	-3	30	0.050	0.000	0.035	0.000	0.024	0.005	0.019	0.018
0.50	-3	50	0.032	0.000	0.009	0.353	0.005	0.715	0.007	0.446
0.25	-3	30	0.062	0.000	0.022	0.000	0.008	0.154	0.011	0.016
0.25	-3	50	0.061	0.000	0.012	0.001	0.005	0.152	0.009	0.006
0.25	-6	30	0.062	0.000	0.012	0.000	0.003	0.437	0.010	0.002
0.25	-6	50	0.055	0.000	0.010	0.000	0.005	0.011	0.013	0.000

Table: S2.C3
MEAN SQUARE ERROR DIFFERENCE
(SIMPLE - M.L.E.)
BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.
SIMULATION 2

T/P ratio	Initial value	N	F3	prob.	prob.	prob.	F7	prob.	F9	prob. diff=0
				diff=0	F5	diff=0		diff=0		
0.75	-3	30	-.013	.0209	-.012	.1563	-.004	.4031	-.007	.6122
0.75	-3	50	-.012	.0092	-.012	.0018	-.013	.0112	-.013	.0256
0.75	-6	30	-.012	.0000	-.012	.0000	-.011	.0001	-.012	.0001
0.75	-6	50	-.001	.5256	-.003	.0078	-.002	.1104	-.005	.0002
0.50	-3	30	-.001	.9059	-.008	.0135	-.006	.0419	-.009	.0053
0.50	-3	50	0.003	.2573	-.003	.3668	-.006	.3212	-.002	.5322
0.25	-3	30	0.016	.0000	-.001	.8333	-.003	.0546	-.003	.0768
0.25	-3	50	0.020	.0000	-.001	.6490	-.001	.3379	-.001	.0700
0.25	-6	30	0.018	.0000	-.000	.6956	-.003	.0007	-.002	.0000
0.25	-6	50	0.018	.0000	0.001	.0024	-.000	.4355	-.001	.0411

Tables: S3.C2
BIAS DIFFERENCE
(SIMPLE - M.L.E.)

BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.

SIMULATION 3

T/P ratio	Initial value	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.75	-3	30	0.060	0.000	0.021	0.063	0.019	0.022	0.011	0.283
0.75	-3	50	0.009	0.193	-0.001	0.919	-0.005	0.638	0.009	0.248
0.50	-3	30	0.060	0.000	0.013	0.314	-0.002	0.944	-0.002	0.509
0.50	-3	50	0.047	0.000	-0.006	0.417	-0.005	0.595	-0.002	0.970
0.25	-3	30	0.079	0.000	0.003	0.744	-0.000	0.854	-0.010	0.022
0.25	-3	50	0.080	0.000	-0.003	0.229	-0.010	0.011	-0.012	0.002

Table: S3.C3
MEAN SQUARE ERROR DIFFERENCE

BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.

SIMULATION 3

T/P ratio	Initial value	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
0.75	-3	30	-0.033	.0001	-.024	.0011	-.024	.0007	-.013	.1295
0.75	-3	50	-.001	.4551	-.001	.5228	0.002	.9734	-.006	.2411
0.50	-3	30	0.002	.1579	-.010	.0068	-.007	.0674	-.005	.1223
0.50	-3	50	0.011	.0002	-.002	.9749	0.003	.6777	-.000	.9026
0.25	-3	30	0.043	.0000	-.008	.0274	-.004	.3160	-.002	.2891
0.25	-3	50	0.048	.0000	-.005	.0165	-.004	.0036	-.001	.2044

Tables: S4.C2
BIAS DIFFERENCE
(SIMPLE - M.L.E.)

BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.

SIMULATION 4

T/P ratio	Initial value	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
1.00	-4	30	0.018	0.181	0.019	0.158	0.022	0.036	0.014	0.061
1.00	-4	50	-0.007	0.364	-0.003	0.516	-0.005	0.446	0.007	0.216
1.00	-12	30	0.022	0.000	0.027	0.000	0.025	0.000	0.022	0.000
1.00	-12	50	-0.001	0.653	-0.000	0.893	-0.001	0.584	-0.000	0.458

Table: S4.C3
MEAN SQUARE ERROR DIFFERENCE

BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.

SIMULATION 4

T/P ratio	Initial value	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
1.00	-4	30	-0.014	.4051	-0.028	.1595	-0.026	.0426	-0.018	.0578
1.00	-4	50	0.005	.5582	0.001	.6051	0.003	.7844	-0.007	.0594
1.00	-12	30	-0.008	.0001	-0.012	.0000	-0.015	.0000	-0.014	.0000
1.00	-12	50	-0.001	.7709	-0.000	.9892	0.000	.4371	-0.001	.4405

Table: S5.C2
BIAS DIFFERENCE
(SIMPLE - M.L.E.)

BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.

SIMULATION 5

Curve	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
1	30	0.017	0.119	0.014	0.113	0.003	0.715	0.001	0.672
1	50	0.016	0.005	0.004	0.255	0.003	0.579	0.001	0.802
2	30	0.027	0.003	0.003	0.679	-0.000	0.960	0.010	0.031
2	50	0.014	0.005	-0.001	0.983	0.002	0.662	0.001	0.874
3	30	0.042	0.000	0.024	0.003	0.029	0.000	0.021	0.002
3	50	0.023	0.000	-0.002	0.794	0.000	0.751	-0.001	0.985
4	30	0.021	0.190	0.028	0.010	0.029	0.006	0.034	0.000
4	50	-0.026	0.000	-0.009	0.103	-0.004	0.623	-0.000	0.764

Table: S5.C3
MEAN SQUARE ERROR DIFFERENCE

BETWEEN SIMPLE FOURIER ESTIMATES AND M.L.E.

SIMULATION 5

Curve	N	F3	prob. diff=0	F5	prob. diff=0	F7	prob. diff=0	F9	prob. diff=0
1	30	-.013	.0004	-.006	.0608	-.005	.1066	-.003	.2480
1	50	-.000	.7361	-.003	.0494	-.003	.2827	-.003	.0268
2	30	-.006	.0091	-.004	.1613	-.002	.1934	-.004	.0412
2	50	0.000	.8544	-.003	.8400	-.003	.6515	-.003	.3498
3	30	0.007	.0200	-.002	.9852	-.007	.0230	-.009	.0092
3	50	0.008	.0087	-.006	.1253	-.004	.0136	-.003	.2617
4	30	-.019	.0290	-.019	.0033	-.023	.0032	-.027	.0001
4	50	0.006	.0191	0.003	.0557	0.001	.3536	-.003	.8800

Table S1.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 1

Initial value	T/P ratio	Peak Hour	Fourier Terms	N	Bias	Variance	M.S.E.
-6	0.75	2	3	30	M*	S	S
-6	0.75	2	3	50	S	S	EQ
-3	0.75	2	3	30	S*	S	S
-3	0.75	2	3	50	M	S	S
-6	0.75	3	3	30	S*	S	S
-6	0.75	3	3	50	M*	S	S
-3	0.75	3	3	30	S	S	S
-3	0.75	3	3	50	S	S	S
-6	0.75	4	3	30	S*	S	S
-6	0.75	4	3	50	M*	S	M
-3	0.75	4	3	30	M*	S	S*
-3	0.75	4	3	50	S	S	S
-6	0.75	6	3	30	S*	S	S*
-6	0.75	6	3	50	M	EQ	EQ
-3	0.75	6	3	30	S	S	S*
-3	0.75	6	3	50	S	S	S
-6	0.75	8	3	30	S*	S	S
-6	0.75	8	3	50	S	S	S
-3	0.75	8	3	30	M	S	S
-3	0.75	8	3	50	S	S	S
-6	0.5	2	3	30	M*	S	M*
-6	0.5	2	3	50	M*	S	M*
-3	0.5	2	3	30	M*	S	S
-3	0.5	2	3	50	M*	S	M
-6	0.5	3	3	30	M*	S	M*
-6	0.5	3	3	50	M*	S	M*
-3	0.5	3	3	30	M*	S	S
-3	0.5	3	3	50	M*	S	M
-6	0.5	4	3	30	M*	S	M*
-6	0.5	4	3	50	M*	S	M*
-3	0.5	4	3	30	M*	S	S
-3	0.5	4	3	50	M*	S	M
-6	0.5	6	3	30	M*	S	M
-6	0.5	6	3	50	M*	S	M*
-3	0.5	6	3	30	S	S	S
-3	0.5	6	3	50	M*	S	M
-6	0.5	8	3	30	M*	S	S
-6	0.5	8	3	50	M*	S	M*
-3	0.5	8	3	30	M*	S	S*

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S1.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 1

Initial value	T/P ratio	Peak Hour	Fourier Terms	N	Bias	Variance	M.S.E.
-3	0.5	8	3	50	M*	S	S
-6	0.25	2	3	30	M*	S	M*
-6	0.25	2	3	50	M*	S	M*
-3	0.25	2	3	30	M*	S	M*
-3	0.25	2	3	50	M*	S	M*
-6	0.25	3	3	30	M*	S	M*
-6	0.25	3	3	50	M*	S	M*
-3	0.25	3	3	30	M*	S	M*
-3	0.25	3	3	50	M*	S	M*
-6	0.25	4	3	30	M*	S	M*
-6	0.25	4	3	50	M*	S	M*
-3	0.25	4	3	30	M*	S	M*
-3	0.25	4	3	50	M*	S	M*
-6	0.25	6	3	30	M*	S	M*
-6	0.25	6	3	50	M*	S	M*
-3	0.25	6	3	30	M*	S	M*
-3	0.25	6	3	50	M*	S	M*
-6	0.25	8	3	30	M*	S	M*
-6	0.25	8	3	50	M*	S	M*
-3	0.25	8	3	30	M*	S	M
-3	0.25	8	3	50	M*	S	M*
-6	0.75	2	5	30	S*	S	S
-6	0.75	2	5	50	S	S	S
-3	0.75	2	5	30	S	S	S
-3	0.75	2	5	50	S	S	S
-6	0.75	3	5	30	S*	S	S*
-6	0.75	3	5	50	S	S	S
-3	0.75	3	5	30	S	S	S
-3	0.75	3	5	50	EQ	S	S
-6	0.75	4	5	30	S	S	S
-6	0.75	4	5	50	S	S	S
-3	0.75	4	5	30	S*	S	S*
-3	0.75	4	5	50	S	S	S
-6	0.75	6	5	30	S	S	S*
-6	0.75	6	5	50	M	EQ	M
-3	0.75	6	5	30	S	S	S*
-3	0.75	6	5	50	S	EQ	S
-6	0.75	8	5	30	S	EQ	S
-6	0.75	8	5	50	S	S	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S1.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 1

Initial value	T/P ratio	Peak Hour	Fourier Terms	N	Bias	Variance	M.S.E.
-3	0.75	8	5	30	S	S	S
-3	0.75	8	5	50	M	S	S
-6	0.5	2	5	30	M	S	S
-6	0.5	2	5	50	M	S	S
-3	0.5	2	5	30	M	S	S
-3	0.5	2	5	50	M	S	S*
-6	0.5	3	5	30	M*	S	S
-6	0.5	3	5	50	EQ	S	S
-3	0.5	3	5	30	S*	S	S
-3	0.5	3	5	50	M	S	S
-6	0.5	4	5	30	M	S	S
-6	0.5	4	5	50	M*	S	S
-3	0.5	4	5	30	S	S	S*
-3	0.5	4	5	50	S	S	S*
-6	0.5	6	5	30	S	S	S*
-6	0.5	6	5	50	EQ	EQ	EQ
-3	0.5	6	5	30	M	S	S
-3	0.5	6	5	50	M	S	S
-6	0.5	8	5	30	S*	S	S*
-6	0.5	8	5	50	M*	S	S
-3	0.5	8	5	30	S	S	S
-3	0.5	8	5	50	S	S	S
-6	0.25	2	5	30	S*	S	S*
-6	0.25	2	5	50	S*	S	S*
-3	0.25	2	5	30	M	S	S*
-3	0.25	2	5	50	S	S	S*
-6	0.25	3	5	30	M	S	S
-6	0.25	3	5	50	M*	S	M*
-3	0.25	3	5	30	M	S	S*
-3	0.25	3	5	50	M*	S	S
-6	0.25	4	5	30	M*	S	S
-6	0.25	4	5	50	M*	S	M
-3	0.25	4	5	30	M	S	S*
-3	0.25	4	5	50	M*	S	M
-6	0.25	6	5	30	EQ	S	S*
-6	0.25	6	5	50	EQ	EQ	S
-3	0.25	6	5	30	S	S	S*
-3	0.25	6	5	50	S	S	S
-6	0.25	8	5	30		S	

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S1.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 1

Initial value	T/P ratio	Peak Hour	Fourier Terms	N	Bias	Variance	M.S.E.
-6	0.25	8	5	50		S	
-3	0.25	8	5	30	M	S	S*
-3	0.25	8	5	50	M	EQ	S
-6	0.75	2	7	30	S	S	S
-6	0.75	2	7	50	M	EQ	M
-3	0.75	2	7	30	S	S	S
-3	0.75	2	7	50	S	S	S
-6	0.75	3	7	30	S*	S	S*
-6	0.75	3	7	50	EQ	S	S
-3	0.75	3	7	30	S	S	S
-3	0.75	3	7	50	M	S	M
-6	0.75	4	7	30	S	S	S
-6	0.75	4	7	50	S	S	S
-3	0.75	4	7	30	S	S	S
-3	0.75	4	7	50	S	S	S
-6	0.75	6	7	30	S	S	S*
-6	0.75	6	7	50	M	S	EQ
-3	0.75	6	7	30	S	S	S
-3	0.75	6	7	50	S	EQ	S
-6	0.75	8	7	30	S	S	S
-6	0.75	8	7	50	S	S	S
-3	0.75	8	7	30	M	S	S
-3	0.75	8	7	50	M	S	S
-6	0.5	2	7	30	M	S	S
-6	0.5	2	7	50	S	S	S
-3	0.5	2	7	30	S	S	S
-3	0.5	2	7	50	M	S	S
-6	0.5	3	7	30	S	S	S
-6	0.5	3	7	50	S	S	S
-3	0.5	3	7	30	S	S	S
-3	0.5	3	7	50	S	S	S
-6	0.5	4	7	30	S*	S	S*
-6	0.5	4	7	50	S*	S	S
-3	0.5	4	7	30	S	S	S*
-3	0.5	4	7	50	S	S	S
-6	0.5	6	7	30	S	S	S*
-6	0.5	6	7	50	M	EQ	EQ
-3	0.5	6	7	30	S	S	S
-3	0.5	6	7	50	M	EQ	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S1.C4
COMPARISON OF FOURIER ESTIMATORS

SIMULATION 1							
Initial value	T/P ratio	Peak Hour	Fourier Terms	N	Bias	Variance	M.S.E.
-6	0.5	8	7	30	S*	S	S
-6	0.5	8	7	50	S	S	S*
-3	0.5	8	7	30	S	S	S
-3	0.5	8	7	50	S	S	S
-6	0.25	2	7	30	S*	S	S*
-6	0.25	2	7	50	S*	S	S*
-3	0.25	2	7	30	M	S	S*
-3	0.25	2	7	50	S*	S	S*
-6	0.25	3	7	30	M	S	S
-6	0.25	3	7	50	M	S	S*
-3	0.25	3	7	30	M	S	S
-3	0.25	3	7	50	M*	EQ	EQ
-6	0.25	4	7	30	S*	S	S*
-6	0.25	4	7	50	S*	EQ	S
-3	0.25	4	7	30	S	S	S
-3	0.25	4	7	50	S*	EQ	EQ
-6	0.25	6	7	30	M	S	S*
-6	0.25	6	7	50	S	S	EQ
-3	0.25	6	7	30	M	S	S*
-3	0.25	6	7	50	M	EQ	EQ
-6	0.25	8	7	30			
-6	0.25	8	7	50			
-3	0.25	8	7	30	M*	S	S
-3	0.25	8	7	50	M	EQ	EQ
-6	0.75	2	9	30	S	S	S*
-6	0.75	2	9	50	S	S	S
-3	0.75	2	9	30	S	S	S
-3	0.75	2	9	50	S	EQ	S
-6	0.75	3	9	30	S*	S	S*
-6	0.75	3	9	50	S	S	S
-3	0.75	3	9	30	S	S	S*
-3	0.75	3	9	50	M	EQ	M
-6	0.75	4	9	30	S	S	S
-6	0.75	4	9	50	S	S	S
-3	0.75	4	9	30	S	S	S
-3	0.75	4	9	50	S	S	S
-6	0.75	6	9	30	S	S	S*
-6	0.75	6	9	50	M	S	S
-3	0.75	6	9	30	M	S	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S1.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 1

Initial value	T/P ratio	Peak Hour	Fourier Terms	N	Bias	Variance	M.S.E.
-3	0.75	6	9	50	M	S	EQ
-6	0.75	8	9	30	S	S	S
-6	0.75	8	9	50	S	S	S
-3	0.75	8	9	30	M	S	S
-3	0.75	8	9	50	M	S	S
-6	0.5	2	9	30	S*	S	S
-6	0.5	2	9	50	S*	S	S
-3	0.5	2	9	30	S	S	S
-3	0.5	2	9	50	S*	S	S
-6	0.5	3	9	30	S*	S	S*
-6	0.5	3	9	50	S	S	S
-3	0.5	3	9	30	S	S	S*
-3	0.5	3	9	50	S	M	S
-6	0.5	4	9	30	S*	S	S*
-6	0.5	4	9	50	S*	S	S
-3	0.5	4	9	30	S	S	S
-3	0.5	4	9	50	S	S	S
-6	0.5	6	9	30	S	S	S*
-6	0.5	6	9	50	S	S	S*
-3	0.5	6	9	30	EQ	S	S
-3	0.5	6	9	50	S	S	S
-6	0.5	8	9	30	S	S	S*
-6	0.5	8	9	50	S*	S	S*
-3	0.5	8	9	30	S	S	S
-3	0.5	8	9	50	S	M	M
-6	0.25	2	9	30	M	S	S*
-6	0.25	2	9	50	M	S	S*
-3	0.25	2	9	30	M	S	S
-3	0.25	2	9	50	M	S	S
-6	0.25	3	9	30	S	S	S*
-6	0.25	3	9	50	S*	S	S*
-3	0.25	3	9	30	M	S	S
-3	0.25	3	9	50	S*	EQS	S
-6	0.25	4	9	30	S*	S	S*
-6	0.25	4	9	50	S*	S	S*
-3	0.25	4	9	30	S*	M	S
-3	0.25	4	9	50	S*	S	EQ
-6	0.25	6	9	30	S	EQ	S*
-6	0.25	6	9	50	S*	S	EQ

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S1.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 1

Initial value	T/P ratio	Peak Hour	Fourier Terms	N	Bias	Variance	M.S.E.
-3	0.25	6	9	30	M	S	S
-3	0.25	6	9	50	M	S	S
-6	0.25	8	9	30	S	S	S*
-6	0.25	8	9	50	M*	S	EQ
-3	0.25	8	9	30	EQ	S	S
-3	0.25	8	9	50	M*	S	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S2.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 2

Initial value	T/P ratio	Fourier Terms	N	Bias	Variance	M.S.E.
-3	0.75	3	30	S	S	S
-3	0.75	3	50	S*	S	S*
-6	0.75	3	30	S*	S	S*
-6	0.75	3	50	M*	S	S
-3	0.5	3	30	M*	S	S
-3	0.5	3	50	M*	S	M
-3	0.25	3	30	M*	S	M*
-3	0.25	3	50	M*	S	M*
-6	0.25	3	30	M*	S	M*
-6	0.25	3	50	M*	S	M*
-3	0.75	5	30	M	S	S
-3	0.75	5	50	S	S	S
-6	0.75	5	30	S*	S	S*
-6	0.75	5	50	S	S	S*
-3	0.5	5	30	S*	S	S
-3	0.5	5	50	M	S	S
-3	0.25	5	30	M*	S	S
-3	0.25	5	50	M*	S	S
-6	0.25	5	30	M*	S	S
-6	0.25	5	50	M*	S	S
-3	0.75	7	30	M	S	S
-3	0.75	7	50	S	S	S
-6	0.75	7	30	S	S	S*
-6	0.75	7	50	S	S	S
-3	0.5	7	30	S*	S	S
-3	0.5	7	50	S	S	S
-3	0.25	7	30	M	S	S
-3	0.25	7	50	M	S	S
-6	0.25	7	30	M	S	S*
-6	0.25	7	50	M	S	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S2.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 2

Initial value	T/P ratio	Fourier Terms	N	Bias	Variance	M.S.E.
-3	0.75	9	30	M	S	S
-3	0.75	9	50	S	S	S
-6	0.75	9	30	S	S	S*
-6	0.75	9	50	S*	S	S*
-3	0.5	9	30	S	S	S*
-3	0.5	9	50	S	EQ	S
-3	0.25	9	30	S	S	S
-3	0.25	9	50	S*	S	S
-6	0.25	9	30	S*	S	S*
-6	0.25	9	50	S*	S	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S3.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 3

T/P ratio	Initial value	Fourier Terms	N	Bias	Variance	M.S.E.
-3	0.75	3	30	S*	S	S*
-3	0.75	3	50	S	S	S
-3	0.5	3	30	M*	S	M
-3	0.5	3	50	M*	S	M*
-3	0.25	3	30	M*	S	M*
-3	0.25	3	50	M*	S	M*
-3	0.75	5	30	S	S	S*
-3	0.75	5	50	M	S	S
-3	0.5	5	30	M	S	S*
-3	0.5	5	50	S	S	S
-3	0.25	5	30	M	S	S
-3	0.25	5	50	S	S	S
-3	0.75	7	30	S	S	S*
-3	0.75	7	50	M	S	M
-3	0.5	7	30	M	S	S
-3	0.5	7	50	M	S	M
-3	0.25	7	30	EQ	S	S
-3	0.25	7	50	S	S	S*
-3	0.75	9	30	S	S	S
-3	0.75	9	50	S	S	S
-3	0.5	9	30	M	S	S
-3	0.5	9	50	M	S	S
-3	0.25	9	30	M*	S	S
-3	0.25	9	50	M*	S	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S4.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 4

Initial value	Fourier Terms	N	Bias	Variance	M.S.E.
-4	3	30	S	S	S
-4	3	50	M	M	M
-12	3	30	S*	S	S*
-12	3	50	M	S	S
-4	5	30	S	S	S
-4	5	50	M	S	M
-12	5	30	S*	S	S*
-12	5	50	EQ	EQ	S
-4	7	30	S	S	S
-4	7	50	M	S	M
-12	7	30	S*	S	S*
-12	7	50	M	EQ	EQ
-4	9	30	S	S	S
-4	9	50	S	S	S
-12	9	30	S*	S	S*
-12	9	50	EQ	S	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Table S5.C4
COMPARISON OF FOURIER ESTIMATORS
SIMULATION 5

Curve	T/P ratio	Fourier Terms	N	Bias	Variance	M.S.E.
1	0.4	3	30	M	S	S*
1	0.4	3	50	M*	EQ	EQ
2	0.385	3	30	M*	S	S*
2	0.385	3	50	M*	EQ	M
3	0.489	3	30	M*	S	M
3	0.489	3	50	M*	S	M*
4	0.911	3	30	S	S	S
4	0.911	3	50	M*	M	M
1	0.4	5	30	S	S	S
1	0.4	5	50	S	S	S
2	0.385	5	30	S	S	S
2	0.385	5	50	M	S	S
3	0.489	5	30	M	S	S
3	0.489	5	50	S	S	S
4	0.911	5	30	S*	S	S*
4	0.911	5	50	M	M	M
1	0.4	7	30	S	S	S
1	0.4	7	50	S	S	S
2	0.385	7	30	EQ	S	S
2	0.385	7	50	S	S	S
3	0.489	7	30	S*	S	S
3	0.489	7	50	EQ	S	S
4	0.911	7	30	S*	S	S*
4	0.911	7	50	M	S	M
1	0.4	9	30	S	S	S
1	0.4	9	50	S	S	S
2	0.385	9	30	S	S	S
2	0.385	9	50	EQ	S	S
3	0.489	9	30	S*	S	S*
3	0.489	9	50	M	S	S
4	0.911	9	30	S*	S	S*
4	0.911	9	50	EQ	S	S

S - Simple Less M - M.L.E. Less EQ - Equal * Significant difference at 0.01 p - value

Simulation Results Hourly Mean versus Simple Fourier T/P Estimators

Next the hourly mean T/P estimators are compared to the Simple Fourier T/P estimators. The results described here comparing the hourly mean T/P estimate to the Simple Fourier T/P estimators will focus primarily on the situations where $N=30$ since these results generalize typically to the other sample sizes studied.

The mean bias of the 400 replicates are plotted for the placebo subtracted drug response curves in simulation 1 for sample size 30 with initial values $=-3, -6$ and T/P ratios $= .75, .5$ and $.25$ in figures S1.F1 through S1.F6 and tabulated in table S1.T1 and S1.T2 . The ratio of the MSE for the hourly mean T/P estimator divided by the MSE of one (3,5,7 or 9 term) of the Simple Fourier T/P estimators (hereafter referred to as Fourier T/P estimators) are plotted in figures S1.F7 through S1.F12 and tabulated in tables S1.T3 and S1.T4. This mean square error ratio (MSER) will be greater than 1 if the MSE for the hourly mean T/P estimator is greater than the MSE for the Fourier T/P estimators. We therefore are interested in T/P estimators with large MSERs. In figures S1.F1 through S1.F6 the average bias and the MSER with their associated asymptotic 95 % confidence intervals are plotted versus the response curve peak hour for each of the estimators.

Clearly the bias of both types of estimators changes, depending on the actual T/P ratio, the initial value and the peak hour. The general shape of the relationship between peak hour and bias appears the same for all of the estimators for both initial values of -3 and -6 , but the bias for the -3 initial value are consistently shifted to a lower value when compared to those for the -6 initial value.. This is probably due to that fact that the final trough to peak estimator is set to 0 if the numerator and denominator of the trough to peak statistic have different signs,

which is more likely to occur when the actual initial (and trough) value is -3. For T/P ratio 0.75 (figures S1.F1 & S1.F2) the 3 term Fourier T/P estimator is least biased, with the bias increasing for the Fourier T/P estimators as the number of terms in the Fourier series increases, with the hourly mean T/P estimator demonstrating the greatest bias (values of 0.030, -0.062, -0.134, -0.171 and -0.262, N=30 initial value =-6, peak hour = 2 for 3,5,7,9 term Fourier and hourly mean). For T/P ratio 0.50 (figures S1.F3 & S1.F4) , depending on the initial value (-3 or -6) and the peak hour, either the 3, 5 or 7 term Fourier T/P estimators have the least bias and the hourly mean T/P estimator is either the most biased or next to the most biased estimator (value of 0.161, 0.031, -0.040, -0.062 and -0.100, N=30 initial value =-6, peak hour = 4 for 3,5,7,9 term Fourier and hourly mean). For T/P ratio 0.25 the hourly mean T/P estimator and the 7 or 9 term Fourier estimators demonstrate least bias and are nearly equal for most peak hours (values of 0.104, 0.023, -0.004, -0.005 and -0.023, N=30 initial value =-6, peak hour = 8 for 3,5,7,9 term Fourier and hourly mean). In table S1.T2 the differences between the T/P ratio based on the Fourier series estimator and the T/P ratio based on the hourly means are tabulated along with the Wilcoxon signed rank p - values associated with the paired differences for the 400 replications of the simulation. All differences in bias are significant at the .01 p-value except between the for the 7 term Fourier T/P and hourly mean T/P estimators for actual T/P ratio 0.25, initial value -3, peak hour = 4, and the difference between the 9 term Fourier T/P and hourly mean T/P estimators for actual T/P=0.25, initial value =-3, peak hour = 3, N = 30.

The MSERs for the 3,5,7 or 9 term Fourier T/P estimator for sample size 30 are plotted in figures S1.F7 through S1.F12 and tabulated in table S1.T4 and the paired difference between the mean square errors and associated p-values are

tabulated in tables S1.T3. For T/P ratio = 0.75 the MSERs for all of the Fourier T/P estimators (3,5,7, and 9 term) are significantly greater than 1, with the Fourier T/P estimators with fewer terms demonstrating the largest MSER (values of 3.85, 2.78, 1.88, and 1.57, N=30, initial value = -6, peak hour = 4 for 3,5,7,9 term Fourier). For T/P ratio 0.50, the 3 term Fourier T/P estimator demonstrates a MSE similar to that for the hourly mean for peak hours 2, 3 and 4, with the Fourier T/P estimators with more terms giving MSERs significantly greater than 1 (values of 0.99, 2.14, 1.82, and 1.61, N=30, initial value = -6, peak hour = 4 for 3,5,7,9 term Fourier). With T/P ratio = 0.25, the MSER for the 3 term Fourier T/P estimator is significantly less than 1 for all peak hours; for the 5 term Fourier series MSER is less than 1 for peak hours 2, 3 and statistically equivalent to 1 for peak hour 4; the 7 term Fourier T/P estimator MSER is less than 1 for peak hour 2 only (greater than 1 for other peak hours), with the 9 term Fourier T/P estimators giving a ratio greater than or equal to 1 for all peak hour values (values of 0.11, 0.26, 0.66, and 1.27, N=30, initial value = -6, peak hour = 2 for 3,5,7,9 term Fourier). In figures S1.F13 through S1.F18 a direct comparison between the T/P estimators based on the various Fourier series fits are presented. The minimum of the MSERs across the peak hours simulated in curve set 1 are plotted in figures S1.F13 and S1.F14, the maximum of the MSERs across the peak hours are plotted in figures S1.F15 and S1.F16, and the average of the MSERs across the peak hours are plotted in figures S1.F17 and S1.F18. These figures further demonstrate that the 3 and 5 term Fourier T/P estimators can perform poorly relative to the hourly mean T/P estimator for low actual T/P ratios (0.25 in the simulation), and very well for high T/P ratios. The 7 and 9 term Fourier T/P estimators generally perform well throughout the spectrum of T/P ratios examined in this simulation. Looking at the overall average of the MSERs over the peak hours, the 7 and 9 term Fourier T/P estimators have an average MSER greater than 1 for all of the T/P ratios tested, the

5 term Fourier T/P estimate with a ratio greater than or equal to 1, with a 95% confidence interval around 1 for T/P of 0.25. Generally speaking, the 5, 7 and 9 term Fourier T/P estimate perform better in this simulation for curve set 1 than the hourly mean T/P estimate as measured by the mean square error criteria.

The curve shape in simulation 2 gradually increases in dose response until hour 8 then a gradual decrease to the initial value at hour 24. Other than sample size, there are two variables in this simulation, the initial value (-3 and -6) and the actual trough to peak ratio (0.25,0.50,0.75). The mean bias of the 400 replicates are plotted against the actual T/P ratio for sample size 30 in figures S2.F1 (initial value -3) and S2.F2 (initial value -6) and the average bias and average bias differences from the hourly mean T/P ratio are tabulated in table S1.T1 and S1.T2 respectively. The MSERs for Fourier T/P estimators (3,5,7 or 9 term) are plotted in figures S2.F3 and S2.F4 and the difference in MSE between hourly mean T/P estimator and the Fourier T/P estimators are tabulated in tables S2.T3 and the MSERs tabulated in S2.T4. The results for this curve set is similar to those for curve set 1. Comparing the bias for each of the estimators between the curves with initial value -3 versus -6, the bias is nearly identical for T/P ratio 0.25, and shifted to a greater negative bias for initial value -3 for T/P ratio 0.75 as was noted in the simulation involving curve set 1. No comparison can be made for T/P ratio 0.50, since the simulation was not attempted for T/P ratio 0.50 and initial value -6.

As in the simulations for curve set 1, with the small T/P ratio of 0.25 the 7 and 9 term Fourier T/P estimate have the least bias (average of 0.016,-0.025 for initial value -3, N=30 and 0.037, -0.006 for initial value -6,N=30) followed by the hourly mean T/P estimator (average of -0.043 for initial value -3,N=30 and -0.027 for initial value -6,N=30). For T/P ratio 0.50, initial value -3, the 5 term Fourier T/P

estimator has least bias(average of -0.020 for $N=30$), followed by the 7 term and 3 term Fourier T/P estimators (average of -0.081 and 0.090 for $N=30$), and for T/P ratio 0.75 the 3 term Fourier T/P estimator has the least bias (average of -0.125, -0.018 for initial values -3, -6, $N=30$), followed by the 5 term (average of -0.221, -0.090 for initial values -3, -6, $N=30$), 7 term (average of -0.273,-0.148 for initial values -3, -6, $N=30$), 9 term (average of -0.309,-0.198 for initial values -3, -6, $N=30$) and the hourly mean T/P ratio estimate (average of -0.375,-0.278 for initial values -3, -6, $N=30$).

The behavior of the MSERs are also similar to that found in simulation 1. For T/P ratio of 0.25, the MSER is less than 1 for the 3 term Fourier T/P estimator for both initial values -3 and -6 and the MSER is also less than 1 for the 5 term series T/P estimator for initial value -6, but not significantly different from 1 for initial value -3 based on the asymptotic confidence interval and the Wilcoxon paired comparison (tabled in S2.T3 and S2.T4). On the other hand for T/P ratio of 0.25 the MSER is significantly larger than 1 for the 7 and 9 term Fourier series T/P estimators (1.42, 1.36 for initial value -3, $N=30$ and 1.41, 1.47 for initial value -6, $N=30$). For T/P value of 0.50, initial value -3, all of the Fourier series T/P estimators tested have a MSER greater than 1, but the 95% confidence interval for the MSER based on the 3 term Fourier series includes 1 and the Wilcoxon test on the paired squared error differences is not statistically significant with a p-value of 0.226. All of the other Fourier series T/P estimators (5,7 and 9 term) have MSERs larger than 1, with the 5 term the largest, followed by the 7 then 9 term series (1.46, 1.33 and 1.22 for initial value -3, $N=30$). For T/P ratio of 0.75 all of the Fourier series T/P estimators have a MSER larger than 1. The ratio is largest for the 3 term followed by the 5, then 7 and 9 term series

(2.33, 1.82, 1.48, 1.32 for initial value -3, N=30 and 4.10, 3.29, 2.23, 1.63 for initial value -6, N=30). The consistent results of the MSER greater than 1 for the 7 and 9 term Fourier series T/P estimator suggest that both of these estimators are consistently superior in behavior for this curve type, T/P ratios and sample size. The 5 term Fourier series T/P estimator is superior for large T/P ratios (≥ 0.5), but performance in terms of mean square error is only equal or slightly larger than for the hourly mean T/P estimator . Similar results were found for sample sizes 10,20 and 50.

The curves in simulation 3 are bath tub shaped, starting at an initial value of -3, decreasing to a the peak dose response at 3 hours, maintaining a constant level until 22 hours, the declining to the trough level at hour 24. The only difference between the three curves is the peak value (and T/P ratio) of -4, -6 and -12 to give T/P ratios of 0.75, 0.50 and 0.25. The mean bias of the 400 replicates are plotted against actual T/P ratio on figure S3.F1 and the MSER in figure S3.F2 and tabled S3.T1 through S3.T4. The results are similar to those found for curve set 1 and 2. The bias associated with each estimator changes (almost linear) as the actual T/P ratio changes. For T/P ratio 0.25 the 9 term Fourier series T/P estimator has the least bias followed by the estimator based on the 7 term series then the T/P estimator based on the hourly mean, the T/P estimator based on the 5 term then 3 term Fourier series (values of -.023, .058, -.055, .179 and .380 , N=30). For T/P ratio 0.50 the 5 terms Fourier T/P estimator has least bias followed by the 7 term Fourier T/P estimator , then the 9 term Fourier T/P estimator, then the 3 term Fourier T/P estimator hourly mean T/P estimator demonstrating the greatest bias (values .014, -.079, -.143, -.231, .182, N=30 for the 5,7,9,3 term Fourier T/P, hourly mean T/P estimators respectively). For T/P ratio 0.75, the Fourier series T/P with few terms demonstrate the least bias with the 3 term Fourier series T/P

estimator the least followed by the 5 term, 7 term, 9 term with the T/P ratio based on the hourly mean having the greatest bias (values $-.087, -.225, -.300, -.343, -.421$, $N=30$). The MSERs for T/P 0.25 are less than 1 for 3 and 5 term Fourier T/P estimators, not statistically different from 1 for the 7 term Fourier T/P estimator and greater than 1 for the 9 term Fourier T/P estimator (values $.149, .512, 1.130, 1.234$, $N=30$). For T/P ratio of 0.5 all of the T/P Fourier estimators have MSER's greater than 1, with the greatest to least the T/P estimator based on the 5 term, then 7 term then 9 term followed by the 3 term Fourier series (values $2.218, 1.80, 1.43, 1.31$, $N=30$). For T/P 0.75 again all MSERs are greater than 1, this time the 3 term has the greatest followed by the 5 term, 7 term and 9 term series (values $3.21, 2.09, 1.57, 1.33$, $N=30$). Using the bias and mean square error as criteria for determining the best estimator, the 7 or 9 term Fourier T/P estimators perform consistently better than the hourly mean T/P estimator for all of the T/P ratios tested.

The two curves in simulation 4 have a dose response curve that is constant over the 24 hour period, one at -4 and the other at -12 . The mean bias of the 400 replicates are plotted against the initial value ($-4, -12$) in figure S4.F1 and the MSERs in figure S4.F2 and tabled in S4.T1 through S4.T4. All of the T/P estimators demonstrate a negative bias (estimate less than actual) with the biases for the curve with initial value -4 consistently more biased than the curve with initial value -12 . For both curves the bias increased as more Fourier terms are added to the T/P estimator with the T/P estimator based on the hourly means showing the greatest bias ($-.285, -.364, -.403, -.445, -.555$, $N=30$ and initial value $=-4$; $-.104, -.152, -.189, -.216, -.295$, $N=30$ and initial value $=-12$ for the 3, 5, 7, 9 and hourly mean respectively). All of the MSERs for the T/P estimators based on the Fourier series are greater than 1 and the difference between the MSEs for the

Fourier T/P estimators and the hourly mean T/P estimator are all statistically significant (tables S4.T3). The Fourier T/P estimators based on few terms have a MSER greater than those of Fourier T/P estimators based on more terms (2.53, 2.00, 1.72, 1.45, N=30 initial value = -4 ; 5.77, 3.29, 2.21, 1.75, N=30 initial value -12 for 3, 5, 7, 9 term Fourier T/P estimators respectively). Clearly the 3 term Fourier T/P estimator has the best overall characteristics for the 2 curves in simulation 4, with minimum bias and mean square error, followed by the Fourier T/P estimators with more series terms with the hourly mean T/P estimator the least favorable with the greatest bias and mean square error.

The curves in simulation 5 are a 3, 5 and 7 term Fourier series (case 1, 2 and 3 respectively) which were included to examine the behavior of the T/P estimators for finite samples when the actual curves are themselves Fourier series. The graphs of the bias associated with the T/P estimators included in the study are plotted versus sample size in figures S5.F1 through S5.F3, and the MSERs plotted versus sample size in figures S5.F4 through S5.F6. The simulation bias and difference in bias between the Fourier T/P estimators and the hourly mean T/P estimator are tabled in S5.T1, S5.T2 and the difference in MSE between the Fourier T/P estimators and the hourly mean T/P estimator, and the MSERs tabled in S5.T3 and S5.T4. In case 1, the 3 term Fourier response curve, the 3 term Fourier T/P estimator has the least bias for all sample sizes tested, and the asymptotic 95% C.I. for the bias includes 0 for all sample sizes tested (values -.013, 0.004, 0.016 and 0.011 for N=10, 20, 30, 50). Each of the other T/P estimators are biased with the 5 term Fourier T/P estimator the least biased followed by the 7 and 9 term Fourier T/P estimators and the hourly mean T/P estimator having the greatest bias for all sample sizes tested. In case 2, the 5 term Fourier series, all of the T/P estimators tested are biased with the 3 term Fourier

T/P estimator consistently having less bias than the 5 term Fourier T/P estimator, although their asymptotic 95% C.I. overlap for all sample sizes (values 3 and 5 term T/P estimators are: -.231, -.273 for N=10, -.129, -.170 for N=20, -.086, -.121 for N=30 and -.066, -.083 for N=50). The bias for the 7 and 9 term Fourier T/P estimators are larger than for the 3 and 5 term T/P estimators and similar with 95 % C.I.'s that also overlap, followed by the hourly mean T/P estimator that shows significantly greater bias than any of the other estimators. In case 3 (7 term Fourier series) sample size N=10 the 5 term Fourier T/P estimator has the least average bias followed by the 7 and 9 term Fourier T/P estimators, the hourly mean T/P estimator and then the 3 term Fourier T/P estimator(values of 0.067, -0.095, -0.103, -0.172, 0.231, N=10). For samples sizes 20, 30 and 50 the 7 and 9 term Fourier T/P estimators have the least average bias(with the 9 term slightly larger than the 7 term with overlapping confidence intervals), followed by the average bias for the hourly mean T/P estimator, and the 5 and 3 term Fourier estimators. Throughout the total range of sample sizes simulated the 7 term Fourier T/P estimator demonstrates the least bias(or close to the smallest bias) of the estimators tested.

Figure S5.F4 contains the case 1 graph of the MSERs for all of the Fourier T/P estimators examined. All are greater than 1 with the 5 term Fourier T/P estimator giving consistently the largest MSER followed by the 3 term (except N=20), then the 7 and 9 term Fourier T/P estimators. The difference in the MSER between the competing Fourier estimators is very little with significant overlap of their asymptotic 95% C.I. for all the sample sizes included in the simulation (values of 1.54, 1.47, 1.43 and 1.26, N=30 for 5,3,7,9 term estimators). Generally the MSERs increase as the sample size increases, and using the results of the

Wilcoxon paired test (table S5.T4) all of the MSEs for these estimators are significantly smaller than the MSE for the hourly mean T/P estimator.

For case 2 (5 term Fourier series), the 3 term Fourier T/P estimator has the greatest MSER followed by the 5 term T/P estimator with values close enough to the 3 term estimator that their 95% C.I.'s overlap for all sample sizes tested (values of 5.53, 3.99, N=30 for 3 and 5 term estimators). The 7 and 9 term T/P estimators also have MSERs greater than 1, but significantly less the 3 and 5 term estimators (values of 2.66, 1.96, N=30 for 7 and 9 term estimators).

Case 3 MSERs are plotted in figure S5.F6. The 3 term Fourier T/P estimator has a MSER less than 1 for all sample sizes simulated and the 5 term Fourier T/P estimator has an MSER less than 1 for sample sizes 30 and 50, and equal to 1 for sample size 20 (table S5.T4 Wilcoxon p-value 0.942). Only the 7 and 9 term Fourier T/P estimators have MSERs significantly greater than 1, and they are very close to each other in value (values of 1.41 and 1.49, N=30 for 7, 9 term estimators).

The following conclusions can be made from the simulation results:

1. For the curves included in the simulation, the hourly mean T/P estimator is highly biased when the true T/P ratio is large (T/P=0.75) and less biased when the T/P ratio is small (T/P=0.25). The bias and M.S.E. associated with the hourly mean T/P ratio is much higher than with the Fourier T/P estimators when the T/P ratio is large, but becomes more comparable with the Fourier T/P estimators when the T/P ratio is small.

For most of the curves, T/P ratios and sample sizes examined in the simulation, at least one of the Fourier T/P estimators has a significantly smaller bias and M.S.E. than the hourly mean T/P estimator.

2. The 3 term Fourier T/P estimator has a low bias and M.S.E. when the actual T/P ratio is large ($T/P = 0.75$), but has poor bias and M.S.E. characteristics for low T/P ratios ($T/P \leq 0.50$).

2. The 9 term Fourier T/P estimator has a low bias and M.S.E. when the actual T/P ratio is small ($T/P = 0.25$); has the worst bias and M.S.E. characteristics of the Fourier estimators for large T/P ratios, but is consistently better than the hourly mean T/P estimator for all T/P ratios tested.

3. The 5 and 7 term Fourier estimators have good bias and M.S.E. characteristics for all (but a few) of the T/P ratios, curves and sample sizes examined. The 5 term Fourier T/P estimator is clearly the better estimator with the mid to high range T/P ratios ($T/P = 0.5, 0.75$), with the 7 term Fourier estimator the better performer with low T/P ratios ($T/P = 0.25$).

Direct comparisons were made between the 5 and 7 term Fourier T/P estimators and summarized in tables S1.T5 through S5.T5. These tables contain a summary of

bias and M.S.E. differences with confidence intervals and p-values associated with the paired Wilcoxon rank test for equality for each of the 5 simulations performed. Tables S1.T6 through S5.T6 summarizes the simulation findings concerning the M.S.E.s of the 5 and 7 term estimators. The tables lists the estimator with the smallest M.S.E. across all sample sizes for each of the simulation conditions. In the column " Minimum M.S.E." a 5 or 7 is indicated depending on which of the estimator's M.S.E. is significantly smaller (Wilcoxon test) than the other for at least 3 of the 4 sample sizes simulated. If neither estimator is favored for at least 3 of the 4 sample sizes simulated an E (for even) is indicated Also noted in the column " F5 M.S.E. LT HR" is whether the M.S.E. of the 5 term estimator is less than the M.S.E. for the hourly mean and in column " F7 M.S.E. LT HR" is whether the M.S.E. of the 7 term estimator is less than the M.S.E. for the hourly mean. Its clear from these tables that the 5 term Fourier T/P estimator is preferred using the M.S.E. criteria when the actual T/P ratio is 0.50 or greater, but when the T/P ratio is small the 7 term estimator generally performs better. Also in all cases the 7 term estimator performs at least as well as the hourly mean estimator, which is not the case for the 5 term estimator, which may have a M.S.E. substantially larger than that for the hourly mean for small T/P ratios.

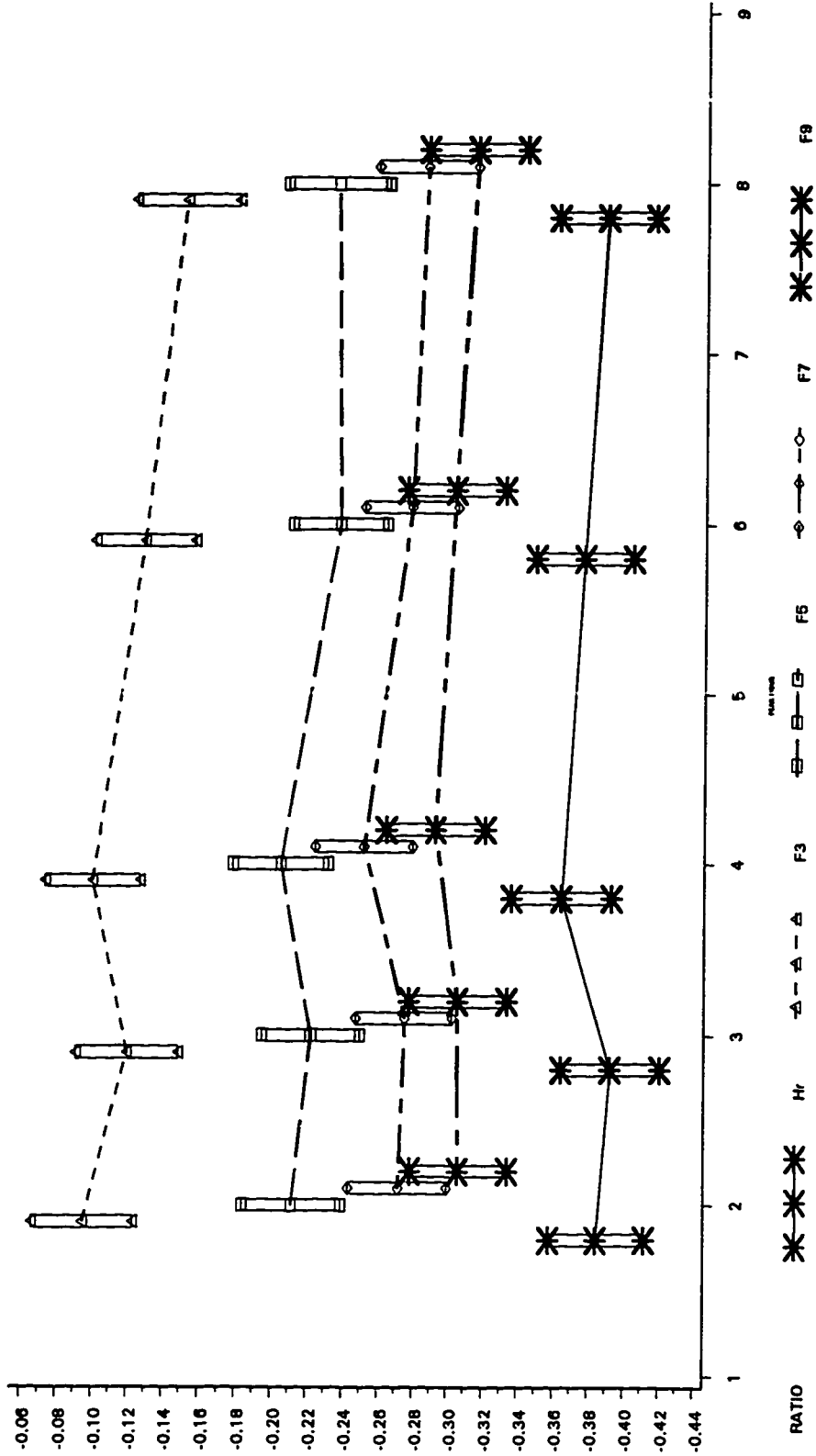


FIGURE: S1.F1: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 1
INITIAL VALUE=-3 T/P RATIO= 0.75 N= 30

...

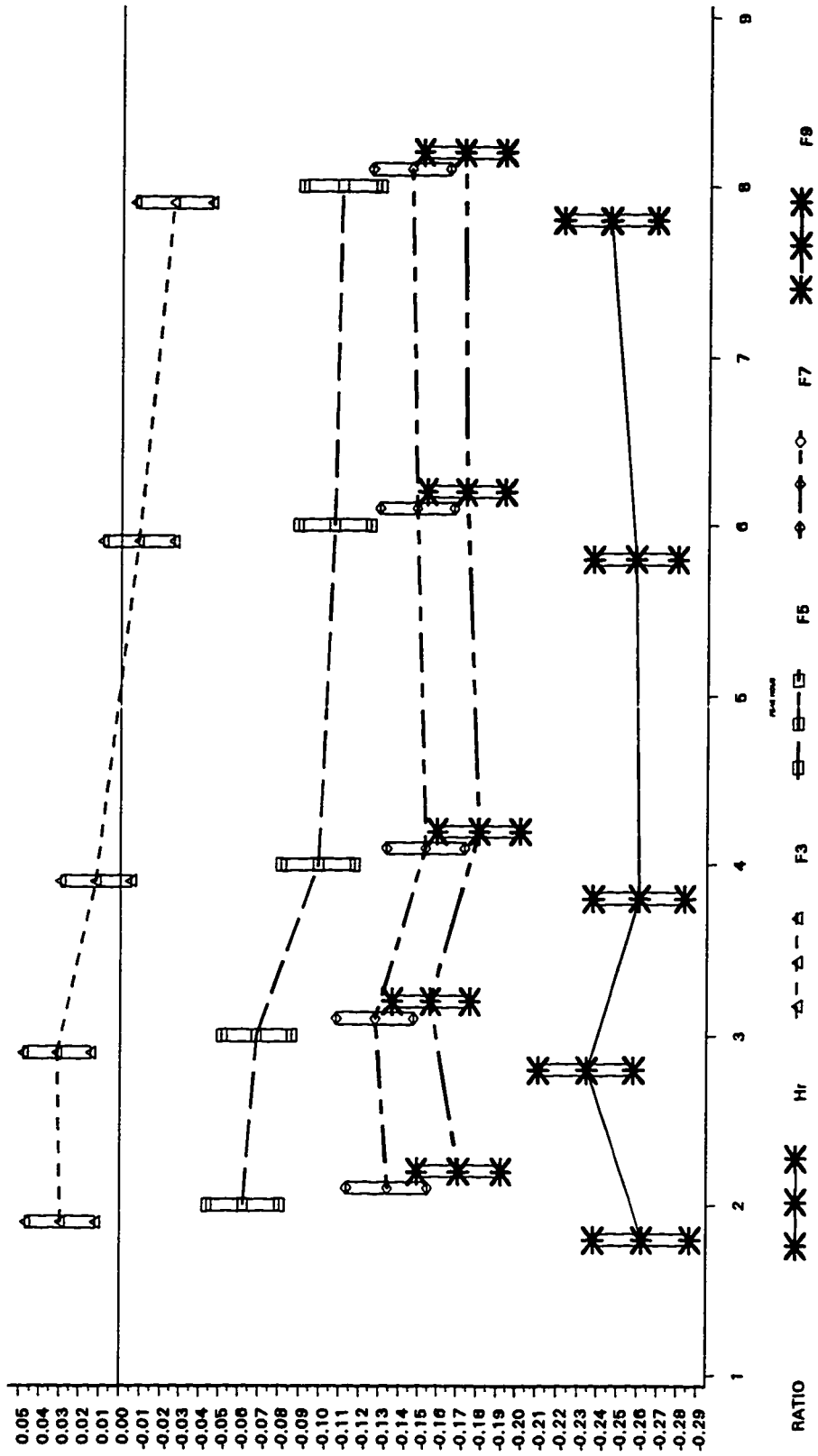


FIGURE: S1.F2: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 1
INITIAL VALUE=-6 T/P RATIO= 0.75 N=30

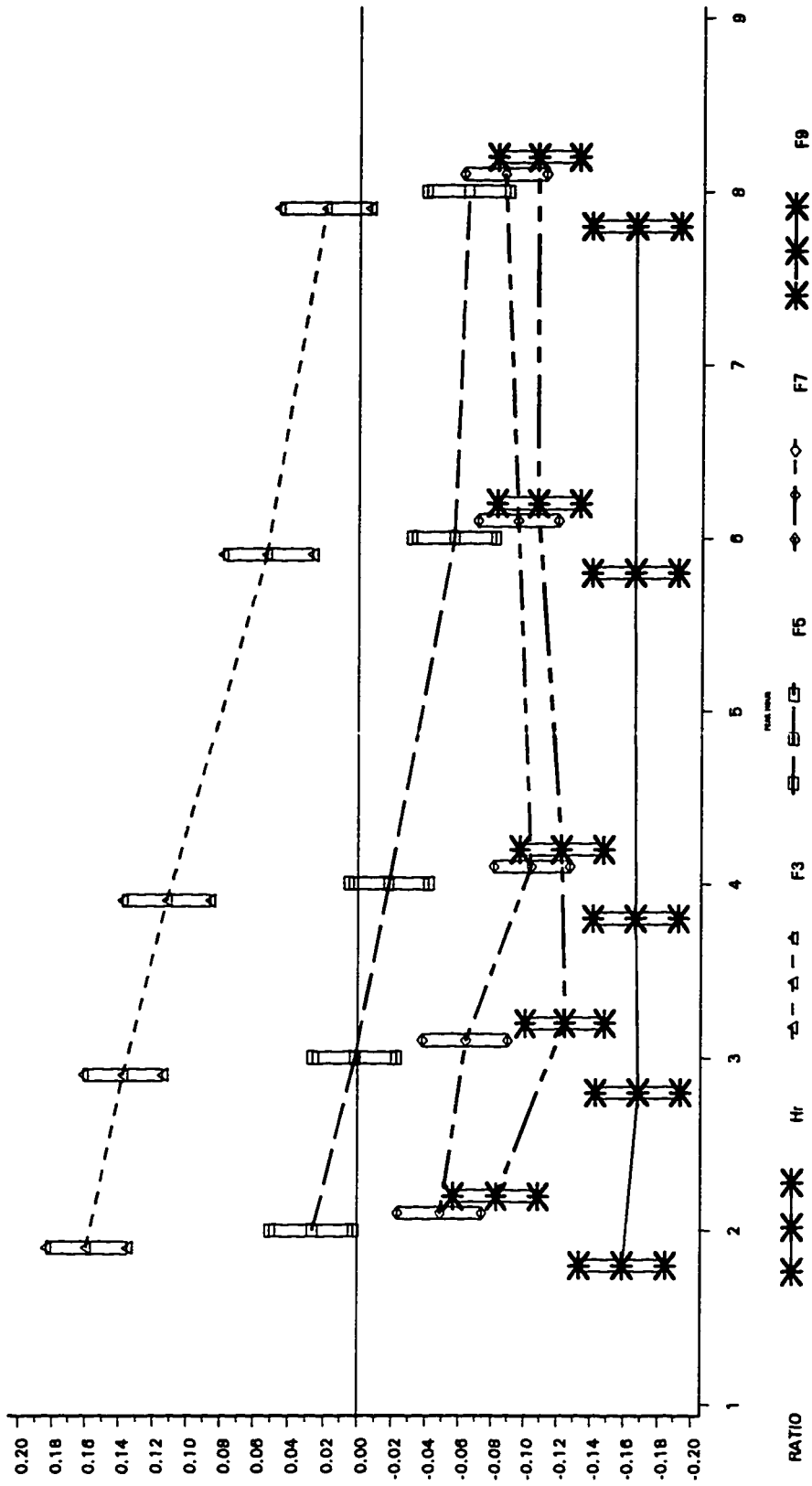


FIGURE: S1.F3: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 1
INITIAL VALUE=-3 T/P RATIO=0.50 N=30

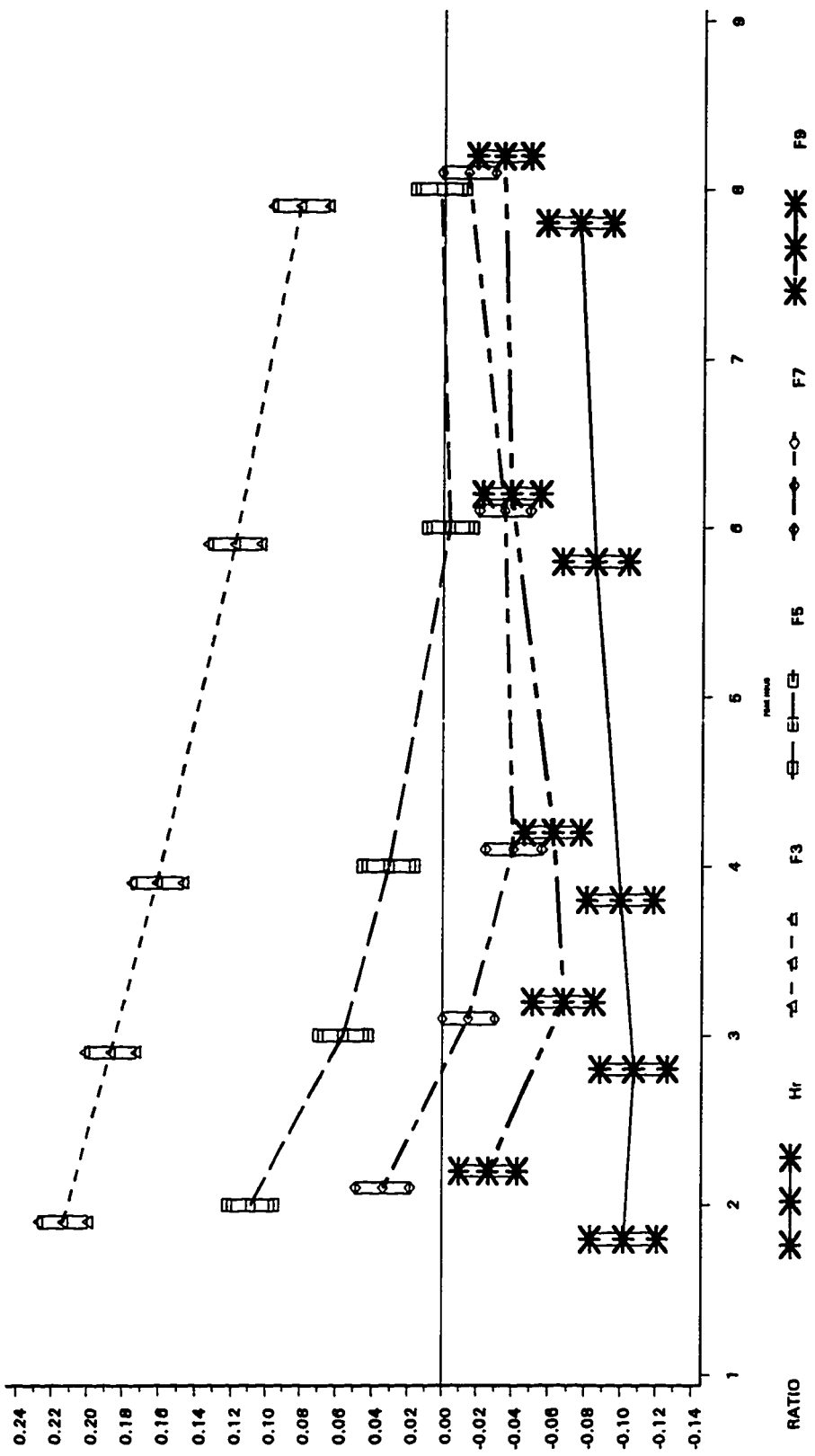


FIGURE: S1.F4: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 1
INITIAL VALUE = -6 T/P RATIO = 0.50 N = 30

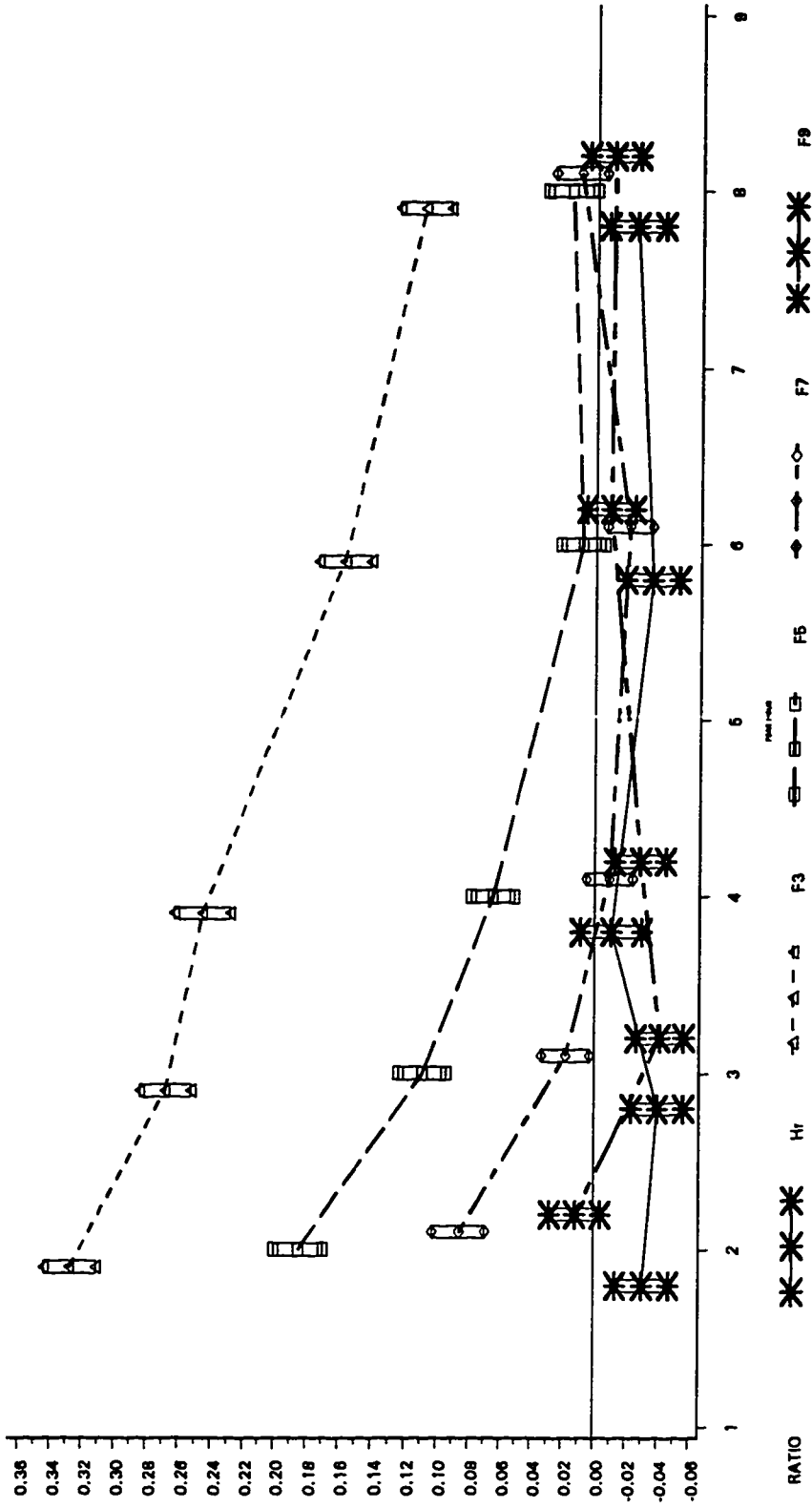


FIGURE: S1.F5: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 1
 INITIAL VALUE = -3 T/P RATIO = 0.25 N = 30

...

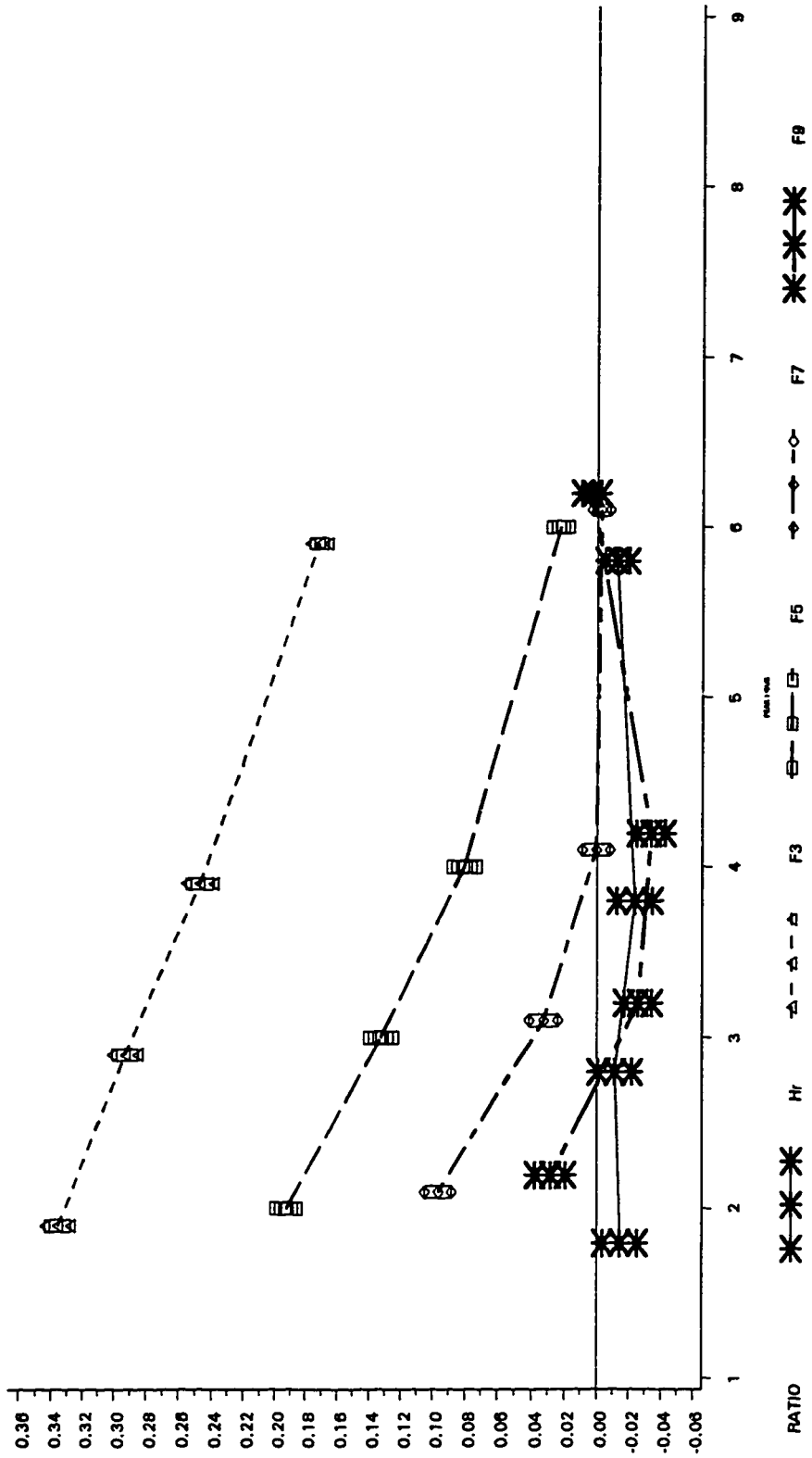


FIGURE: S1.F6: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 1
 INITIAL VALUE=-6 T/P RATIO= 0.25 N= 30

...

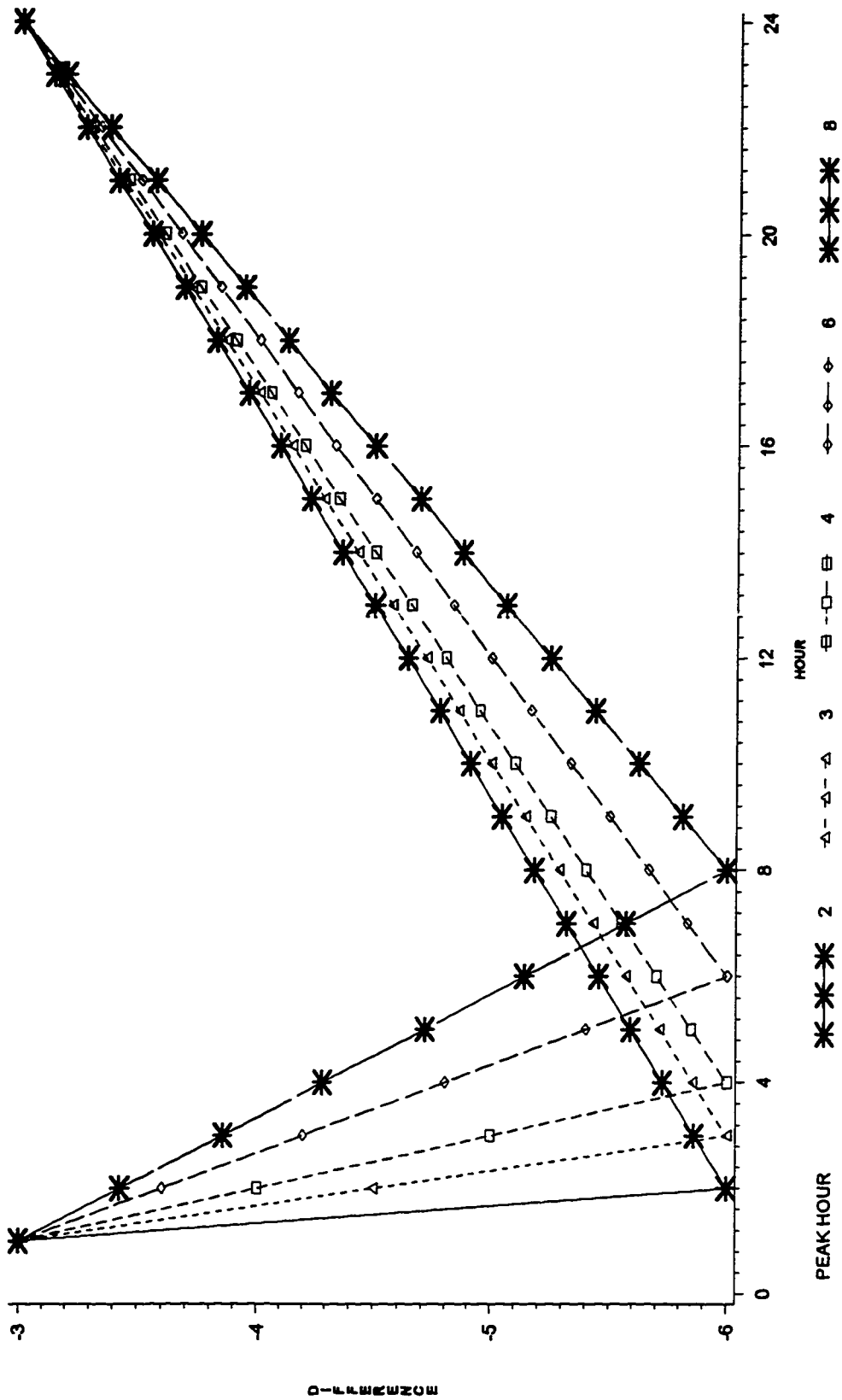


FIGURE S1: PLOT OF SIMULATED DRUG EFFECT CURVES - SIMULATION 1

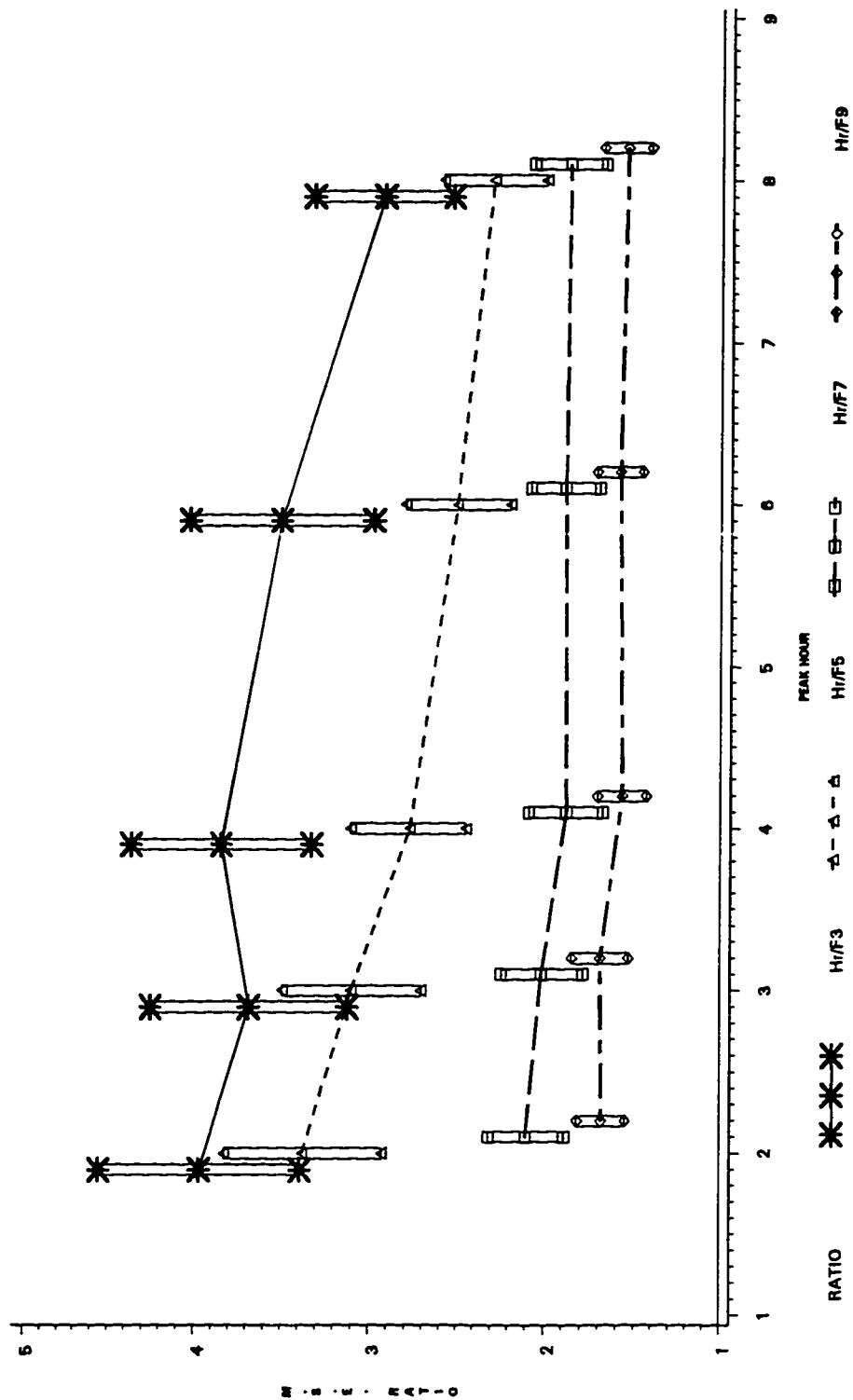


FIGURE: S1.F8: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1

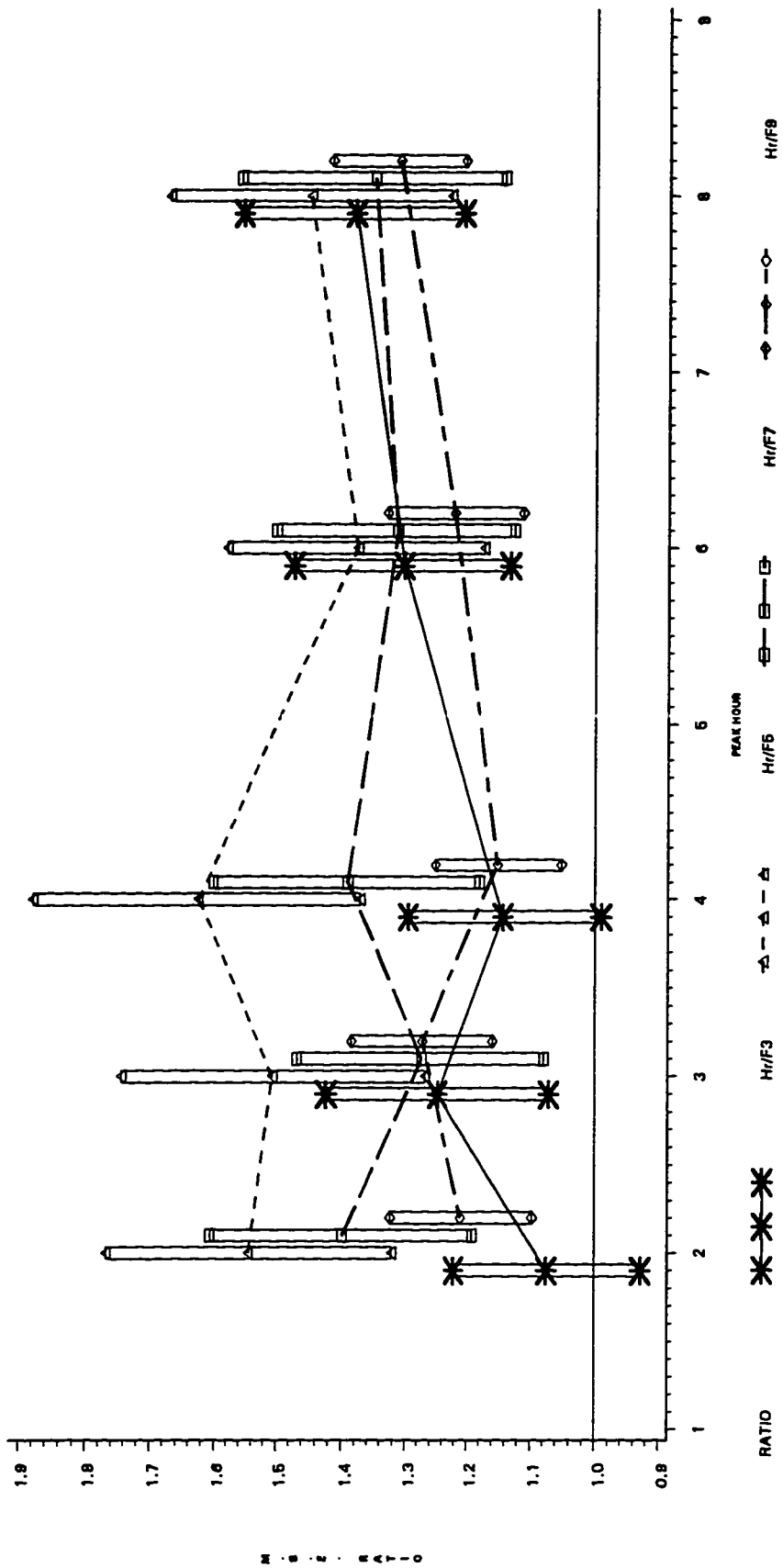


FIGURE: S1.F9: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
 INITIAL VALUE=-3 T/P RATIO=0.50 N=30

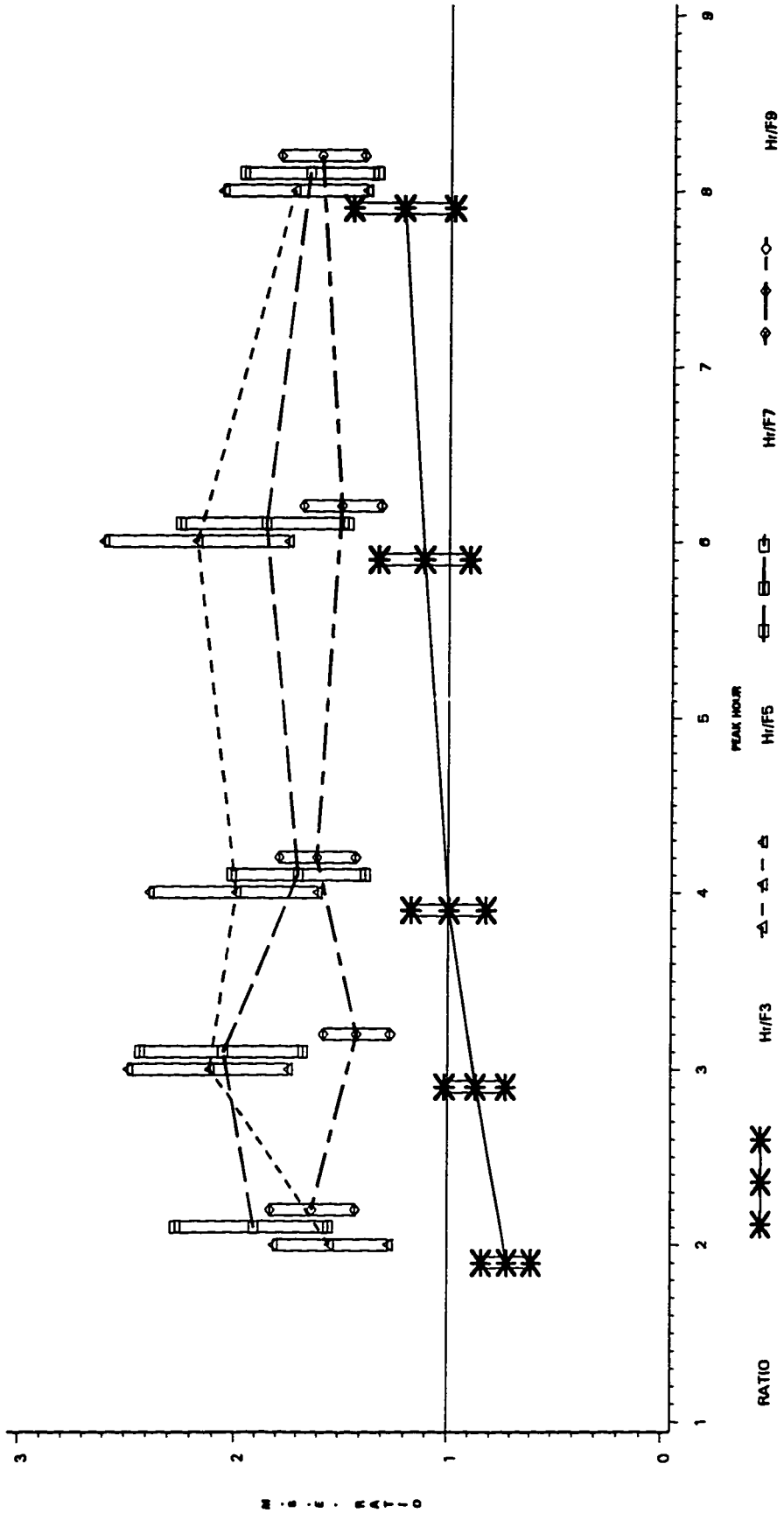


FIGURE: S1.F10: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
 INITIAL VALUE = -6 T/P RATIO = 0.50 N = 30

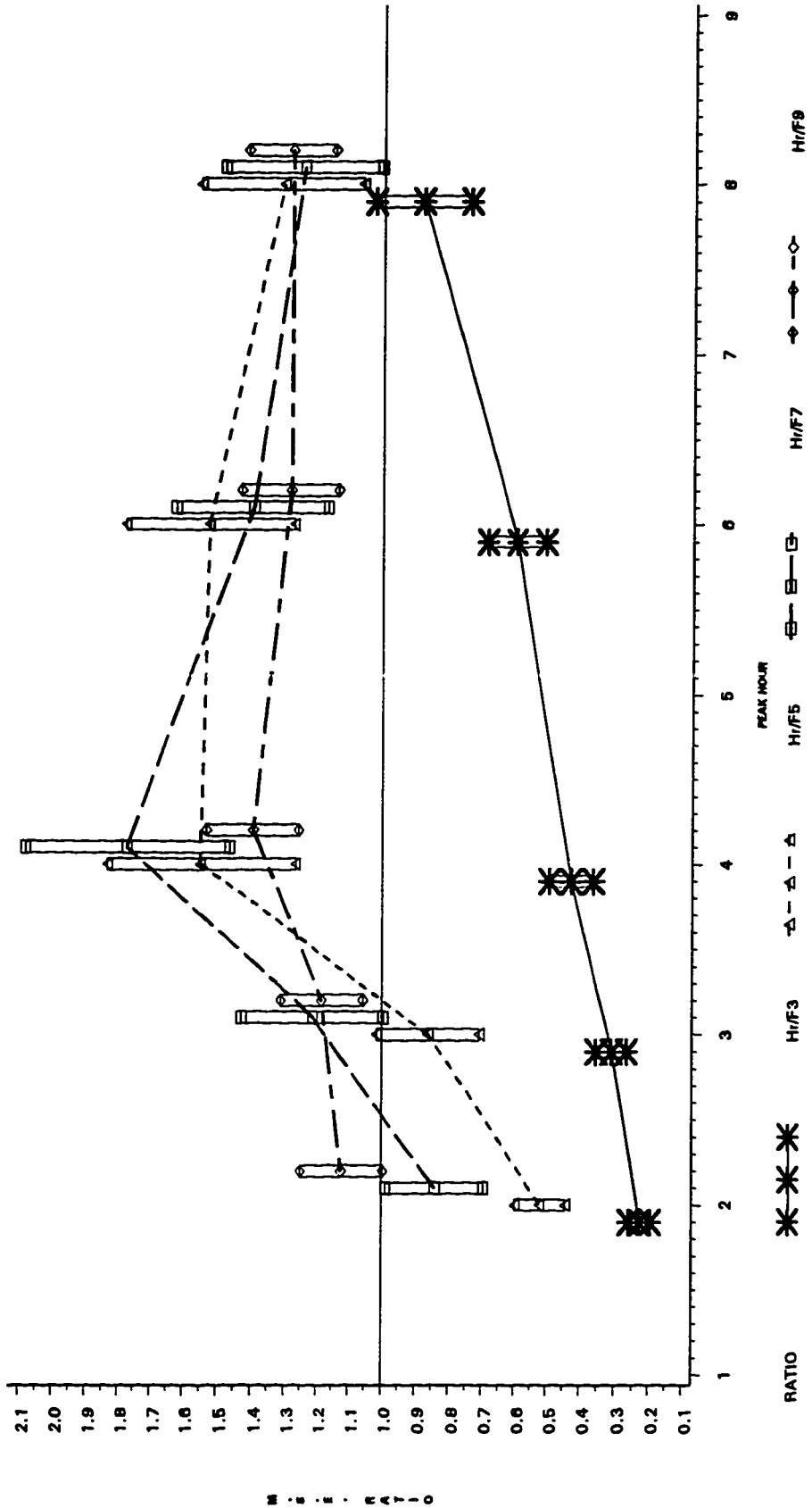


FIGURE: S1.F11: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
 INITIAL VALUE = -3 T/P RATIO = 0.25 N = 30

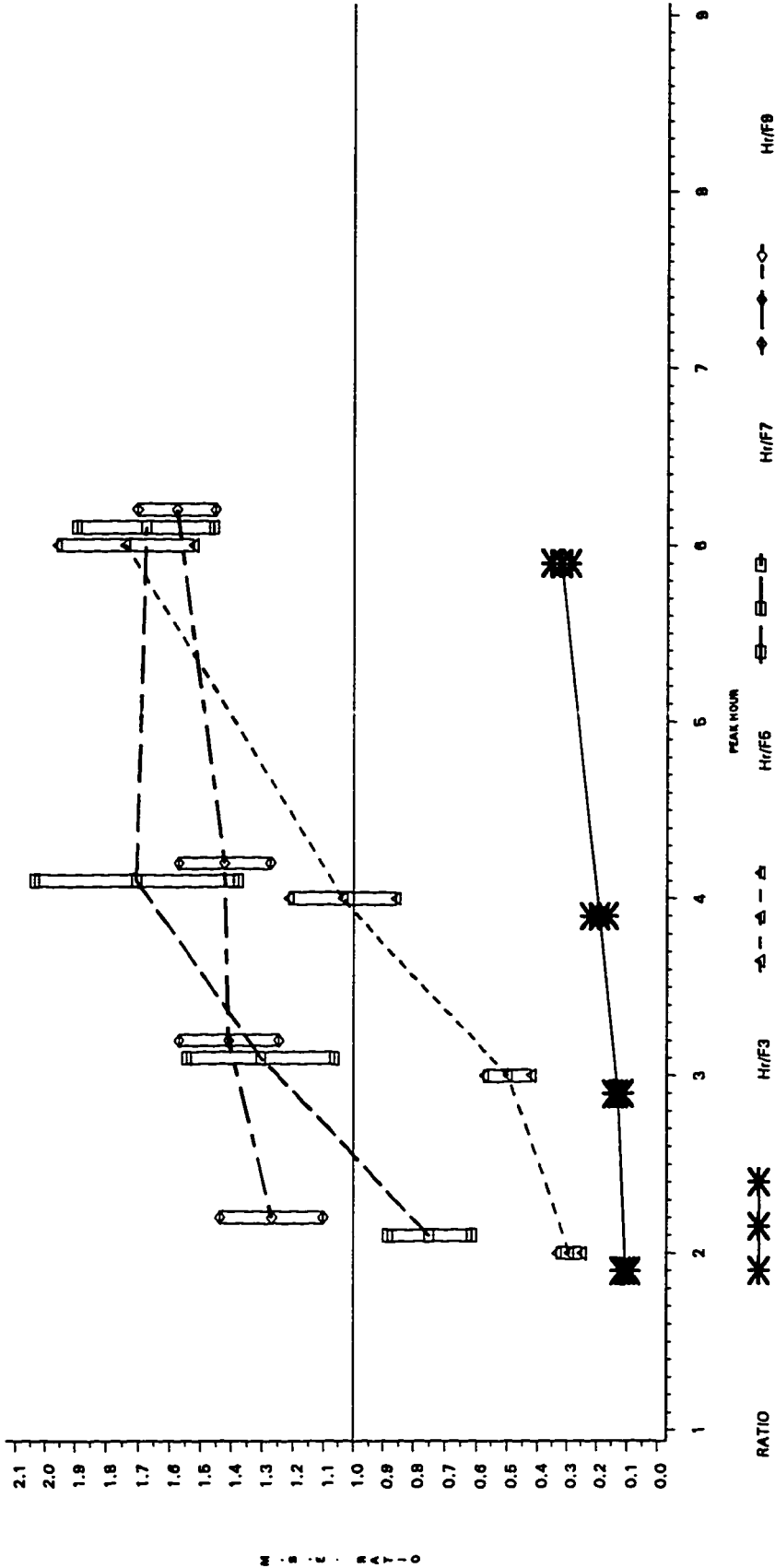
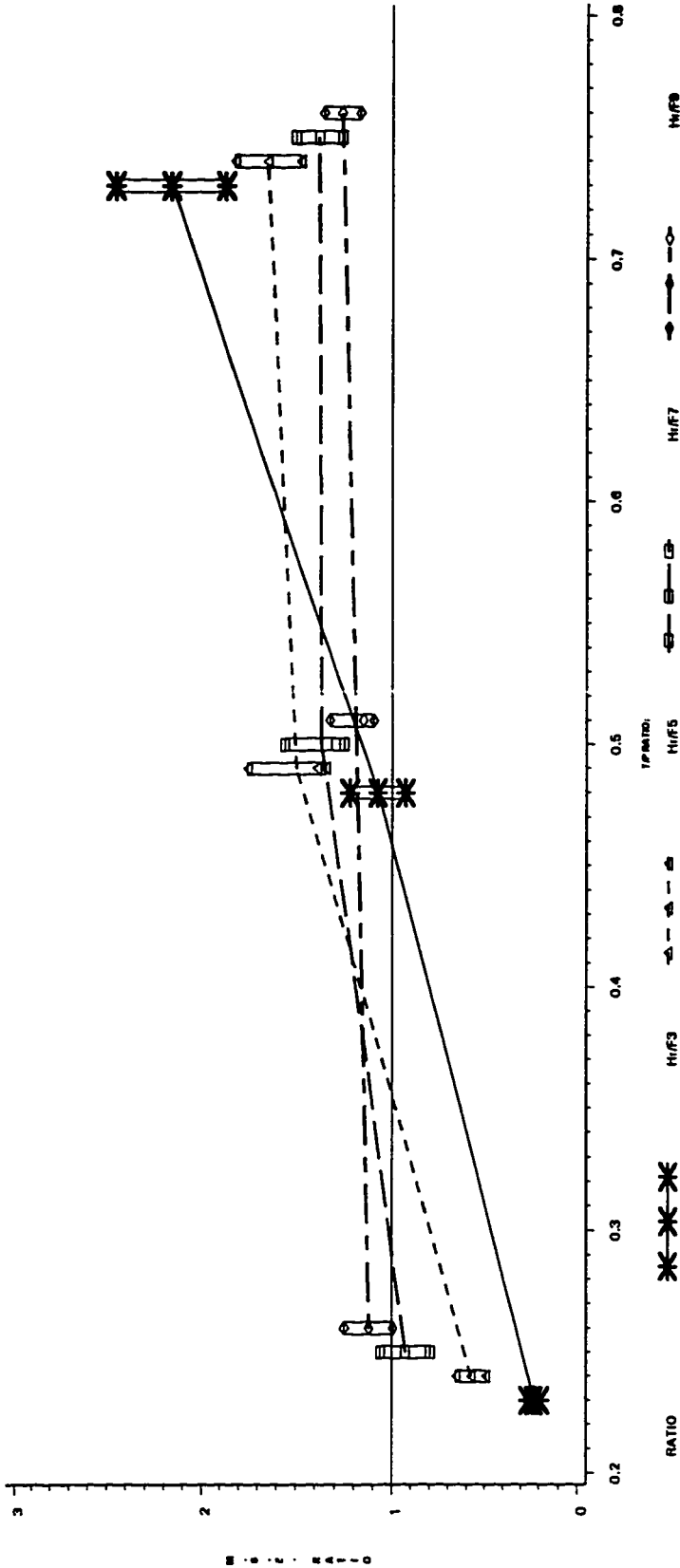


FIGURE: S1.F12: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
INITIAL VALUE=-6 T/P RATIO=0.25 N=30



**FIGURE: S1.F13: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
MINIMUM VALUES ACROSS PEAK HOURS
INITIAL VALUE = -3**

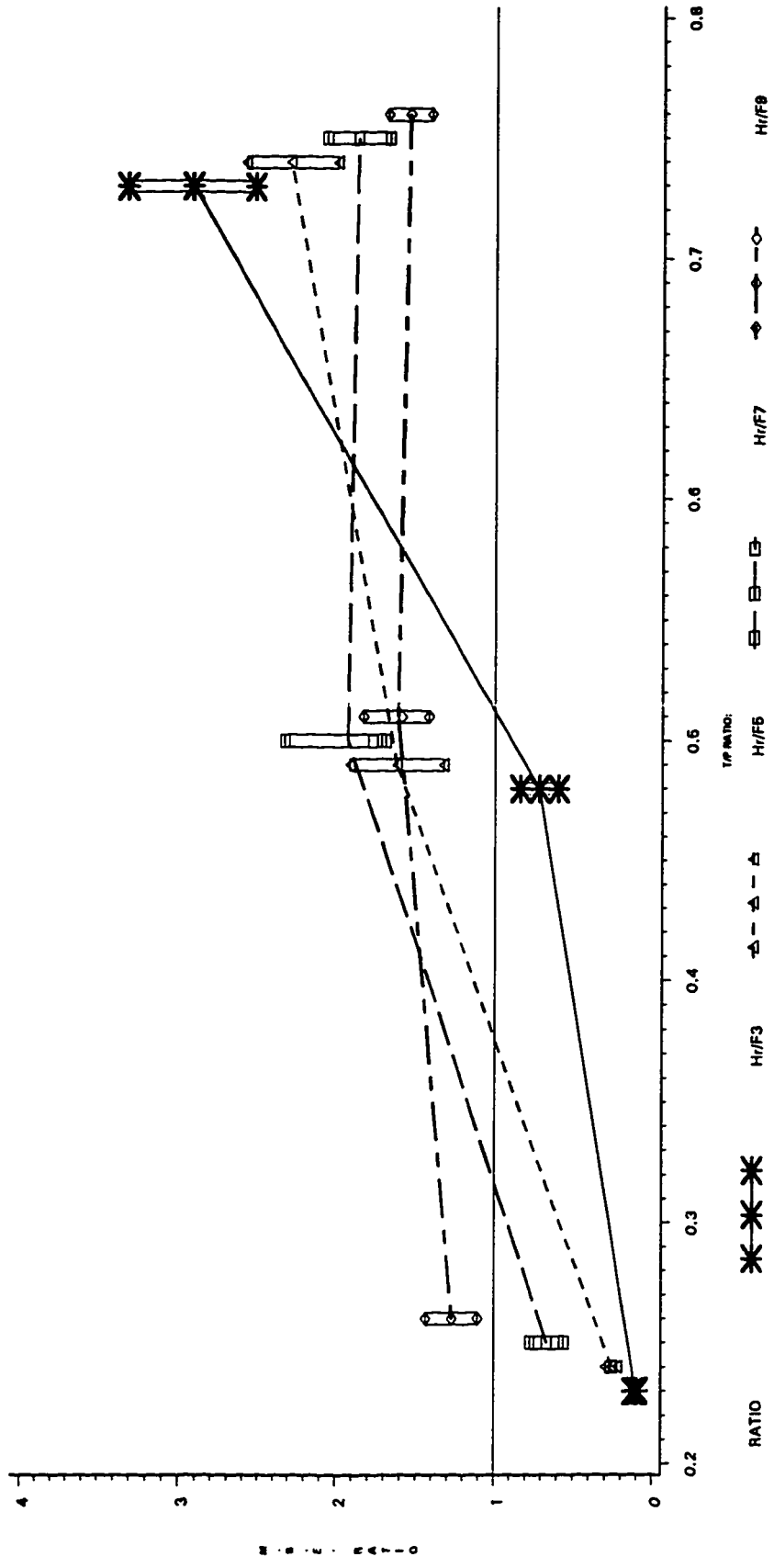
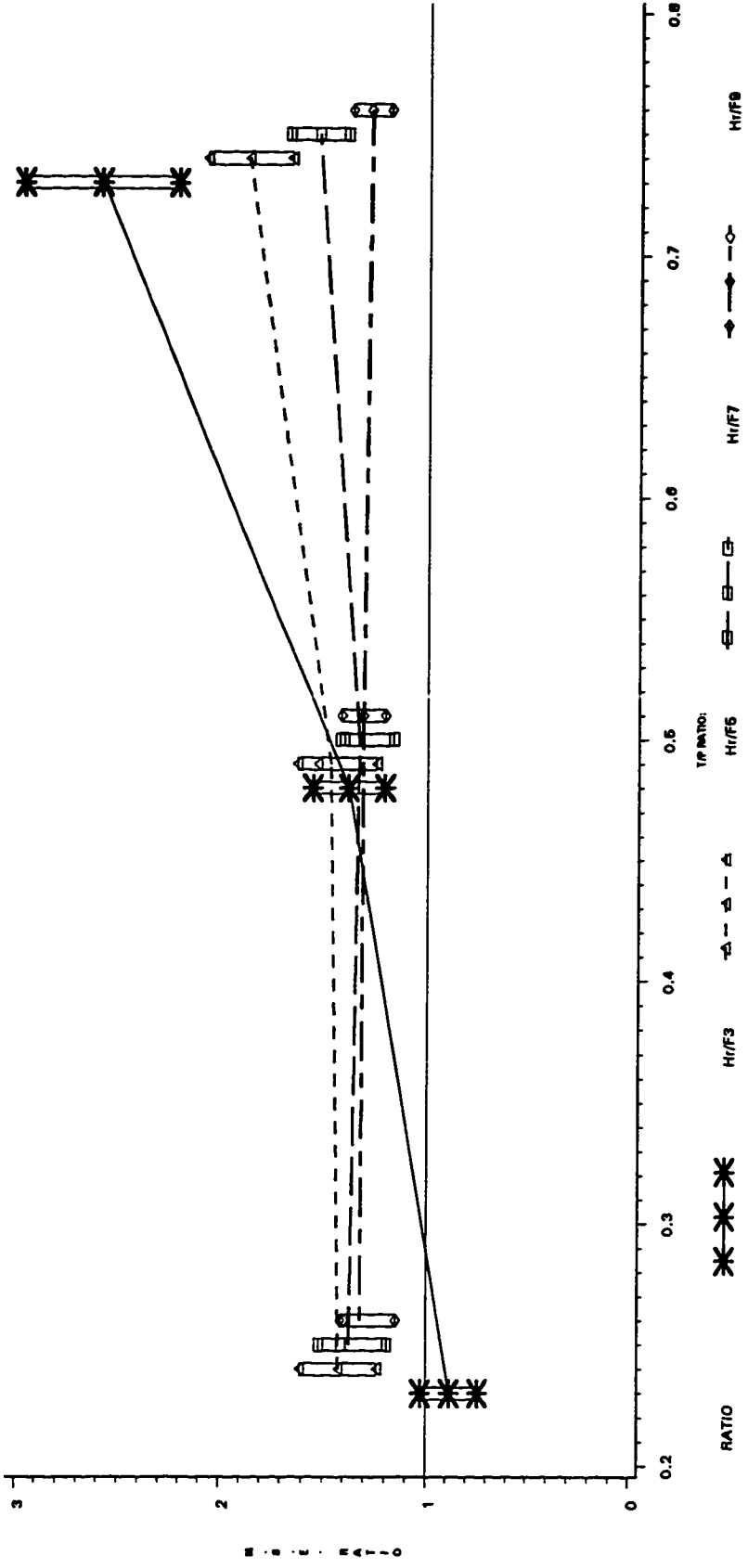
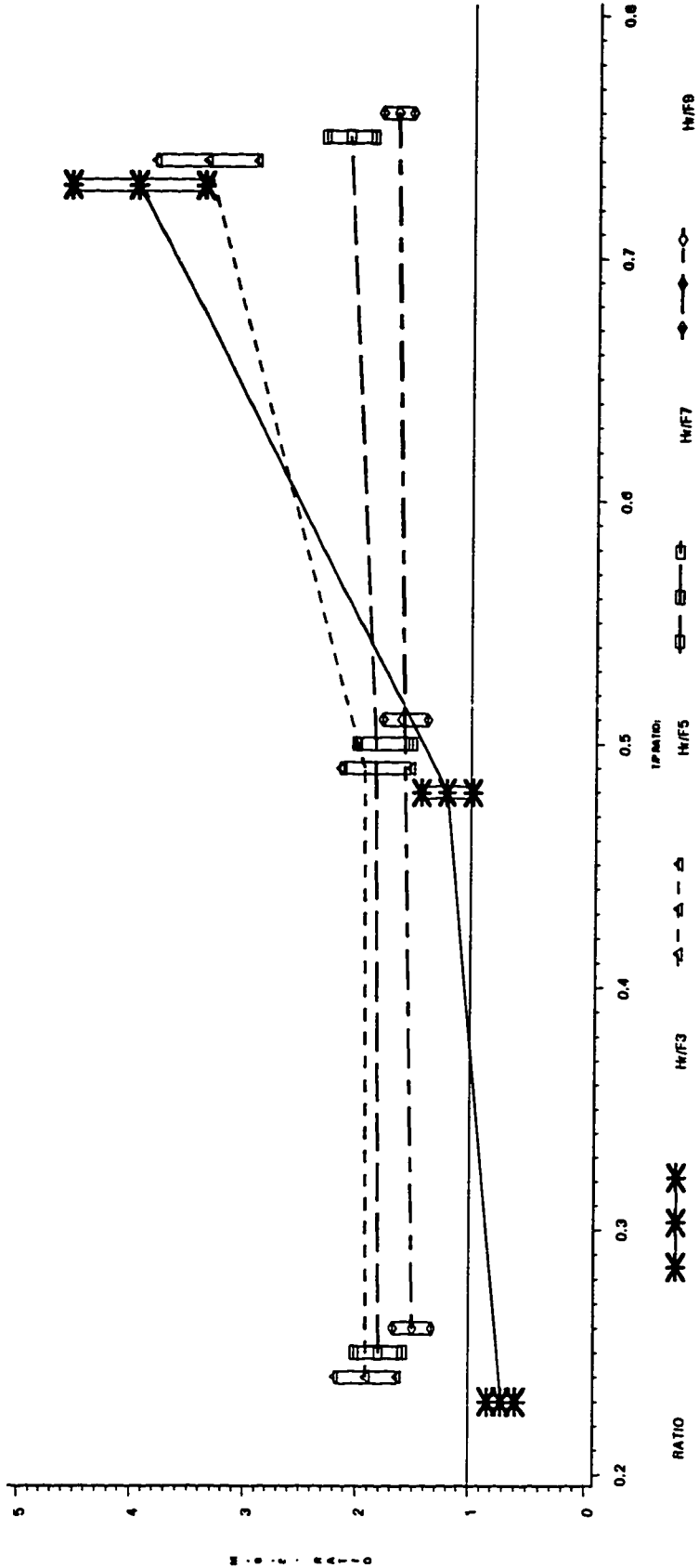


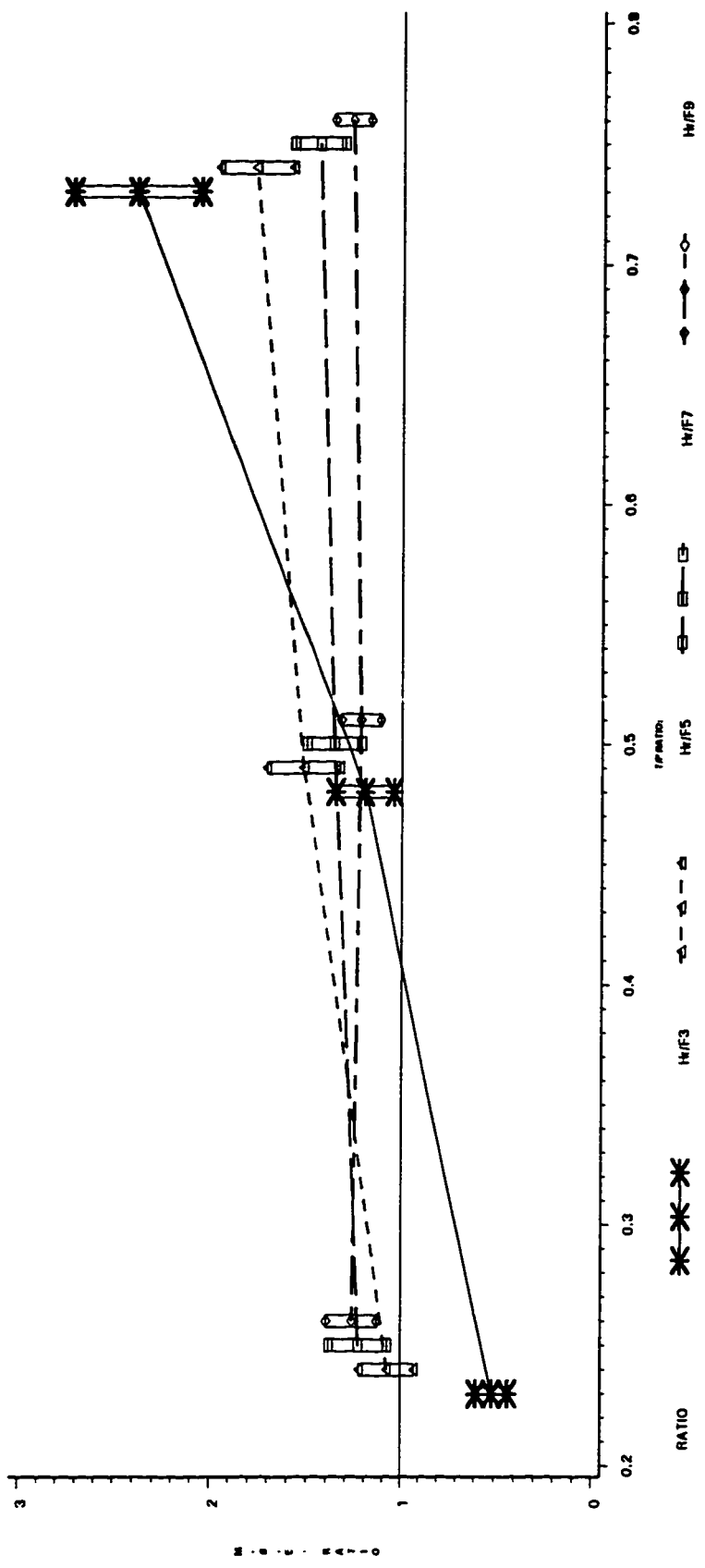
FIGURE: S1.F14: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
MINIMUM VALUES ACROSS PEAK HOURS
INITIAL VALUE = -6



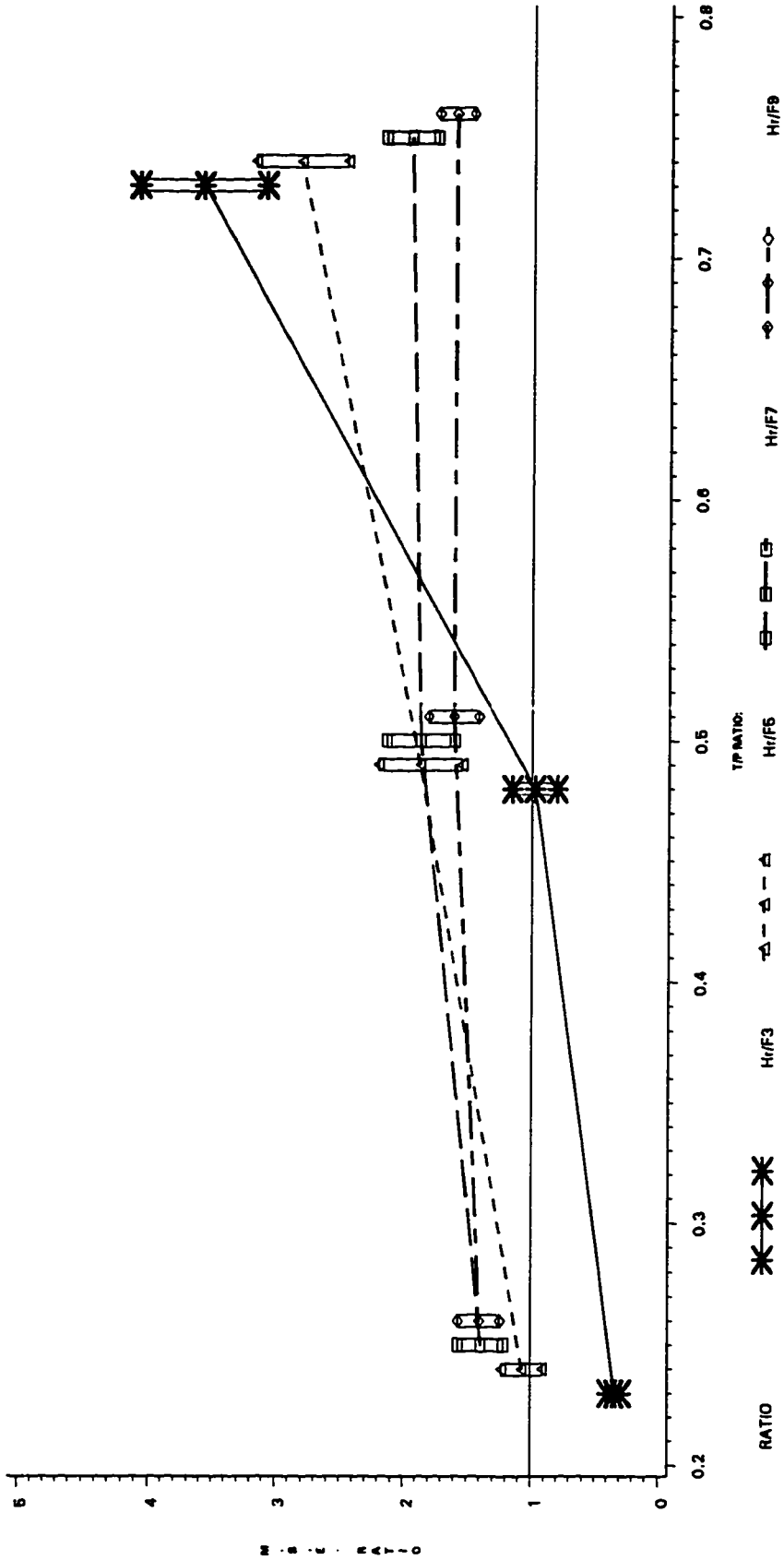
**FIGURE: S1.F15: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
MAXIMUM VALUES ACROSS PEAK HOURS
INITIAL VALUE = -3**



**FIGURE: S1.F16: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
 MAXIMUM VALUES ACROSS PEAK HOURS
 INITIAL VALUE = -6**



**FIGURE: S1.F17: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
AVERAGE ACROSS PEAK HOURS
INITIAL VALUE = -3**



**FIGURE: S1.F18: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 1
AVERAGE ACROSS PEAK HOURS
INITIAL VALUE = -6**

Table S1.T1
BIAS ESTIMATE
SIMULATION 1

t/p ratio	initial value	peak hour	N	F3 bias	Lower 95% C.L.	Upper 95% C.L.	F5 bias	Lower 95% C.L.	Upper 95% C.L.	F7 bias	Lower 95% C.L.	Upper 95% C.L.
0.75	-3	2	30	-0.095	-0.123	-0.066	-0.212	-0.239	-0.184	-0.272	-0.300	-0.243
0.75	-6	2	30	0.030	0.012	0.047	-0.062	-0.081	-0.044	-0.134	-0.155	-0.113
0.50	-3	2	30	0.159	0.135	0.184	0.026	0.002	0.051	-0.049	-0.074	-0.024
0.50	-6	2	30	0.214	0.200	0.228	0.109	0.095	0.122	0.034	0.019	0.049
0.25	-3	2	30	0.328	0.311	0.344	0.185	0.169	0.200	0.086	0.069	0.103
0.25	-6	2	30	0.336	0.328	0.344	0.193	0.185	0.200	0.097	0.088	0.105
0.75	-3	4	30	-0.100	-0.127	-0.073	-0.205	-0.232	-0.178	-0.252	-0.279	-0.224
0.75	-6	4	30	0.012	-0.005	0.030	-0.099	-0.117	-0.081	-0.153	-0.173	-0.133
0.50	-3	4	30	0.112	0.086	0.138	-0.018	-0.042	0.005	-0.104	-0.128	-0.081
0.50	-6	4	30	0.161	0.147	0.175	0.031	0.016	0.046	-0.040	-0.056	-0.025
0.25	-3	4	30	0.246	0.229	0.263	0.065	0.051	0.079	-0.009	-0.024	0.005
0.25	-6	4	30	0.247	0.239	0.256	0.081	0.073	0.088	0.000	-0.008	0.009
0.75	-3	8	30	-0.152	-0.180	-0.124	-0.236	-0.265	-0.208	-0.287	-0.315	-0.258
0.75	-6	8	30	-0.026	-0.045	-0.006	-0.110	-0.129	-0.090	-0.145	-0.165	-0.125
0.50	-3	8	30	0.020	-0.006	0.046	-0.064	-0.089	-0.039	-0.087	-0.112	-0.062
0.50	-6	8	30	0.081	0.065	0.097	0.002	-0.013	0.017	-0.014	-0.029	0.002
0.25	-3	8	30	0.109	0.094	0.125	0.016	0.000	0.032	0.010	-0.006	0.026
0.25	-6	8	30	0.104	0.096	0.113						

Table S1.T1
BIAS ESTIMATE
SIMULATION 1

t/p ratio	initial value	peak hour	N	F9 bias	Lower 95 % C.I.	Upper 95 % C.I.	Hr bias	Lower 95 % C.I.	Upper 95 % C.I.
0.75	-3	2	30	-0.306	-0.334	-0.278	-0.385	-0.412	-0.358
0.75	-6	2	30	-0.171	-0.193	-0.149	-0.262	-0.287	-0.238
0.50	-3	2	30	-0.083	-0.109	-0.057	-0.159	-0.185	-0.133
0.50	-6	2	30	-0.027	-0.043	-0.010	-0.102	-0.121	-0.083
0.25	-3	2	30	0.012	-0.004	0.028	-0.030	-0.047	-0.014
0.25	-6	2	30	0.028	0.019	0.038	-0.015	-0.026	-0.004
0.75	-3	4	30	-0.293	-0.321	-0.264	-0.365	-0.393	-0.336
0.75	-6	4	30	-0.181	-0.202	-0.160	-0.261	-0.284	-0.238
0.50	-3	4	30	-0.122	-0.148	-0.097	-0.167	-0.192	-0.141
0.50	-6	4	30	-0.062	-0.078	-0.047	-0.100	-0.119	-0.081
0.25	-3	4	30	-0.029	-0.045	-0.013	-0.011	-0.030	0.009
0.25	-6	4	30	-0.034	-0.043	-0.025	-0.024	-0.035	-0.013
0.75	-3	8	30	-0.315	-0.344	-0.287	-0.389	-0.417	-0.362
0.75	-6	8	30	-0.172	-0.193	-0.151	-0.245	-0.268	-0.222
0.50	-3	8	30	-0.107	-0.132	-0.083	-0.166	-0.192	-0.140
0.50	-6	8	30	-0.034	-0.049	-0.019	-0.076	-0.094	-0.058
0.25	-3	8	30	-0.011	-0.027	0.005	-0.025	-0.043	-0.008
0.25	-6	8	30	-0.005	-0.014	0.004	-0.023	-0.034	-0.012

**Tables S1.T2
BIAS DIFFERENCE BETWEEN FOURIER ESTIMATE AND HOURLY MEAN
SIMULATION 1**

t/p ratio	initia l value	peak hour	N	F3-Hr	Lower 95 % C.L.	Upper 95 % C.L.	prob. F3-Hr $\rightarrow 0$	FS-Hr	Lower 95 % C.L.	Upper 95 % C.L.	prob. FS-Hr $\rightarrow 0$
0.75	-3	2	30	0.290	0.261	0.318	0.000	0.173	0.148	0.198	0.000
0.75	-6	2	30	0.292	0.269	0.315	0.000	0.200	0.181	0.220	0.000
0.50	-3	2	30	0.319	0.293	0.344	0.000	0.186	0.151	0.220	0.000
0.50	-6	2	30	0.316	0.297	0.334	0.000	0.211	0.187	0.234	0.000
0.25	-3	2	30	0.358	0.340	0.376	0.000	0.215	0.193	0.237	0.000
0.25	-6	2	30	0.351	0.340	0.362	0.000	0.207	0.194	0.221	0.000
0.75	-3	4	30	0.264	0.235	0.294	0.000	0.160	0.136	0.183	0.000
0.75	-6	4	30	0.273	0.251	0.295	0.000	0.162	0.143	0.180	0.000
0.50	-3	4	30	0.279	0.254	0.304	0.000	0.149	0.113	0.184	0.000
0.50	-6	4	30	0.261	0.244	0.278	0.000	0.131	0.107	0.155	0.000
0.25	-3	4	30	0.257	0.238	0.275	0.000	0.075	0.052	0.099	0.000
0.25	-6	4	30	0.271	0.261	0.281	0.000	0.105	0.091	0.118	0.000
0.75	-3	8	30	0.237	0.208	0.266	0.000	0.153	0.128	0.179	0.000
0.75	-6	8	30	0.220	0.198	0.241	0.000	0.135	0.117	0.153	0.000
0.50	-3	8	30	0.186	0.160	0.212	0.000	0.102	0.065	0.138	0.000
0.50	-6	8	30	0.157	0.140	0.174	0.000	0.078	0.055	0.101	0.000
0.25	-3	8	30	0.135	0.118	0.151	0.000	0.041	0.018	0.065	0.000
0.25	-6	8	30	0.127	0.118	0.136	0.000				

Tables S1.T2
BIAS DIFFERENCE BETWEEN FOURIER ESTIMATE AND HOURLY MEAN
SIMULATION 1

t/p ratio	initia l value	peak hour	N	F7-Hr	Lower 95 % C.I.	Upper 95 % C.I.	prob. F7-Hr	F9-Hr	Lower 95 % C.I.	Upper 95 % C.I.	prob. F9-Hr
0.75	-3	2	30	0.113	0.091	0.136	0.000	0.079	0.058	0.099	0.000
0.75	-6	2	30	0.128	0.111	0.145	0.000	0.092	0.077	0.106	0.000
0.50	-3	2	30	0.110	0.075	0.146	0.000	0.076	0.058	0.095	0.000
0.50	-6	2	30	0.136	0.112	0.160	0.000	0.075	0.064	0.087	0.000
0.25	-3	2	30	0.117	0.093	0.140	0.000	0.042	0.031	0.053	0.000
0.25	-6	2	30	0.111	0.097	0.125	0.000	0.043	0.037	0.050	0.000
0.75	-3	4	30	0.113	0.091	0.134	0.000	0.072	0.053	0.090	0.000
0.75	-6	4	30	0.107	0.091	0.124	0.000	0.080	0.065	0.095	0.000
0.50	-3	4	30	0.062	0.027	0.098	0.001	0.044	0.027	0.061	0.000
0.50	-6	4	30	0.060	0.035	0.085	0.000	0.038	0.026	0.049	0.000
0.25	-3	4	30	0.001	-0.22	0.025	0.530	-0.18	-0.29	-0.08	0.002
0.25	-6	4	30	0.024	0.011	0.038	0.001	-0.10	-0.17	-0.04	0.004
0.75	-3	8	30	0.103	0.079	0.126	0.000	0.074	0.054	0.094	0.000
0.75	-6	8	30	0.100	0.084	0.116	0.000	0.073	0.058	0.087	0.000
0.50	-3	8	30	0.079	0.042	0.116	0.000	0.058	0.043	0.074	0.000
0.50	-6	8	30	0.062	0.039	0.086	0.000	0.042	0.030	0.054	0.000
0.25	-3	8	30	0.036	0.011	0.060	0.001	0.014	0.004	0.025	0.006
0.25	-6	8	30	0.018	0.011	0.024	0.000

Table: S1.T3
MEAN SQUARE ERROR DIFFERENCE
BETWEEN FOURIER ESTIMATE AND HOURLY MEAN

		SIMULATION 1									
		N=30					N=60				
t/p ratio	initial value	peak hour	F3-Hr	Lower 95 % C.I.	Upper 95 % C.I.	prob. F3-Hr =0	F5 - Hr	lower 95 % C.I.	Upper 95 % C.I.	prob. F5-Hr =0	
0.75	-6	2	-0.98	-1.11	-0.85	0.000	-0.92	-1.04	-0.80	0.000	
0.75	-3	2	-1.31	-1.50	-1.13	0.000	-1.00	-1.17	-0.83	0.000	
0.50	-6	2	0.019	0.009	0.028	0.000	-0.19	-0.26	-0.12	0.000	
0.50	-3	2	-0.06	-0.19	0.006	0.538	-0.34	-0.44	-0.23	0.000	
0.25	-6	2	0.107	0.101	0.113	0.000	0.032	0.028	0.035	0.000	
0.25	-3	2	0.104	0.093	0.116	0.000	0.025	0.018	0.032	0.000	
0.75	-6	4	-0.91	-1.05	-0.78	0.000	-0.79	-0.91	-0.67	0.000	
0.75	-3	4	-1.33	-1.52	-1.14	0.000	-1.01	-1.17	-0.84	0.000	
0.50	-6	4	0.000	-0.08	0.008	0.162	-0.27	-0.33	-0.20	0.000	
0.50	-3	4	-0.12	-0.24	0.000	0.072	-0.36	-0.46	-0.27	0.000	
0.25	-6	4	0.055	0.051	0.060	0.000	-0.00	-0.02	0.002	0.602	
0.25	-3	4	0.052	0.043	0.062	0.000	-0.06	-0.10	-0.02	0.000	
0.75	-6	8	-0.77	-0.89	-0.64	0.000	-0.66	-0.77	-0.55	0.000	
0.75	-3	8	-1.23	-1.42	-1.04	0.000	-0.90	-1.08	-0.73	0.000	
0.50	-6	8	-0.07	-0.14	0.000	0.035	-0.20	-0.26	-0.14	0.000	
0.50	-3	8	-0.27	-0.38	-0.17	0.000	-0.27	-0.35	-0.18	0.000	
0.25	-6	8	0.005	0.003	0.008	0.000	-0.06	-0.08	-0.05	0.000	
0.25	-3	8	0.005	-0.001	0.010	0.630	-0.11	-0.15	-0.07	0.000	

Table: S1.T3
MEAN SQUARE ERROR DIFFERENCE
BETWEEN FOURIER ESTIMATE AND HOURLY MEAN
N=30
SIMULATION 1

t/p ratio	initial value	peak hour	F7 -Hr	lower 95 % C.L.	Upper 95 % C.L.	prob. FS-Hr = 0	F9-Hr	Lower 95 % C.L.	Upper 95 % C.L.	prob. F9-Hr =0
0.75	-6	2	-0.69	-0.79	-0.58	0.000	-0.53	-0.62	-0.44	0.000
0.75	-3	2	-0.67	-0.83	-0.51	0.000	-0.49	-0.64	-0.34	0.000
0.50	-6	2	-0.25	-0.31	-0.19	0.000	-0.18	-0.23	-0.13	0.000
0.50	-3	2	-0.27	-0.36	-0.19	0.000	-0.16	-0.24	-0.08	0.000
0.25	-6	2	0.006	0.003	0.008	0.000	-0.03	-0.04	-0.01	0.001
0.25	-3	2	0.003	-0.002	0.008	0.875	-0.03	-0.07	-0.00	0.046
0.75	-6	4	-0.58	-0.68	-0.47	0.000	-0.45	-0.54	-0.36	0.000
0.75	-3	4	-0.75	-0.91	-0.60	0.000	-0.47	-0.61	-0.33	0.000
0.50	-6	4	-0.22	-0.28	-0.17	0.000	-0.18	-0.22	-0.13	0.000
0.50	-3	4	-0.27	-0.35	-0.18	0.000	-0.12	-0.20	-0.05	0.001
0.25	-6	4	-0.05	-0.07	-0.04	0.000	-0.04	-0.05	-0.03	0.000
0.25	-3	4	-0.09	-0.12	-0.06	0.000	-0.11	-0.15	-0.07	0.000
0.75	-6	8	-0.54	-0.64	-0.45	0.000	-0.41	-0.50	-0.33	0.000
0.75	-3	8	-0.63	-0.80	-0.47	0.000	-0.48	-0.63	-0.33	0.000
0.50	-6	8	-0.19	-0.24	-0.14	0.000	-0.15	-0.19	-0.10	0.000
0.50	-3	8	-0.22	-0.30	-0.13	0.000	-0.24	-0.31	-0.17	0.000
0.25	-6	8	-0.06	-0.07	-0.04	0.000	-0.04	-0.06	-0.03	0.000
0.25	-3	8	-0.09	-0.13	-0.06	0.000	-0.07	-0.10	-0.04	0.000

Table: S1.T4
RATIO OF MEAN SQUARE ERRORS
M.S.E. HOURLY / M.S.E. FOURIER

N=30

SIMULATION 1

t/p ratio	initial value	peak hour	MSE Hr/F3	Lower 95 %		MSE Hr/FS	Upper 95 %	
				C.L.	C.L.		C.L.	C.L.
0.75	-6	2	3.969	3.389	4.549	3.377	2.928	3.825
0.75	-3	2	2.411	2.087	2.735	1.798	1.606	1.990
0.50	-6	2	0.717	0.596	0.838	1.623	1.329	1.918
0.50	-3	2	1.074	0.928	1.220	1.551	1.346	1.755
0.25	-6	2	0.105	0.090	0.120	0.258	0.219	0.297
0.25	-3	2	0.226	0.194	0.258	0.575	0.492	0.657
0.75	-6	4	3.845	3.326	4.364	2.776	2.446	3.106
0.75	-3	4	2.585	2.210	2.961	1.866	1.663	2.069
0.50	-6	4	0.995	0.819	1.170	2.144	1.762	2.527
0.50	-3	4	1.143	0.991	1.295	1.628	1.417	1.839
0.25	-6	4	0.192	0.164	0.220	1.030	0.865	1.195
0.25	-3	4	0.427	0.361	0.492	1.233	1.048	1.419
0.75	-6	8	2.922	2.525	3.318	2.294	2.001	2.587
0.75	-3	8	2.159	1.866	2.451	1.648	1.475	1.821
0.50	-6	8	1.213	0.980	1.446	1.853	1.543	2.162
0.50	-3	8	1.380	1.205	1.554	1.389	1.246	1.532
0.25	-6	8	0.712	0.591	0.832	1.917	1.645	2.189
0.25	-3	8	0.881	0.738	1.023	1.423	1.238	1.608

Table: S1.T4
RATIO OF MEAN SQUARE ERRORS
M.S.E. HOURLY / M.S.E. FOURIER

N=30

SIMULATION 1

t/p ratio	initial value	peak hour	MSE Hr/F7	Lower 95 %		Upper 95 %		MSE Hr/F9	Lower 95 %		Upper 95 %	
				C.L	C.L	C.L	C.L		C.L	C.L		
0.75	-6	2	2.101	1.890	2.312	1.685	1.551	1.819	1.685	1.551	1.819	
0.75	-3	2	1.426	1.296	1.556	1.282	1.183	1.382	1.282	1.183	1.382	
0.50	-6	2	2.009	1.691	2.327	1.628	1.424	1.832	1.628	1.424	1.832	
0.50	-3	2	1.404	1.251	1.557	1.210	1.097	1.323	1.210	1.097	1.323	
0.25	-6	2	0.663	0.556	0.770	1.270	1.102	1.437	1.270	1.102	1.437	
0.25	-3	2	0.928	0.796	1.061	1.123	0.995	1.250	1.123	0.995	1.250	
0.75	-6	4	1.883	1.681	2.086	1.572	1.434	1.710	1.572	1.434	1.710	
0.75	-3	4	1.533	1.394	1.671	1.279	1.185	1.372	1.279	1.185	1.372	
0.50	-6	4	1.824	1.584	2.064	1.608	1.425	1.791	1.608	1.425	1.791	
0.50	-3	4	1.394	1.250	1.537	1.152	1.052	1.252	1.152	1.052	1.252	
0.25	-6	4	1.695	1.483	1.907	1.424	1.275	1.572	1.424	1.275	1.572	
0.25	-3	4	1.410	1.244	1.576	1.395	1.258	1.533	1.395	1.258	1.533	
0.75	-6	8	1.871	1.674	2.067	1.549	1.414	1.684	1.549	1.414	1.684	
0.75	-3	8	1.381	1.262	1.499	1.263	1.170	1.355	1.263	1.170	1.355	
0.50	-6	8	1.774	1.528	2.020	1.593	1.395	1.792	1.593	1.395	1.792	
0.50	-3	8	1.294	1.164	1.423	1.310	1.204	1.416	1.310	1.204	1.416	
0.25	-6	8	1.805	1.595	2.014	1.509	1.339	1.679	1.509	1.339	1.679	
0.25	-3	8	1.353	1.188	1.519	1.280	1.147	1.414	1.280	1.147	1.414	

Table: S1.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 1

t/p ratio	initial value	peak hour	N	BIAS FS-F7	Lower 95 %C.I.	Upper 95 %C.I.	prob. FS-F7=0	M.S.E. FS-F7	Lower 95 %C.I.	Upper 95 %C.I.	prob. FS-F7=0
0.75	-3	2	10	0.057	0.038	0.075	0.000	-0.033	-0.047	-0.020	0.000
0.75	-3	2	20	0.060	0.043	0.078	0.000	-0.038	-0.049	-0.026	0.000
0.75	-3	2	30	0.060	0.045	0.075	0.000	-0.033	-0.042	-0.023	0.000
0.75	-3	2	50	0.058	0.044	0.071	0.000	-0.025	-0.033	-0.018	0.000
0.75	-3	3	10	0.055	0.035	0.076	0.000	-0.035	-0.049	-0.021	0.000
0.75	-3	3	20	0.048	0.031	0.065	0.000	-0.024	-0.036	-0.013	0.000
0.75	-3	3	30	0.053	0.037	0.068	0.000	-0.029	-0.039	-0.019	0.000
0.75	-3	3	50	0.063	0.049	0.077	0.000	-0.031	-0.039	-0.022	0.000
0.75	-3	4	10	0.043	0.025	0.062	0.000	-0.031	-0.044	-0.018	0.000
0.75	-3	4	20	0.043	0.028	0.059	0.000	-0.021	-0.032	-0.011	0.000
0.75	-3	4	30	0.047	0.033	0.061	0.000	-0.025	-0.034	-0.017	0.000
0.75	-3	4	50	0.060	0.046	0.074	0.000	-0.027	-0.035	-0.019	0.000
0.75	-3	6	10	0.033	0.016	0.050	0.004	-0.016	-0.029	-0.004	0.088
0.75	-3	6	20	0.039	0.024	0.054	0.000	-0.022	-0.032	-0.012	0.001
0.75	-3	6	30	0.040	0.026	0.055	0.000	-0.024	-0.034	-0.015	0.000
0.75	-3	6	50	0.041	0.028	0.054	0.000	-0.015	-0.023	-0.008	0.000
0.75	-3	8	10	0.037	0.019	0.055	0.000	-0.022	-0.035	-0.010	0.004
0.75	-3	8	20	0.027	0.011	0.043	0.003	-0.016	-0.026	-0.006	0.027
0.75	-3	8	30	0.051	0.035	0.066	0.000	-0.027	-0.037	-0.017	0.000
0.75	-3	8	50	0.032	0.020	0.044	0.000	-0.020	-0.028	-0.011	0.002
0.50	-3	2	10	0.059	0.042	0.075	0.000	-0.005	-0.013	0.003	0.121
0.50	-3	2	20	0.067	0.052	0.082	0.000	-0.010	-0.016	-0.003	0.008
0.50	-3	2	30	0.075	0.062	0.089	0.000	-0.006	-0.013	-0.000	0.018
0.50	-3	2	50	0.086	0.074	0.097	0.000	-0.005	-0.011	0.000	0.223
0.50	-3	3	10	0.062	0.046	0.077	0.000	-0.012	-0.019	-0.005	0.001
0.50	-3	3	20	0.073	0.059	0.088	0.000	-0.007	-0.014	0.000	0.016
0.50	-3	3	30	0.066	0.053	0.078	0.000	-0.011	-0.018	-0.005	0.001

Table: S1.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 1

t/p ratio	initia l value	peak hour	N	BIAS		Lower 95 %		Upper 95 %		M.S.E.		Lower 95 %	Upper 95 %	prob.	
				FS- F7	F7	C.I.	C.I.	C.I.	C.I.	FS-F7	FS-F7	C.I.	C.I.	FS- F7	FS- F7
0.50	-3	3	50	0.076	0.076	0.065	0.088	0.000	0.000	-0.005	-0.005	-0.10	-0.00	=0	0.009
0.50	-3	4	10	0.074	0.074	0.058	0.091	0.000	0.000	-0.13	-0.13	-0.21	-0.06	0.001	0.001
0.50	-3	4	20	0.062	0.062	0.049	0.076	0.000	0.000	-0.09	-0.09	-0.15	-0.03	0.020	0.020
0.50	-3	4	30	0.086	0.086	0.073	0.100	0.000	0.000	-0.10	-0.10	-0.15	-0.04	0.001	0.001
0.50	-3	4	50	0.075	0.075	0.065	0.086	0.000	0.000	-0.14	-0.14	-0.19	-0.09	0.000	0.000
0.50	-3	6	10	0.025	0.025	0.009	0.040	0.007	0.007	-0.03	-0.03	-0.09	0.004	0.514	0.514
0.50	-3	6	20	0.038	0.038	0.025	0.052	0.000	0.000	-0.06	-0.06	-0.12	0.000	0.089	0.089
0.50	-3	6	30	0.039	0.039	0.027	0.051	0.000	0.000	-0.03	-0.03	-0.09	0.002	0.152	0.152
0.50	-3	6	50	0.031	0.031	0.022	0.041	0.000	0.000	-0.07	-0.07	-0.11	-0.03	0.001	0.001
0.50	-3	8	10	0.023	0.023	0.008	0.038	0.004	0.004	-0.11	-0.11	-0.18	-0.03	0.000	0.000
0.50	-3	8	20	0.028	0.028	0.015	0.041	0.000	0.000	-0.08	-0.08	-0.14	-0.02	0.007	0.007
0.50	-3	8	30	0.023	0.023	0.011	0.035	0.006	0.006	-0.05	-0.05	-0.10	-0.00	0.026	0.026
0.50	-3	8	50	0.024	0.024	0.013	0.034	0.000	0.000	-0.04	-0.04	-0.08	-0.00	0.008	0.008

Table: S1.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 1

t/p ratio	initial value	peak hour	N	BIAS FS-F7	Lower 95 %C.L.	Upper 95 %C.L.	prob. FS-F7=0	M.S.E. FS-F7	Lower 95 %C.L.	Upper 95 %C.L.	prob. FS-F7=0
0.25	-3	2	10	0.081	0.069	0.094	0.000	0.022	0.014	0.029	0.000
0.25	-3	2	20	0.099	0.089	0.109	0.000	0.023	0.018	0.029	0.000
0.25	-3	2	30	0.099	0.090	0.107	0.000	0.022	0.018	0.027	0.000
0.25	-3	2	50	0.093	0.086	0.100	0.000	0.023	0.019	0.026	0.000
0.25	-3	3	10	0.086	0.074	0.099	0.000	0.014	0.008	0.020	0.004
0.25	-3	3	20	0.097	0.088	0.107	0.000	0.009	0.005	0.013	0.002
0.25	-3	3	30	0.091	0.083	0.099	0.000	0.010	0.007	0.013	0.000
0.25	-3	3	50	0.096	0.089	0.103	0.000	0.015	0.012	0.018	0.000
0.25	-3	4	10	0.064	0.053	0.075	0.000	0.004	-0.001	0.008	0.633
0.25	-3	4	20	0.076	0.067	0.085	0.000	0.005	0.002	0.009	0.091
0.25	-3	4	30	0.074	0.066	0.082	0.000	0.003	0.000	0.006	0.081
0.25	-3	4	50	0.080	0.075	0.086	0.000	0.005	0.003	0.008	0.000
0.25	-3	6	10	0.026	0.016	0.035	0.000	0.003	-0.001	0.006	0.767
0.25	-3	6	20	0.029	0.021	0.036	0.000	0.002	-0.001	0.005	0.302
0.25	-3	6	30	0.030	0.023	0.036	0.000	-0.002	-0.004	-0.000	0.002
0.25	-3	6	50	0.023	0.018	0.028	0.000	-0.001	-0.002	-0.000	0.151
0.25	-3	8	10	0.005	-0.003	0.014	0.362	-0.000	-0.004	0.003	0.227
0.25	-3	8	20	0.008	0.001	0.016	0.212	-0.001	-0.004	0.001	0.202
0.25	-3	8	30	0.006	-0.000	0.011	0.251	-0.001	-0.003	0.000	0.019
0.25	-3	8	50	0.005	0.000	0.010	0.110	-0.001	-0.002	-0.000	0.026
0.75	-6	2	10	0.061	0.046	0.076	0.000	-0.028	-0.037	-0.019	0.000
0.75	-6	2	20	0.062	0.050	0.075	0.000	-0.025	-0.032	-0.019	0.000
0.75	-6	2	30	0.072	0.061	0.083	0.000	-0.024	-0.029	-0.018	0.000
0.75	-6	2	50	0.060	0.052	0.069	0.000	-0.014	-0.017	-0.011	0.000
0.75	-6	3	10	0.056	0.040	0.071	0.000	-0.027	-0.037	-0.018	0.000
0.75	-6	3	20	0.055	0.045	0.066	0.000	-0.020	-0.026	-0.015	0.000
0.75	-6	3	30	0.059	0.049	0.069	0.000	-0.019	-0.024	-0.015	0.000

Table: S1.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 1

t/p ratio	initia l value	peak hour	N	BIAS		Lower 95 %		Upper 95 %		prob.		M.S.E. FS-F7		Lower 95 % C.I.		Upper 95 % C.I.		prob. FS-F7	
				FS-F7	F7	C.I.	C.I.	C.I.	C.I.	FS-F7	F7	FS-F7	F7	C.I.	C.I.	FS-F7	F7	FS-F7	F7
0.75	-6	3	50	0.069	0.060	0.060	0.078	0.000	0.000	-0.13	-0.17	-0.10	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	4	10	0.061	0.047	0.047	0.076	0.000	0.000	-0.42	-0.51	-0.33	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	4	20	0.046	0.034	0.034	0.058	0.000	0.000	-0.23	-0.30	-0.16	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	4	30	0.054	0.044	0.044	0.064	0.000	0.000	-0.21	-0.27	-0.15	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	4	50	0.056	0.047	0.047	0.065	0.000	0.000	-0.15	-0.18	-0.12	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	6	10	0.041	0.028	0.028	0.053	0.000	0.000	-0.22	-0.30	-0.13	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	6	20	0.053	0.041	0.041	0.065	0.000	0.000	-0.28	-0.35	-0.21	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	6	30	0.042	0.032	0.032	0.051	0.000	0.000	-0.15	-0.19	-0.10	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	6	50	0.048	0.039	0.039	0.057	0.000	0.000	-0.14	-0.17	-0.11	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	8	10	0.047	0.033	0.033	0.062	0.000	0.000	-0.27	-0.37	-0.17	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	8	20	0.038	0.027	0.027	0.049	0.000	0.000	-0.17	-0.23	-0.11	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	8	30	0.035	0.026	0.026	0.045	0.000	0.000	-0.11	-0.16	-0.07	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000
0.75	-6	8	50	0.029	0.020	0.020	0.037	0.000	0.000	-0.09	-0.12	-0.05	0.000	-0.000	-0.000	0.000	0.000	0.000	0.000

Table: S1.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 1

t/p ratio	initial value	peak hour	N	BIAS F5-F7	Lower 95 %C.I.	Upper 95 %C.I.	prob. FS-F7=0	M.S.E. FS-F7	Lower 95 %C.I.	Upper 95 %C.I.	prob. FS-F7=0
0.50	-6	2	10	0.075	0.062	0.088	0.000	0.000	-0.005	0.005	0.748
0.50	-6	2	20	0.081	0.071	0.091	0.000	0.007	0.002	0.011	0.009
0.50	-6	2	30	0.075	0.066	0.083	0.000	0.006	0.003	0.009	0.000
0.50	-6	2	50	0.071	0.064	0.078	0.000	0.008	0.006	0.011	0.000
0.50	-6	3	10	0.085	0.073	0.096	0.000	-0.14	-0.20	-0.09	0.000
0.50	-6	3	20	0.073	0.063	0.083	0.000	-0.07	-0.11	-0.03	0.001
0.50	-6	3	30	0.071	0.063	0.079	0.000	-0.01	-0.03	0.002	0.969
0.50	-6	3	50	0.073	0.067	0.080	0.000	0.002	-0.01	0.004	0.029
0.50	-6	4	10	0.071	0.058	0.083	0.000	-0.13	-0.19	-0.08	0.000
0.50	-6	4	20	0.075	0.066	0.084	0.000	-0.04	-0.08	0.000	0.006
0.50	-6	4	30	0.071	0.064	0.079	0.000	-0.04	-0.07	-0.01	0.001
0.50	-6	4	50	0.064	0.057	0.070	0.000	0.000	-0.02	0.002	0.744
0.50	-6	6	10	0.042	0.032	0.053	0.000	-0.11	-0.16	-0.07	0.000
0.50	-6	6	20	0.032	0.024	0.039	0.000	-0.04	-0.07	-0.01	0.032
0.50	-6	6	30	0.031	0.024	0.038	0.000	-0.03	-0.06	-0.01	0.052
0.50	-6	6	50	0.024	0.019	0.029	0.000	-0.01	-0.03	0.000	0.037
0.50	-6	8	10	0.031	0.020	0.042	0.000	-0.00	-0.05	0.004	0.659
0.50	-6	8	20	0.021	0.013	0.029	0.000	-0.02	-0.05	0.001	0.051
0.50	-6	8	30	0.016	0.009	0.023	0.000	-0.01	-0.03	0.001	0.208
0.50	-6	8	50	0.014	0.009	0.019	0.001	-0.01	-0.02	0.001	0.018
0.25	-6	2	10	0.097	0.089	0.105	0.000	0.022	0.018	0.026	0.000
0.25	-6	2	20	0.098	0.093	0.104	0.000	0.027	0.024	0.029	0.000
0.25	-6	2	30	0.096	0.091	0.101	0.000	0.026	0.024	0.028	0.000
0.25	-6	2	50	0.098	0.094	0.102	0.000	0.027	0.026	0.029	0.000
0.25	-6	3	10	0.100	0.093	0.107	0.000	0.012	0.009	0.015	0.000
0.25	-6	3	20	0.100	0.094	0.106	0.000	0.016	0.014	0.018	0.000
0.25	-6	3	30	0.100	0.095	0.105	0.000	0.015	0.013	0.017	0.000

Table: S1.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 1

t/p ratio	initial value	peak hour	N	BIAS FS-F7	Lower 95% C.I.	Upper 95% C.I.	prob. FS-F7	M.S.E. FS-F7	Lower 95% C.I.	Upper 95% C.I.	prob. FS-F7
0.25	-6	3	50	0.100	0.096	0.103	0.000	0.015	0.014	0.016	0.000
0.25	-6	4	10	0.076	0.070	0.083	0.000	0.004	0.001	0.006	0.008
0.25	-6	4	20	0.081	0.076	0.085	0.000	0.005	0.003	0.007	0.000
0.25	-6	4	30	0.080	0.076	0.084	0.000	0.005	0.004	0.006	0.000
0.25	-6	4	50	0.080	0.077	0.083	0.000	0.006	0.004	0.007	0.000
0.25	-6	6	10	0.028	0.024	0.032	0.000	-0.000	-0.001	0.001	0.405
0.25	-6	6	20	0.030	0.027	0.033	0.000	0.000	-0.000	0.001	0.312
0.25	-6	6	30	0.025	0.023	0.028	0.000	-0.000	-0.001	0.000	0.901
0.25	-6	6	50	0.024	0.023	0.026	0.000	0.000	-0.000	0.000	0.012

Table S1.T6
COMPARISON OF 5 AND 7 TERM FOURIER T/P ESTIMATORS
MINIMUM M.S.E. OVER ALL SAMPLE SIZES TESTED
SIMULATION 1

t/p ratio	initial value	peak hour	Minimum * M.S.E.	F5 M.S.E. ** LT HR	F7 M.S.E. ** LT HR
0.75	-3	2	5	Y	Y
0.75	-3	3	5	Y	Y
0.75	-3	4	5	Y	Y
0.75	-3	6	5	Y	Y
0.75	-3	8	5	Y	Y
0.50	-3	2	E	Y	Y
0.50	-3	3	5	Y	Y
0.50	-3	4	5	Y	Y
0.50	-3	6	E	Y	Y
0.50	-3	8	5	Y	Y
0.25	-3	2	7	N	E
0.25	-3	3	7	E	Y
0.25	-3	4	E	E	E
0.25	-3	6	E	E	E
0.25	-3	8	E	Y	Y
0.75	-6	2	5	Y	Y
0.75	-6	3	5	Y	Y
0.75	-6	4	5	Y	Y
0.75	-6	6	5	Y	Y
0.75	-6	8	5	Y	Y
0.50	-6	2	7	Y	Y
0.50	-6	3	E	Y	Y
0.50	-6	4	5	Y	Y
0.50	-6	6	E	Y	Y
0.50	-6	8	E	Y	Y
0.25	-6	2	7	N	E
0.25	-6	3	7	N	Y
0.25	-6	4	7	E	Y
0.25	-6	6	E	Y	Y

* 5 - 5 Term fourier T/P estimator

7 - 7 Term fourier T/P estimator

E - 5 Term fourier M.S.E. = 7 Term fourier M.S.E.

** Y: Yes

N: No

E: M.S.E's equal

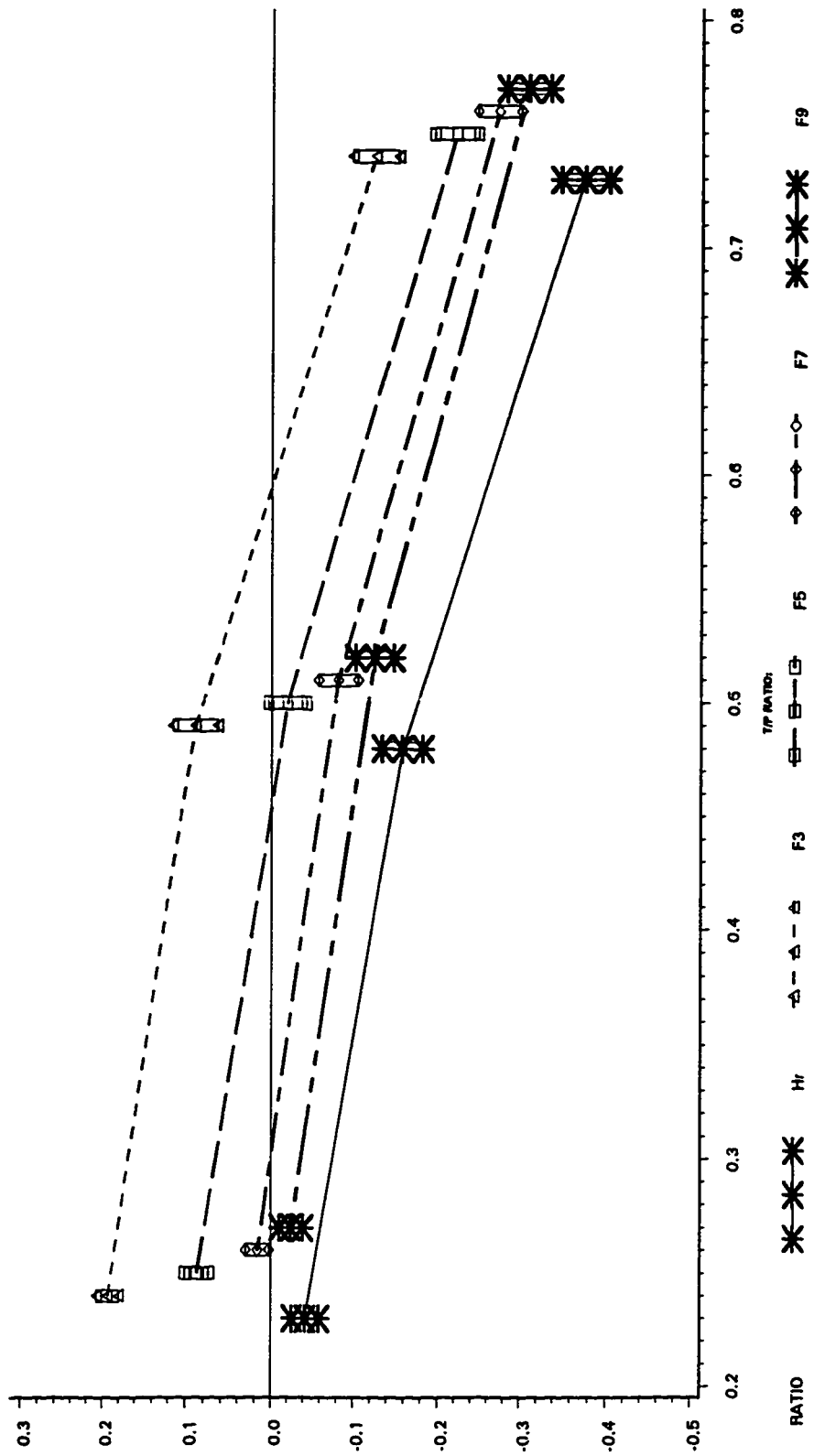


FIGURE: S2.F1: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 2
INITIAL VALUE= -3 N= 30

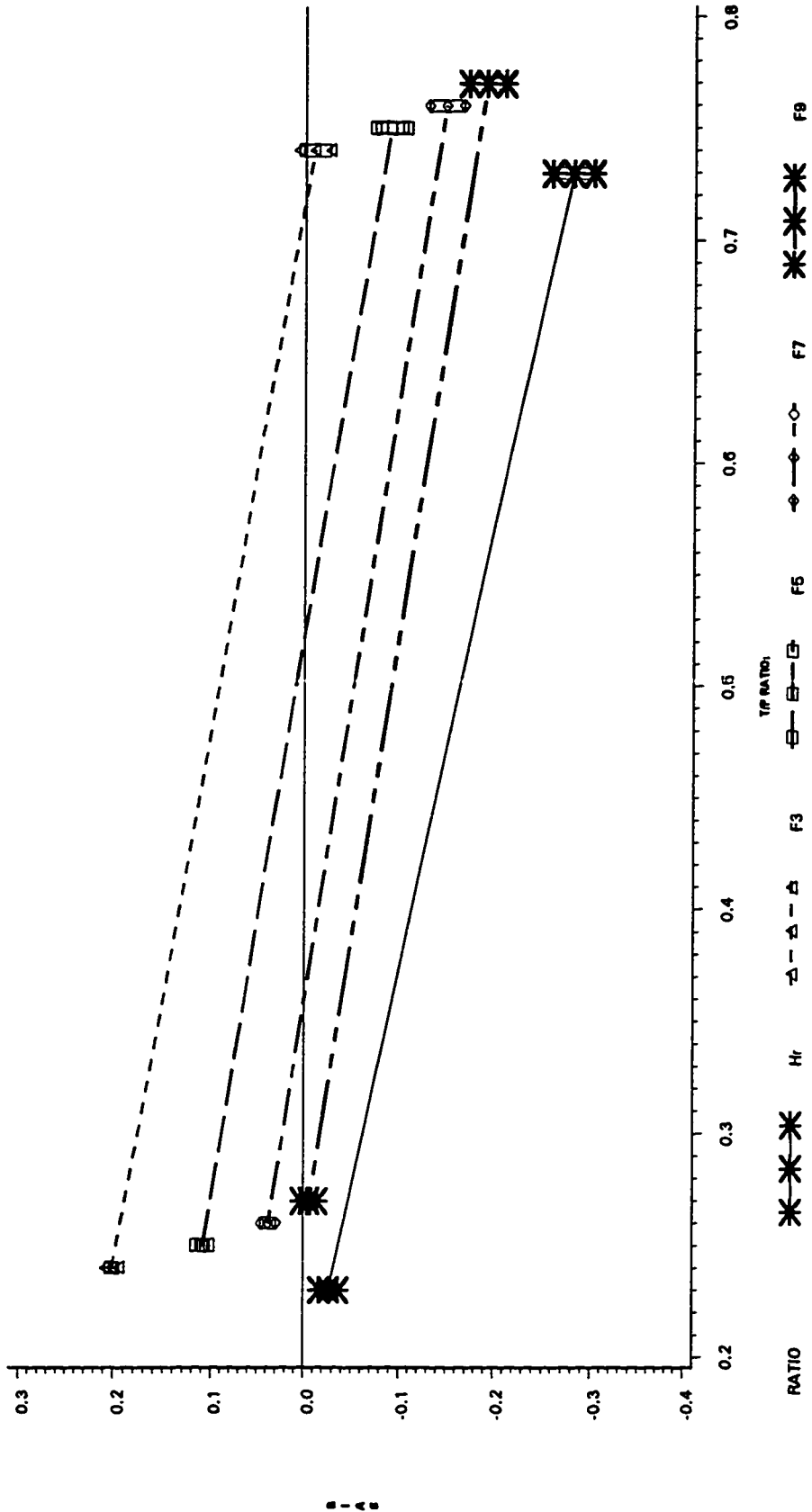


FIGURE: S2.F2: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 2
INITIAL VALUE= -6 N= 30

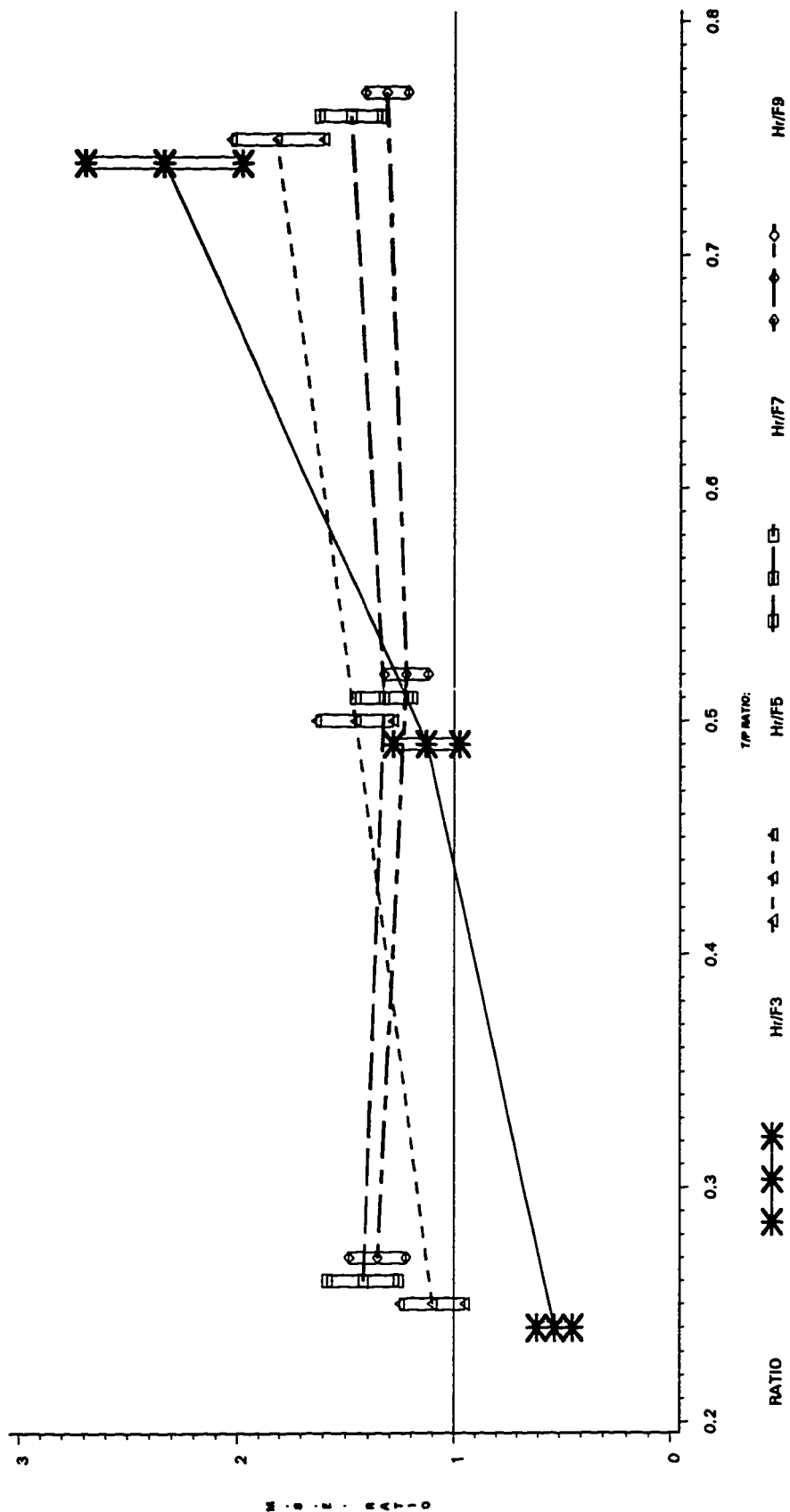


FIGURE: S2.F3: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 2
INITIAL VALUE = -3 N = 30

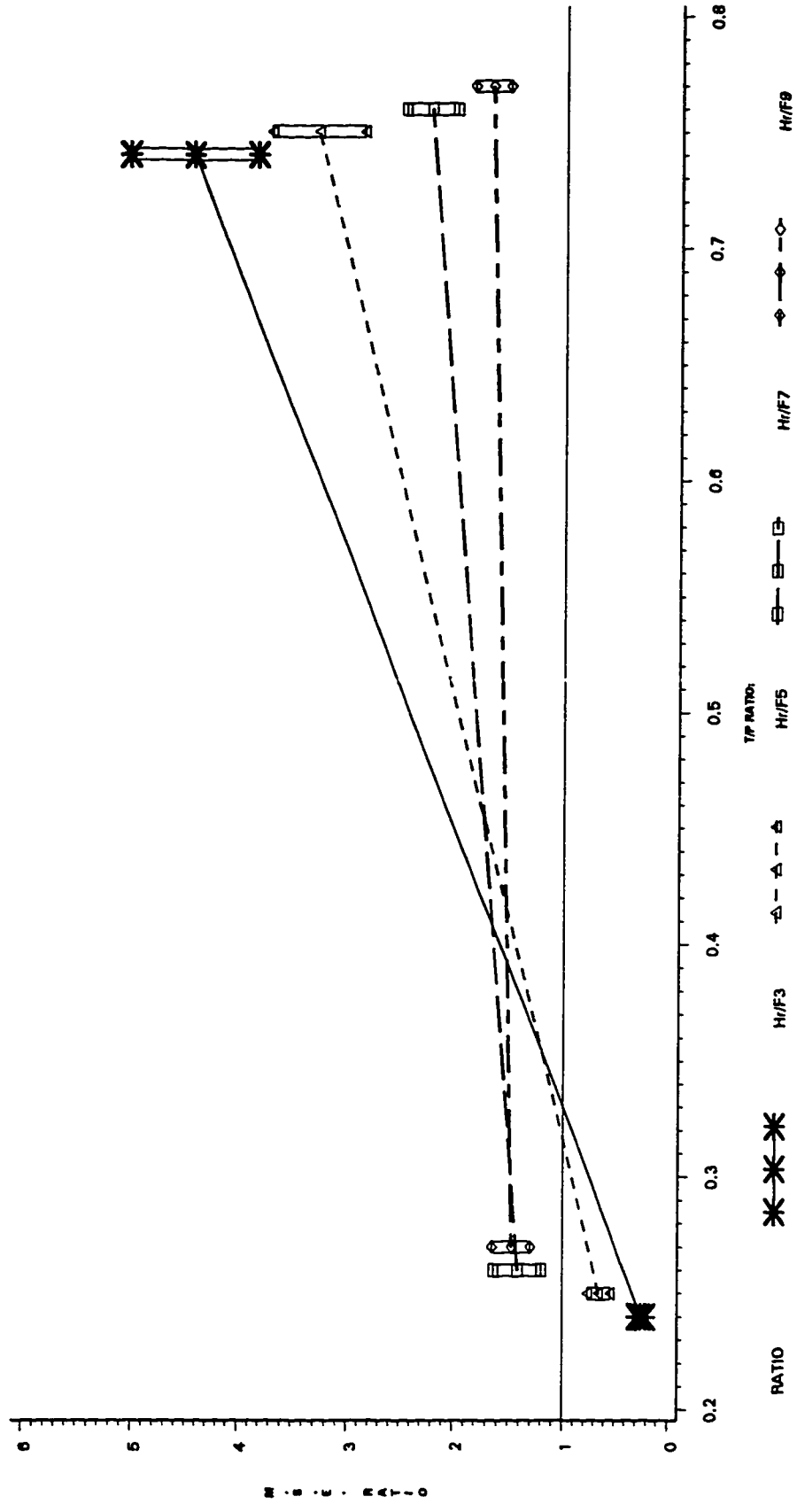


FIGURE: S2.F4: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 2
INITIAL VALUE = -6 N = 30

Table S2.T1
BIAS ESTIMATE
SIMULATION 2

t/p actual	initial value	N	F3 bias	Lower 95 % C.I	Upper 95 % C.I	F5 bias	Lower 95 % C.I	Upper 95 % C.I	F7 bias	Lower 95 % C.I	Upper 95 % C.I
0.75	-3	10	-.205	-.240	-.169	-.293	-.325	-.261			
0.75	-3	20	-.146	-.178	-.115	-.256	-.286	-.226			
0.75	-3	30	-.125	-.152	-.097	-.221	-.247	-.194			
0.75	-3	50	-.070	-.094	-.046	-.174	-.197	-.152			
0.50	-3	10	-.008	-.041	0.024	-.100	-.130	-.070			
0.50	-3	20	0.057	0.030	0.085	-.056	-.082	-.030			
0.50	-3	30	0.090	0.064	0.115	-.020	-.044	0.003			
0.50	-3	50	0.104	0.082	0.125	0.014	-.006	0.035			
0.25	-3	10	0.163	0.140	0.186	0.069	0.049	0.089			
0.25	-3	20	0.193	0.176	0.210	0.089	0.073	0.105			
0.25	-3	30	0.193	0.180	0.207	0.087	0.074	0.101			
0.25	-3	50	0.201	0.190	0.212	0.103	0.092	0.113			
0.75	-6	10	-.107	-.125	-.089	-.221	-.246	-.196			
0.75	-6	20	-.038	-.052	-.023	-.143	-.164	-.121			
0.75	-6	30	-.018	-.030	-.005	-.090	-.107	-.073			
0.75	-6	50	0.023	0.012	0.033	-.063	-.079	-.048			
0.25	-6	10	0.197	0.185	0.209	0.099	0.087	0.112			
0.25	-6	20	0.197	0.189	0.206	0.102	0.094	0.110			
0.25	-6	30	0.201	0.194	0.208	0.108	0.101	0.116			
0.25	-6	50	0.199	0.194	0.205	0.116	0.111	0.122			
0.75	-3	10	-.339	-.371	-.307	-.361	-.393	-.330	-.416	-.446	-.385
0.75	-3	20	-.304	-.333	-.274	-.333	-.363	-.304	-.429	-.457	-.402
0.75	-3	30	-.273	-.299	-.246	-.309	-.335	-.283	-.375	-.403	-.348
0.75	-3	50	-.234	-.258	-.211	-.273	-.298	-.248	-.350	-.375	-.324
0.50	-3	10	-.149	-.178	-.121	-.185	-.213	-.156	-.235	-.262	-.208
0.50	-3	20	-.118	-.145	-.092	-.163	-.189	-.138	-.214	-.239	-.188
0.50	-3	30	-.081	-.105	-.058	-.125	-.148	-.102	-.158	-.182	-.134
0.50	-3	50	-.055	-.076	-.035	-.093	-.114	-.072	-.167	-.189	-.145
0.25	-3	10	0.008	-.012	0.028	-.024	-.043	-.005	-.039	-.059	-.019
0.25	-3	20	0.018	0.000	0.035	-.024	-.040	-.008	-.049	-.066	-.032
0.25	-3	30	0.016	0.002	0.030	-.025	-.040	-.011	-.043	-.059	-.027
0.25	-3	50	0.023	0.012	0.034	-.022	-.034	-.011	-.039	-.052	-.025
0.75	-6	10	-.271	-.297	-.244	-.294	-.313	-.276	-.385	-.404	-.367
0.75	-6	20	-.209	-.232	-.186	-.240	-.256	-.224	-.332	-.349	-.315
0.75	-6	30	-.148	-.166	-.130	-.198	-.212	-.184	-.278	-.294	-.263
0.75	-6	50	-.112	-.128	-.096	-.141	-.153	-.129	-.222	-.236	-.208
0.25	-6	10	0.020	0.007	0.033	-.020	-.034	-.007	-.045	-.060	-.031
0.25	-6	20	0.028	0.019	0.037	-.018	-.027	-.008	-.040	-.052	-.029
0.25	-6	30	0.037	0.029	0.045	-.006	-.015	0.002	-.027	-.037	-.017
0.25	-6	50	0.046	0.040	0.053	0.00	-.006	0.007	-.018	-.027	-.009

Table: S2.T2
BIAS DIFFERENCE BETWEEN FOURIER ESTIMATE AND HOURLY
MEAN
SIMULATION 2

t/p actual	initial value	N	F3- Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F3- Hr=0	F5- Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F5- Hr=0
0.75	-3	10	0.211	0.177	0.246	0.000	0.123	0.096	0.150	0.000
0.75	-3	20	0.283	0.253	0.313	0.000	0.173	0.148	0.198	0.000
0.75	-3	30	0.250	0.219	0.282	0.000	0.154	0.128	0.181	0.000
0.75	-3	50	0.280	0.253	0.307	0.000	0.175	0.154	0.196	0.000
0.50	-3	10	0.227	0.198	0.256	0.000	0.135	0.112	0.159	0.000
0.50	-3	20	0.271	0.244	0.298	0.000	0.158	0.135	0.180	0.000
0.50	-3	30	0.248	0.223	0.273	0.000	0.138	0.116	0.159	0.000
0.50	-3	50	0.271	0.249	0.293	0.000	0.181	0.163	0.200	0.000
0.25	-3	10	0.202	0.180	0.224	0.000	0.108	0.092	0.124	0.000
0.25	-3	20	0.242	0.224	0.259	0.000	0.138	0.124	0.151	0.000
0.25	-3	30	0.236	0.221	0.252	0.000	0.130	0.118	0.143	0.000
0.25	-3	50	0.240	0.227	0.252	0.000	0.141	0.131	0.152	0.000
0.75	-6	10	0.278	0.258	0.297	0.000	0.174	0.150	0.197	0.000
0.75	-6	20	0.294	0.277	0.311	0.000	0.197	0.177	0.216	0.000
0.75	-6	30	0.261	0.245	0.276	0.000	0.191	0.173	0.208	0.000
0.75	-6	50	0.245	0.231	0.258	0.000	0.168	0.153	0.184	0.000
0.25	-6	10	0.242	0.229	0.255	0.000	0.145	0.134	0.156	0.000
0.25	-6	20	0.238	0.228	0.248	0.000	0.143	0.134	0.151	0.000
0.25	-6	30	0.228	0.219	0.237	0.000	0.135	0.128	0.143	0.000
0.25	-6	50	0.217	0.210	0.224	0.000	0.134	0.128	0.141	0.000

t/p actual	initial value	N	F7-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F7-Hr =0	F9- Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F9-Hr =0
0.75	-3	10	0.077	0.054	0.100	0.000	0.054	0.034	0.075	0.000
0.75	-3	20	0.126	0.102	0.149	0.000	0.096	0.075	0.117	0.000
0.75	-3	30	0.102	0.078	0.127	0.000	0.066	0.046	0.086	0.000
0.75	-3	50	0.115	0.096	0.134	0.000	0.076	0.059	0.094	0.000
0.50	-3	10	0.086	0.066	0.106	0.000	0.051	0.032	0.069	0.000
0.50	-3	20	0.095	0.075	0.115	0.000	0.050	0.033	0.068	0.000
0.50	-3	30	0.077	0.057	0.096	0.000	0.033	0.018	0.048	0.000
0.50	-3	50	0.112	0.096	0.127	0.000	0.074	0.060	0.089	0.000
0.25	-3	10	0.048	0.033	0.062	0.000	0.015	0.002	0.028	0.049
0.25	-3	20	0.067	0.054	0.079	0.000	0.025	0.014	0.036	0.000
0.25	-3	30	0.059	0.048	0.070	0.000	0.018	0.008	0.027	0.000
0.25	-3	50	0.062	0.052	0.071	0.000	0.016	0.008	0.025	0.000
0.75	-6	10	0.124	0.104	0.144	0.000	0.091	0.078	0.104	0.000
0.75	-6	20	0.131	0.113	0.149	0.000	0.092	0.081	0.103	0.000
0.75	-6	30	0.132	0.116	0.149	0.000	0.081	0.070	0.091	0.000
0.75	-6	50	0.120	0.106	0.134	0.000	0.081	0.072	0.089	0.000
0.25	-6	10	0.065	0.055	0.076	0.000	0.025	0.016	0.034	0.000
0.25	-6	20	0.069	0.061	0.077	0.000	0.023	0.016	0.030	0.000
0.25	-6	30	0.064	0.058	0.071	0.000	0.021	0.015	0.027	0.000
0.25	-6	50	0.064	0.059	0.070	0.000	0.018	0.014	0.023	0.000

Table: S2.T3
MEAN SQUARE ERROR DIFFERENCE
BETWEEN FOURIER ESTIMATE AND HOURLY MEAN
SIMULATION 2

t/p actual	initial value	N	F3-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F3-Hr =0	F5-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F5-Hr =0
0.75	-3	10	-.095	-.117	-.072	0.000	-.076	-.095	-.057	0.000
0.75	-3	20	-.138	-.159	-.118	0.000	-.104	-.122	-.086	0.000
0.75	-3	30	-.125	-.146	-.104	0.000	-.098	-.117	-.080	0.000
0.75	-3	50	-.127	-.145	-.110	0.000	-.108	-.123	-.093	0.000
0.50	-3	10	-.020	-.032	-.008	0.001	-.027	-.037	-.016	0.000
0.50	-3	20	-.032	-.044	-.020	0.000	-.037	-.047	-.028	0.000
0.50	-3	30	-.010	-.021	0.001	0.226	-.027	-.035	-.018	0.000
0.50	-3	50	-.021	-.031	-.010	0.000	-.035	-.043	-.026	0.000
0.25	-3	10	0.039	0.027	0.050	0.000	0.006	-.001	0.012	0.570
0.25	-3	20	0.034	0.026	0.042	0.000	0.001	-.003	0.006	0.236
0.25	-3	30	0.027	0.020	0.034	0.000	-.003	-.007	0.001	0.123
0.25	-3	50	0.033	0.027	0.038	0.000	0.002	-.002	0.005	0.483
0.75	-6	10	-.144	-.157	-.131	0.000	-.114	-.132	-.097	0.000
0.75	-6	20	-.124	-.136	-.113	0.000	-.107	-.121	-.093	0.000
0.75	-6	30	-.098	-.107	-.089	0.000	-.088	-.099	-.077	0.000
0.75	-6	50	-.067	-.074	-.060	0.000	-.066	-.076	-.057	0.000
0.25	-6	10	0.030	0.024	0.037	0.000	0.001	-.003	0.005	0.860
0.25	-6	20	0.030	0.026	0.034	0.000	0.001	-.002	0.003	0.160
0.25	-6	30	0.034	0.031	0.038	0.000	0.006	0.004	0.008	0.000
0.25	-6	50	0.035	0.032	0.037	0.000	0.009	0.007	0.010	0.000
t/p actual	initial value	N	F7-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F7-Hr =0	F9-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F9-Hr =0
0.75	-3	10	-.048	-.064	-.031	0.000	-.037	-.053	-.022	0.000
0.75	-3	20	-.082	-.098	-.065	0.000	-.061	-.076	-.045	0.000
0.75	-3	30	-.071	-.087	-.054	0.000	-.052	-.067	-.038	0.000
0.75	-3	50	-.078	-.092	-.064	0.000	-.054	-.067	-.042	0.000
0.50	-3	10	-.022	-.031	-.012	0.000	-.011	-.020	-.003	0.013
0.50	-3	20	-.028	-.037	-.018	0.000	-.017	-.025	-.009	0.000
0.50	-3	30	-.021	-.028	-.014	0.000	-.016	-.022	-.009	0.000
0.50	-3	50	-.031	-.038	-.024	0.000	-.023	-.030	-.016	0.000
0.25	-3	10	-.001	-.006	0.005	0.172	-.004	-.008	0.000	0.048
0.25	-3	20	-.003	-.007	0.001	0.000	-.006	-.009	-.003	0.000
0.25	-3	30	-.009	-.012	-.006	0.000	-.008	-.011	-.005	0.000
0.25	-3	50	-.007	-.009	-.005	0.000	-.007	-.009	-.005	0.000
0.75	-6	10	-.082	-.097	-.066	0.000	-.065	-.075	-.055	0.000
0.75	-6	20	-.078	-.091	-.066	0.000	-.057	-.065	-.050	0.000
0.75	-6	30	-.069	-.079	-.060	0.000	-.050	-.056	-.043	0.000
0.75	-6	50	-.056	-.065	-.047	0.000	-.040	-.045	-.035	0.000
0.25	-6	10	-.005	-.008	-.003	0.000	-.005	-.007	-.003	0.000
0.25	-6	20	-.007	-.009	-.005	0.000	-.007	-.009	-.006	0.000
0.25	-6	30	-.003	-.005	-.002	0.002	-.004	-.005	-.002	0.000
0.25	-6	50	-.002	-.003	-.001	0.213	-.003	-.004	-.003	0.000

Table: S2.T4
RATIO OF MEAN SQUARE ERRORS
MSE HOURLY / MSE FOURIER
SIMULATION 2

t/p actual	initial value	N	MSE Hr/F3	Lower 95 % C.I	Upper 95 % C.I	MSE Hr/F5	Lower 95 % C.I	Upper 95 % C.I
0.75	-3	10	1.542	1.371	1.713	1.393	1.274	1.513
0.75	-3	20	2.114	1.842	2.385	1.657	1.501	1.813
0.75	-3	30	2.334	1.976	2.692	1.815	1.601	2.029
0.75	-3	50	2.955	2.480	3.431	2.278	2.002	2.555
0.50	-3	10	1.185	1.066	1.305	1.261	1.143	1.379
0.50	-3	20	1.399	1.225	1.572	1.499	1.336	1.662
0.50	-3	30	1.129	0.973	1.284	1.460	1.286	1.633
0.50	-3	50	1.362	1.154	1.569	1.784	1.534	2.034
0.25	-3	10	0.522	0.435	0.609	0.884	0.753	1.016
0.25	-3	20	0.494	0.423	0.564	0.960	0.824	1.096
0.25	-3	30	0.522	0.440	0.605	1.102	0.949	1.255
0.25	-3	50	0.382	0.325	0.438	0.927	0.782	1.072
0.75	-6	10	2.856	2.554	3.158	1.999	1.776	2.223
0.75	-6	20	3.748	3.324	4.172	2.560	2.262	2.857
0.75	-6	30	4.100	3.666	4.533	3.290	2.867	3.713
0.75	-6	50	3.884	3.471	4.297	3.301	2.877	3.724
0.25	-6	10	0.443	0.378	0.508	0.958	0.813	1.103
0.25	-6	20	0.352	0.300	0.404	0.967	0.807	1.127
0.25	-6	30	0.245	0.207	0.283	0.652	0.542	0.762
0.25	-6	50	0.188	0.159	0.217	0.481	0.400	0.562

t/p actual	initial value	N	MSE Hr/F7	Lower 95 % C.I	Upper 95 % C.I	MSE Hr/F9	Lower 95 % C.I	Upper 95 % C.I
0.75	-3	10	1.216	1.132	1.300	1.160	1.088	1.233
0.75	-3	20	1.452	1.334	1.570	1.301	1.212	1.390
0.75	-3	30	1.480	1.340	1.619	1.316	1.216	1.415
0.75	-3	50	1.685	1.521	1.849	1.394	1.287	1.502
0.50	-3	10	1.199	1.102	1.297	1.095	1.019	1.171
0.50	-3	20	1.325	1.201	1.449	1.180	1.089	1.270
0.50	-3	30	1.327	1.194	1.459	1.224	1.122	1.327
0.50	-3	50	1.654	1.460	1.849	1.405	1.259	1.551
0.25	-3	10	1.014	0.885	1.144	1.106	0.985	1.226
0.25	-3	20	1.096	0.947	1.246	1.220	1.100	1.340
0.25	-3	30	1.421	1.260	1.582	1.355	1.224	1.486
0.25	-3	50	1.557	1.339	1.774	1.510	1.333	1.688
0.75	-6	10	1.558	1.423	1.692	1.415	1.338	1.492
0.75	-6	20	1.805	1.635	1.975	1.507	1.424	1.589
0.75	-6	30	2.229	1.991	2.467	1.627	1.526	1.729
0.75	-6	50	2.436	2.182	2.689	1.795	1.680	1.910
0.25	-6	10	1.286	1.126	1.446	1.232	1.115	1.349
0.25	-6	20	1.739	1.486	1.992	1.799	1.597	2.001
0.25	-6	30	1.413	1.196	1.630	1.471	1.298	1.643
0.25	-6	50	1.321	1.092	1.549	1.725	1.520	1.930

Table: S2.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 2

t/p ratio	initial value	N	BIAS F5-F7	Lower 95 % C.I	Upper 95 % C.I	prob. F5-F7 =0	M.S.E. F5-F7	Lower 95 % C.I	Upper 95 % C.I	prob. F5-F7 =0
0.75	-3	10	0.046	0.029	0.062	0.000	-.028	-.040	-.016	0.000
0.75	-3	20	0.048	0.033	0.063	0.000	-.022	-.032	-.013	0.000
0.75	-3	30	0.052	0.036	0.068	0.000	-.027	-.038	-.017	0.000
0.75	-3	50	0.060	0.048	0.072	0.000	-.030	-.037	-.022	0.000
0.50	-3	10	0.050	0.036	0.063	0.000	-.005	-.012	0.001	0.101
0.50	-3	20	0.062	0.050	0.075	0.000	-.010	-.016	-.004	0.000
0.50	-3	30	0.061	0.048	0.074	0.000	-.006	-.011	-.000	0.216
0.50	-3	50	0.070	0.059	0.080	0.000	-.003	-.008	0.001	0.028
0.25	-3	10	0.060	0.050	0.071	0.000	0.006	0.001	0.011	0.370
0.25	-3	20	0.071	0.064	0.079	0.000	0.004	0.001	0.007	0.053
0.25	-3	30	0.071	0.065	0.077	0.000	0.006	0.004	0.008	0.000
0.25	-3	50	0.080	0.074	0.085	0.000	0.009	0.007	0.011	0.000
0.75	-6	10	0.052	0.043	0.062	0.000	-.027	-.033	-.022	0.000
0.75	-6	20	0.060	0.052	0.068	0.000	-.025	-.030	-.021	0.000
0.75	-6	30	0.057	0.051	0.064	0.000	-.019	-.022	-.015	0.000
0.75	-6	50	0.049	0.043	0.055	0.000	-.010	-.012	-.008	0.000
0.25	-6	10	0.079	0.073	0.086	0.000	0.006	0.004	0.009	0.000
0.25	-6	20	0.074	0.069	0.079	0.000	0.007	0.006	0.009	0.000
0.25	-6	30	0.071	0.067	0.075	0.000	0.009	0.008	0.011	0.000
0.25	-6	50	0.070	0.067	0.073	0.000	0.011	0.010	0.012	0.000

Table S2.T6
COMPARISON OF 5 AND 7 TERM FOURIER T/P ESTIMATORS
MINIMUM M.S.E. OVER ALL SAMPLE SIZES TESTED

SIMULATION 2

t/p ratio	initial value	Minimum * M.S.E.	5 Term M.S.E. ** LT H.M.	7 Term M.S.E. ** LT H.M.
0.75	-6	5	Y	Y
0.75	-3	5	Y	Y
0.50	-3	E	Y	Y
0.25	-6	7	E	Y
0.25	-3	E	E	Y

* 5 - 5 Term fourier T/P estimator

7 - 7 Term fourier T/P estimator

E - 5 Term fourier M.S.E. = 7 Term fourier M.S.E.

** Y: Yes

N: No

E: M.S.E's equal

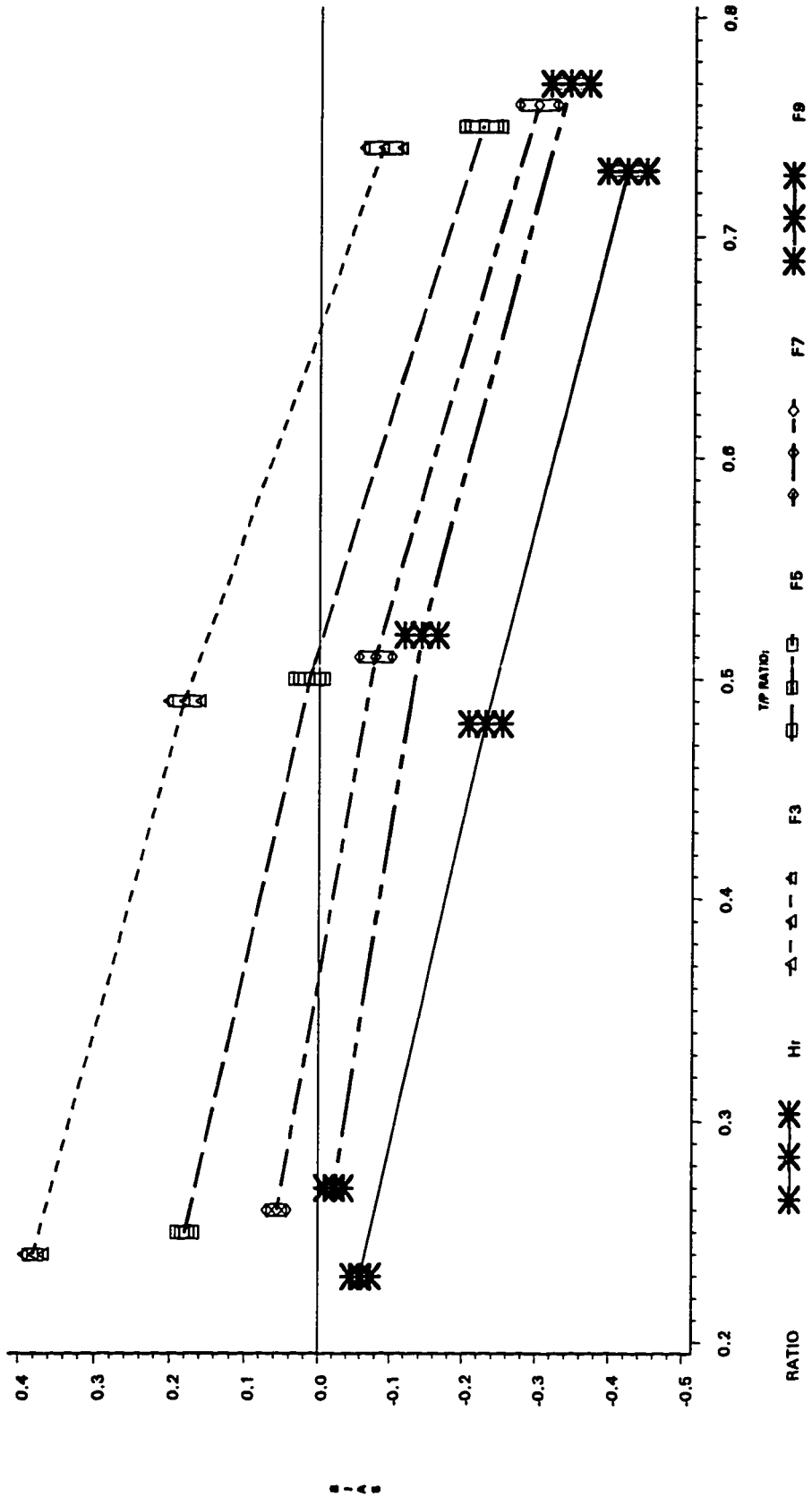


FIGURE: S3.F1: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 3

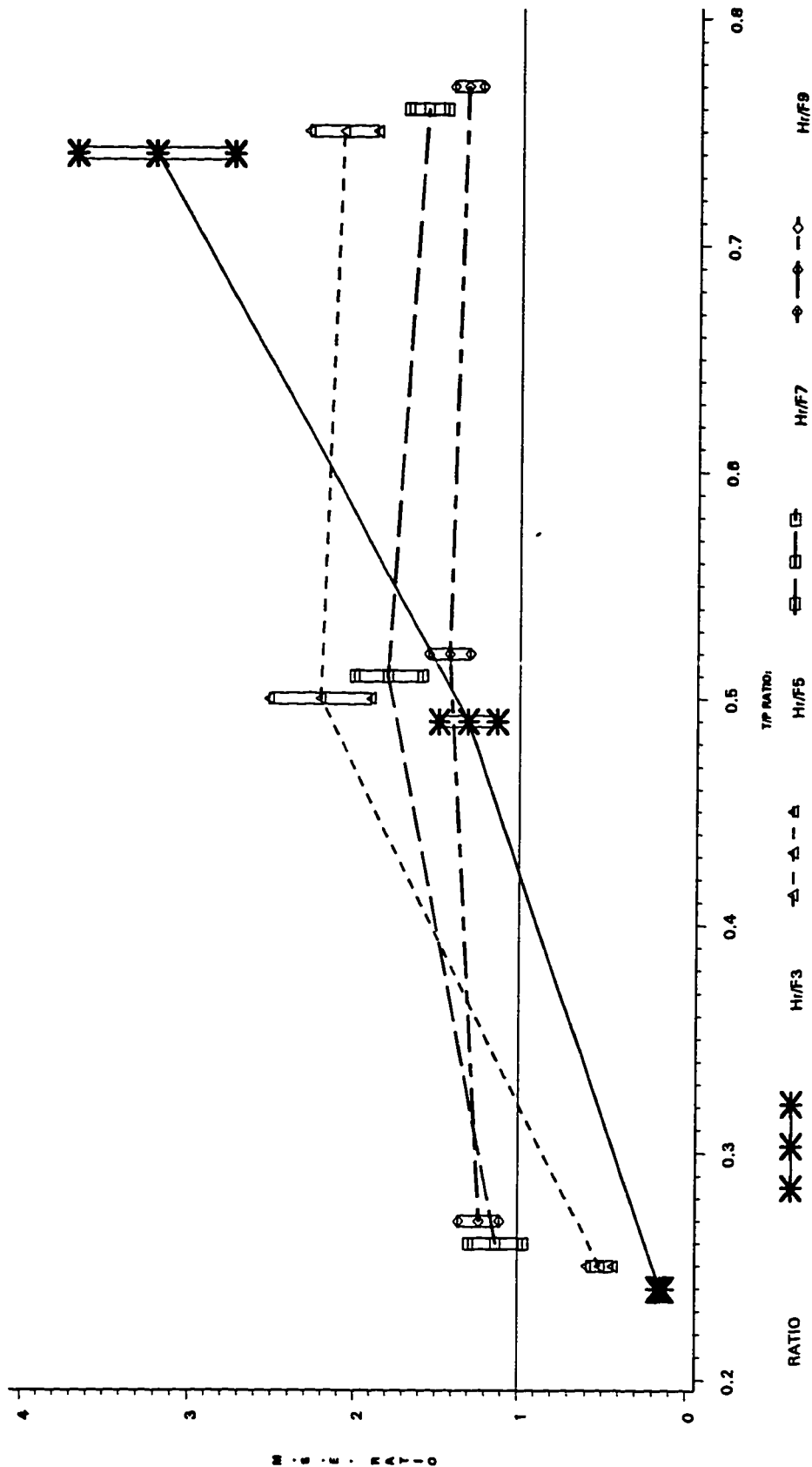


FIGURE: S3.F2: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 3
INITIAL VALUE = -3 N = 30

Table: S3.T1
BIAS ESTIMATE
SIMULATION 3

t/p actual	initial value	N	F3 bias	Lower 95 % C.I.	Upper 95 % C.I.	F5 bias	Lower 95 % C.I.	Upper 95 % C.I.			
0.75	-3	10	-206	-239	-172	-317	-348	-285			
0.75	-3	20	-143	-174	-113	-242	-271	-213			
0.75	-3	30	-087	-113	-061	-225	-250	-199			
0.75	-3	50	-025	-048	-003	-132	-154	-110			
0.50	-3	10	0.071	0.040	0.102	-070	-100	-041			
0.50	-3	20	0.153	0.128	0.178	-005	-030	0.019			
0.50	-3	30	0.182	0.160	0.204	0.014	-008	0.035			
0.50	-3	50	0.201	0.183	0.220	0.037	0.019	0.056			
0.25	-3	10	0.336	0.314	0.358	0.143	0.124	0.163			
0.25	-3	20	0.375	0.359	0.391	0.182	0.167	0.197			
0.25	-3	30	0.380	0.366	0.394	0.179	0.167	0.192			
0.25	-3	50	0.383	0.373	0.394	0.191	0.182	0.200			
t/p actual	initial value	N	F7 bias	Lower 95 % C.I.	Upper 95 % C.I.	F9 bias	Lower 95 % C.I.	Upper 95 % C.I.	Hr	Lower 95 % C.I.	Upper 95 % C.I.
0.75	-3	10	-.367	-.398	-.336	-.402	-.434	-.371	-.469	-.499	-.440
0.75	-3	20	-.301	-.329	-.272	-.346	-.374	-.317	-.400	-.428	-.371
0.75	-3	30	-.300	-.326	-.274	-.343	-.370	-.317	-.421	-.448	-.394
0.75	-3	50	-.201	-.224	-.179	-.248	-.272	-.224	-.329	-.355	-.303
0.50	-3	10	-.143	-.171	-.115	-.198	-.224	-.171	-.264	-.289	-.238
0.50	-3	20	-.094	-.118	-.070	-.134	-.158	-.110	-.223	-.247	-.199
0.50	-3	30	-.079	-.102	-.056	-.143	-.166	-.120	-.231	-.253	-.208
0.50	-3	50	-.060	-.079	-.041	-.119	-.138	-.099	-.210	-.231	-.189
0.25	-3	10	0.031	0.012	0.050	-0.029	-0.046	-0.011	-0.056	-0.075	-0.037
0.25	-3	20	0.058	0.043	0.073	-0.013	-0.027	0.002	-0.055	-0.071	-0.039
0.25	-3	30	0.056	0.043	0.069	-0.023	-0.036	-0.009	-0.060	-0.074	-0.046
0.25	-3	50	0.070	0.059	0.081	-0.007	-0.018	0.004	-0.057	-0.070	-0.044

Table: S3.T2
BIAS DIFFERENCE BETWEEN FOURIER ESTIMATE AND HOURLY
MEAN
SIMULATION 3

t/p actual	initial value	N	F3-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F3-Hr =0	F5- Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F5-Hr =0
0.75	-3	10	0.263	0.229	0.298	0.000	0.153	0.125	0.180	0.000
0.75	-3	20	0.256	0.225	0.288	0.000	0.157	0.132	0.183	0.000
0.75	-3	30	0.334	0.306	0.362	0.000	0.196	0.173	0.220	0.000
0.75	-3	50	0.304	0.278	0.330	0.000	0.197	0.175	0.218	0.000
0.50	-3	10	0.335	0.305	0.365	0.000	0.193	0.170	0.217	0.000
0.50	-3	20	0.376	0.350	0.402	0.000	0.218	0.197	0.240	0.000
0.50	-3	30	0.413	0.389	0.437	0.000	0.244	0.225	0.264	0.000
0.50	-3	50	0.412	0.389	0.434	0.000	0.248	0.229	0.266	0.000
0.25	-3	10	0.392	0.371	0.413	0.000	0.199	0.183	0.216	0.000
0.25	-3	20	0.430	0.412	0.448	0.000	0.237	0.223	0.251	0.000
0.25	-3	30	0.440	0.426	0.455	0.000	0.240	0.228	0.251	0.000
0.25	-3	50	0.440	0.428	0.452	0.000	0.248	0.238	0.258	0.000

t/p actual	initial value	N	F7- Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F7-Hr =0	F9-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F9-Hr =0
0.75	-3	10	0.102	0.078	0.126	0.000	0.067	0.045	0.088	0.000
0.75	-3	20	0.099	0.077	0.120	0.000	0.054	0.034	0.074	0.000
0.75	-3	30	0.121	0.101	0.141	0.000	0.078	0.059	0.096	0.000
0.75	-3	50	0.128	0.108	0.147	0.000	0.081	0.064	0.098	0.000
0.50	-3	10	0.120	0.100	0.141	0.000	0.066	0.048	0.084	0.000
0.50	-3	20	0.129	0.112	0.147	0.000	0.089	0.073	0.105	0.000
0.50	-3	30	0.152	0.134	0.169	0.000	0.088	0.072	0.104	0.000
0.50	-3	50	0.150	0.135	0.166	0.000	0.092	0.078	0.105	0.000
0.25	-3	10	0.087	0.073	0.101	0.000	0.027	0.015	0.039	0.000
0.25	-3	20	0.113	0.101	0.125	0.000	0.042	0.032	0.052	0.000
0.25	-3	30	0.116	0.107	0.126	0.000	0.037	0.029	0.046	0.000
0.25	-3	50	0.127	0.118	0.136	0.000	0.050	0.042	0.058	0.000

Table S3.T3
MEAN SQUARE ERROR DIFFERENCE
BETWEEN FOURIER ESTIMATE AND HOURLY MEAN
SIMULATION 3

t/p actual	initial value	N	F3-Hr	Lower 95 % C.I.	Upper 95 % C.I.	prob. F3-Hr =0	F5-Hr	Lower 95 % C.I.	Upper 95 % C.I.	prob. F5-Hr =0
0.75	-3	10	-0.150	-0.172	-0.127	0.000	-0.107	-0.127	-0.088	0.000
0.75	-3	20	-0.130	-0.151	-0.108	0.000	-0.100	-0.119	-0.081	0.000
0.75	-3	30	-0.173	-0.192	-0.155	0.000	-0.131	-0.147	-0.115	0.000
0.75	-3	50	-0.123	-0.140	-0.107	0.000	-0.110	-0.124	-0.096	0.000
0.50	-3	10	-0.030	-0.043	-0.018	0.000	-0.041	-0.052	-0.030	0.000
0.50	-3	20	-0.023	-0.037	-0.010	0.001	-0.049	-0.060	-0.039	0.000
0.50	-3	30	-0.025	-0.038	-0.013	0.000	-0.059	-0.069	-0.049	0.000
0.50	-3	50	-0.015	-0.027	-0.003	0.088	-0.054	-0.063	-0.044	0.000
0.25	-3	10	0.123	0.107	0.138	0.000	0.022	0.014	0.030	0.000
0.25	-3	20	0.137	0.125	0.149	0.000	0.026	0.019	0.033	0.000
0.25	-3	30	0.140	0.128	0.152	0.000	0.023	0.017	0.029	0.000
0.25	-3	50	0.138	0.129	0.147	0.000	0.025	0.020	0.029	0.000

t/p actual	initial value	N	F7- Hr	Lower 95 % C.I.	Upper 95 % C.I.	prob. F7-Hr =0	F9- Hr	Lower 95 % C.I.	Upper 95 % C.I.	prob. F9-Hr =0
0.75	-3	10	-0.074	-0.092	-0.057	0.000	-0.046	-0.061	-0.030	0.000
0.75	-3	20	-0.069	-0.085	-0.053	0.000	-0.041	-0.056	-0.027	0.000
0.75	-3	30	-0.092	-0.106	-0.077	0.000	-0.062	-0.076	-0.048	0.000
0.75	-3	50	-0.084	-0.097	-0.071	0.000	-0.057	-0.069	-0.045	0.000
0.50	-3	10	-0.033	-0.043	-0.024	0.000	-0.023	-0.031	-0.014	0.000
0.50	-3	20	-0.042	-0.050	-0.034	0.000	-0.031	-0.039	-0.024	0.000
0.50	-3	30	-0.048	-0.057	-0.039	0.000	-0.032	-0.040	-0.024	0.000
0.50	-3	50	-0.049	-0.057	-0.042	0.000	-0.036	-0.042	-0.029	0.000
0.25	-3	10	-0.002	-0.007	0.003	0.054	-0.007	-0.011	-0.003	0.000
0.25	-3	20	-0.004	-0.008	0.000	0.000	-0.008	-0.010	-0.005	0.000
0.25	-3	30	-0.003	-0.006	0.001	0.026	-0.005	-0.007	-0.002	0.000
0.25	-3	50	-0.003	-0.006	-0.000	0.026	-0.007	-0.009	-0.006	0.000

Table S3.T4
RATIO OF MEAN SQUARE ERRORS
MSE HOURLY / MSE FOURIER
SIMULATION 3

t/p actual	initial value	N	MSE Hr/F3	Lower 95 % C.L	Upper 95 % C.L	MSE Hr/F5	Lower 95 % C.L	Upper 95 % C.L
0.75	-3	10	1.935	1.712	2.159	1.529	1.402	1.657
0.75	-3	20	2.124	1.837	2.410	1.690	1.509	1.871
0.75	-3	30	3.213	2.747	3.679	2.092	1.881	2.304
0.75	-3	50	3.268	2.786	3.751	2.619	2.308	2.929
0.50	-3	10	1.288	1.154	1.422	1.432	1.287	1.577
0.50	-3	20	1.264	1.091	1.436	1.806	1.581	2.031
0.50	-3	30	1.312	1.134	1.489	2.218	1.905	2.530
0.50	-3	50	1.199	1.023	1.375	2.490	2.106	2.874
0.25	-3	10	0.246	0.211	0.282	0.649	0.553	0.744
0.25	-3	20	0.182	0.161	0.204	0.539	0.459	0.618
0.25	-3	30	0.149	0.129	0.170	0.512	0.431	0.592
0.25	-3	50	0.129	0.112	0.146	0.451	0.385	0.517

t/p actual	initial value	N	MSE Hr/F7	Lower 95 % C.L	Upper 95 % C.L	MSE Hr/F9	Lower 95 % C.L	Upper 95 % C.L
0.75	-3	10	1.316	1.227	1.406	1.173	1.109	1.238
0.75	-3	20	1.393	1.283	1.503	1.202	1.124	1.281
0.75	-3	30	1.573	1.454	1.692	1.328	1.241	1.415
0.75	-3	50	1.893	1.712	2.074	1.468	1.353	1.584
0.50	-3	10	1.328	1.220	1.435	1.200	1.116	1.283
0.50	-3	20	1.611	1.451	1.770	1.393	1.281	1.506
0.50	-3	30	1.801	1.593	2.010	1.428	1.300	1.555
0.50	-3	50	2.209	1.939	2.479	1.662	1.511	1.814
0.25	-3	10	1.061	0.929	1.192	1.215	1.086	1.344
0.25	-3	20	1.144	0.979	1.308	1.347	1.216	1.478
0.25	-3	30	1.130	0.965	1.296	1.234	1.109	1.359
0.25	-3	50	1.188	0.997	1.378	1.578	1.402	1.753

Table: S3.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 3

t/p ratio	initial value	N	BIAS F5-F7	Lower 95 % C.I	Upper 95 % C.I	prob. F5-F7 =0	M.S.E. F5-F7	Lower 95 % C.I	Upper 95 % C.I	prob. F5-F7 =0
0.75	-3	10	0.051	0.033	0.068	0.000	-0.033	-0.044	-0.022	0.000
0.75	-3	20	0.059	0.041	0.076	0.000	-0.031	-0.042	-0.020	0.000
0.75	-3	30	0.075	0.060	0.091	0.000	-0.040	-0.050	-0.030	0.000
0.75	-3	50	0.069	0.056	0.082	0.000	-0.026	-0.033	-0.019	0.000
0.50	-3	10	0.073	0.058	0.088	0.000	-0.007	-0.015	-0.000	0.027
0.50	-3	20	0.089	0.075	0.103	0.000	-0.007	-0.014	-0.001	0.063
0.50	-3	30	0.093	0.081	0.104	0.000	-0.011	-0.017	-0.005	0.000
0.50	-3	50	0.098	0.087	0.108	0.000	-0.005	-0.010	0.000	0.064
0.25	-3	10	0.112	0.102	0.123	0.000	0.024	0.018	0.030	0.000
0.25	-3	20	0.124	0.115	0.133	0.000	0.030	0.025	0.035	0.000
0.25	-3	30	0.123	0.116	0.130	0.000	0.026	0.022	0.030	0.000
0.25	-3	50	0.121	0.115	0.127	0.000	0.028	0.026	0.031	0.000

Table S3.T6
COMPARISON OF 5 AND 7 TERM FOURIER T/P ESTIMATORS
MINIMUM M.S.E. OVER ALL SAMPLE SIZES TESTED

SIMULATION 3

t/p ratio	Minimum * M.S.E.	5 Term M.S.E. ** LT H.M.	7 Term M.S.E. ** LT H.M.
0.75	5	Y	Y
0.50	E	Y	Y
0.25	7	N	E

* 5 - 5 Term fourier T/P estimator
 7 - 7 Term fourier T/P estimator
 E - 5 Term fourier M.S.E. = 7 Term fourier M.S.E.

** Y: Yes
 N: No
 E: M.S.E's equal

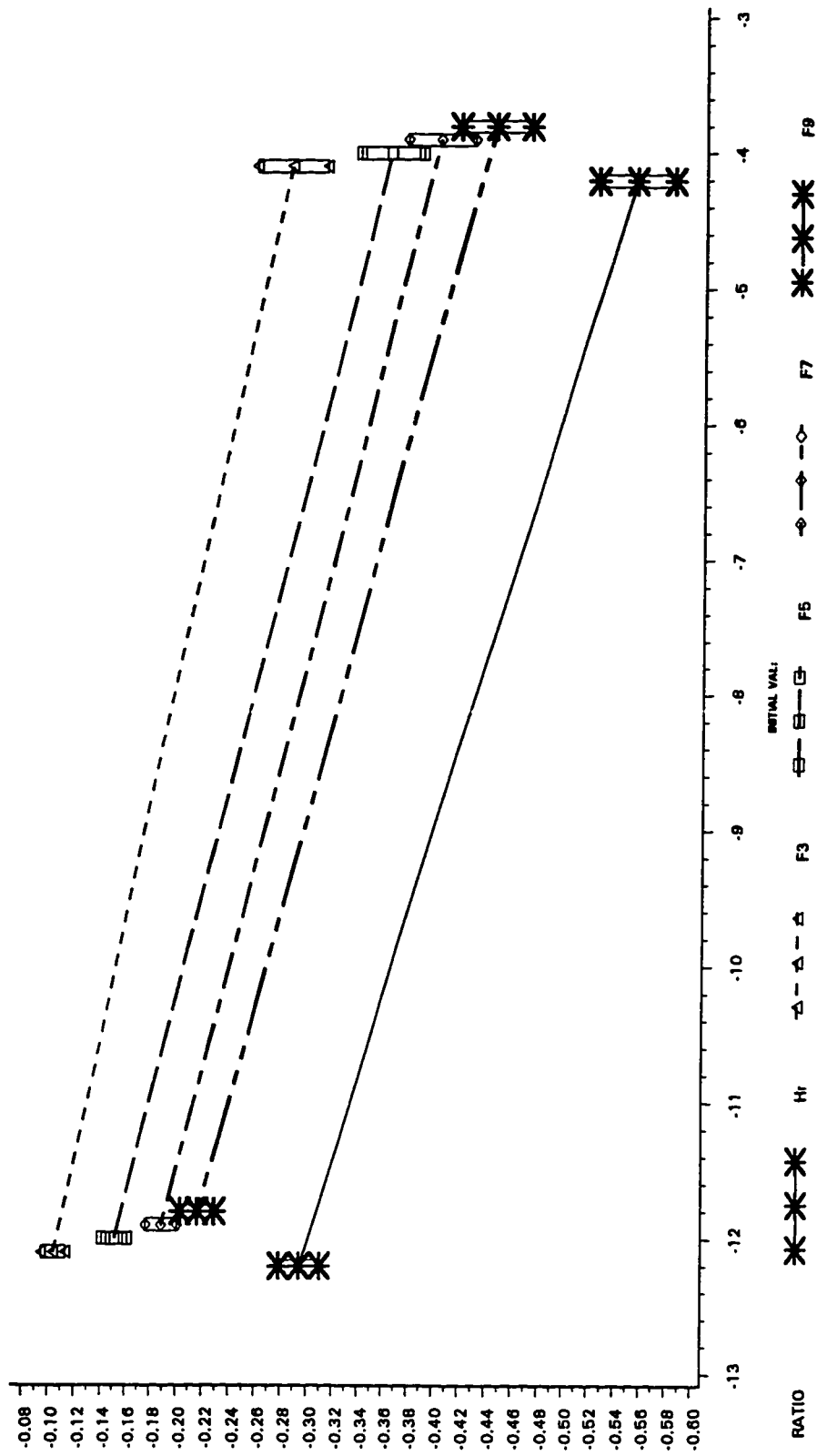


FIGURE: S4.F1: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 4
N= 30

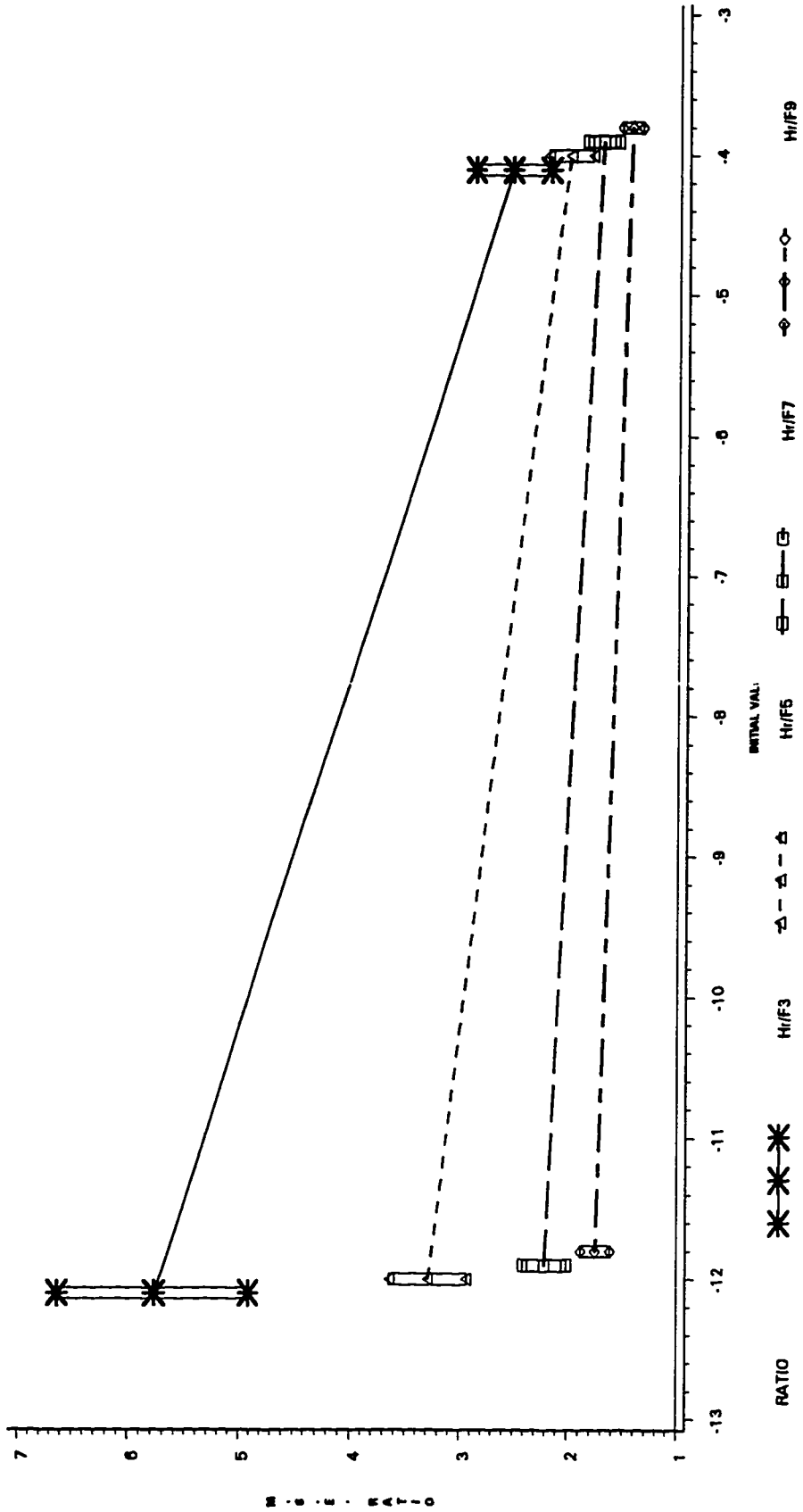


FIGURE: S4.F2: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 4
N= 30

Table: S4.T1
BIAS ESTIMATE
SIMULATION 4

t/p ratio	initial value	N	F3 bias	Lower 95 % C.I.	Upper 95 % C.I.	F5 bias	Lower 95 % C.I.	Upper 95 % C.I.	F7 bias	Lower 95 % C.I.	Upper 95 % C.I.	F9 bias	Lower 95 % C.I.	Upper 95 % C.I.	Hr	Lower 95 % C.I.	Upper 95 % C.I.
1.00	-4	10	-0.410	-0.442	-0.378	-0.496	-0.527	-0.465	-0.552	-0.583	-0.522	-0.584	-0.613	-0.554	-0.646	-0.677	-0.616
1.00	-4	20	-0.315	-0.343	-0.287	-0.403	-0.430	-0.375	-0.445	-0.473	-0.417	-0.470	-0.498	-0.441	-0.574	-0.602	-0.545
1.00	-4	30	-0.285	-0.312	-0.258	-0.364	-0.389	-0.339	-0.403	-0.428	-0.377	-0.445	-0.472	-0.418	-0.555	-0.584	-0.525
1.00	-4	50	-0.223	-0.243	-0.202	-0.308	-0.329	-0.286	-0.346	-0.368	-0.323	-0.374	-0.399	-0.350	-0.493	-0.519	-0.467
1.00	-12	10	-0.179	-0.193	-0.164	-0.245	-0.261	-0.229	-0.292	-0.310	-0.274	-0.323	-0.342	-0.303	-0.428	-0.450	-0.406
1.00	-12	20	-0.131	-0.142	-0.120	-0.194	-0.207	-0.181	-0.235	-0.249	-0.220	-0.258	-0.273	-0.243	-0.348	-0.367	-0.330
1.00	-12	30	-0.104	-0.113	-0.095	-0.152	-0.162	-0.141	-0.189	-0.201	-0.176	-0.216	-0.229	-0.203	-0.295	-0.310	-0.279
1.00	-12	50	-0.085	-0.092	-0.078	-0.124	-0.133	-0.116	-0.150	-0.160	-0.140	-0.174	-0.185	-0.164	-0.250	-0.263	-0.237

Table: S4.T2
BIAS DIFFERENCE BETWEEN FOURIER ESTIMATE AND HOURLY
MEAN
SIMULATION 4

t/p ratio	initial value	N	F3-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F3-Hr =0	F5-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F5-Hr =0
1.00	-4	10	0.236	0.203	0.270	0.000	0.150	0.123	0.178	0.000
1.00	-4	20	0.259	0.228	0.289	0.000	0.171	0.146	0.195	0.000
1.00	-4	30	0.270	0.239	0.300	0.000	0.191	0.165	0.216	0.000
1.00	-4	50	0.271	0.245	0.296	0.000	0.186	0.164	0.207	0.000
1.00	-12	10	0.250	0.229	0.270	0.000	0.184	0.166	0.202	0.000
1.00	-12	20	0.217	0.201	0.234	0.000	0.155	0.139	0.170	0.000
1.00	-12	30	0.191	0.175	0.206	0.000	0.143	0.129	0.157	0.000
1.00	-12	50	0.165	0.153	0.178	0.000	0.126	0.115	0.137	0.000

t/p ratio	initial value	N	F7-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F7-Hr =0	F9-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F9-Hr =0
1.00	-4	10	0.094	0.070	0.118	0.000	0.063	0.041	0.085	0.000
1.00	-4	20	0.129	0.106	0.152	0.000	0.104	0.082	0.125	0.000
1.00	-4	30	0.152	0.128	0.175	0.000	0.109	0.089	0.130	0.000
1.00	-4	50	0.148	0.128	0.167	0.000	0.119	0.101	0.137	0.000
1.00	-12	10	0.136	0.119	0.153	0.000	0.106	0.090	0.121	0.000
1.00	-12	20	0.114	0.101	0.127	0.000	0.090	0.078	0.103	0.000
1.00	-12	30	0.106	0.094	0.118	0.000	0.078	0.067	0.090	0.000
1.00	-12	50	0.100	0.090	0.110	0.000	0.076	0.066	0.085	0.000

Table: S4.T3
MEAN SQUARE ERROR DIFFERENCE
BETWEEN FOURIER ESTIMATE AND HOURLY MEAN
SIMULATION 4

t/p ratio	initial value	N	F3-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F3-Hr =0	F5-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F5-Hr =0
1.00	-4	10	-239	-276	-203	0.000	-169	-200	-.138	0.000
1.00	-4	20	-234	-266	-201	0.000	-171	-198	-.144	0.000
1.00	-4	30	-240	-271	-210	0.000	-199	-226	-.173	0.000
1.00	-4	50	-221	-246	-196	0.000	-173	-194	-.151	0.000
1.00	-12	10	-179	-198	-160	0.000	-147	-164	-.130	0.000
1.00	-12	20	-127	-139	-114	0.000	-103	-114	-.091	0.000
1.00	-12	30	-.093	-.103	-.084	0.000	-.078	-.087	-.070	0.000
1.00	-12	50	-.068	-.075	-.061	0.000	-.057	-.063	-.051	0.000

t/p ratio	initial value	N	F7-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F7-Hr =0	F9-Hr	Lower 95 % C.I	Upper 95 % C.I	prob. F9-Hr =0
1.00	-4	10	-.113	-.140	-.085	0.000	-.082	-.107	-.056	0.000
1.00	-4	20	-.133	-.158	-.108	0.000	-.107	-.130	-.084	0.000
1.00	-4	30	-.166	-.190	-.141	0.000	-.123	-.145	-.102	0.000
1.00	-4	50	-.141	-.161	-.120	0.000	-.112	-.130	-.095	0.000
1.00	-12	10	-.113	-.128	-.097	0.000	-.088	-.102	-.074	0.000
1.00	-12	20	-.080	-.091	-.070	0.000	-.066	-.076	-.057	0.000
1.00	-12	30	-.062	-.070	-.053	0.000	-.048	-.056	-.041	0.000
1.00	-12	50	-.048	-.054	-.042	0.000	-.038	-.043	-.033	0.000

Table: S4.T4
RATIO OF MEAN SQUARE ERRORS
MSE HOURLY / MSE FOURIER
SIMULATION 4

t/p ratio	initial value	N	MSE Hr/F3	Lower 95 % C.I.	Upper 95 % C.I.	MSE Hr/F5	Lower 95 % C.I.	Upper 95 % C.I.
1.00	-4	10	1.870	1.665	2.075	1.488	1.371	1.605
1.00	-4	20	2.307	1.990	2.624	1.707	1.551	1.863
1.00	-4	30	2.534	2.184	2.885	2.009	1.812	2.206
1.00	-4	50	3.365	2.848	3.883	2.219	2.008	2.430
1.00	-12	10	4.295	3.724	4.866	2.703	2.444	2.963
1.00	-12	20	5.136	4.464	5.809	2.891	2.617	3.165
1.00	-12	30	5.770	4.909	6.632	3.286	2.933	3.639
1.00	-12	50	6.481	5.526	7.437	3.443	3.088	3.799

t/p ratio	initial value	N	MSE Hr/F7	Lower 95 % C.I.	Upper 95 % C.I.	MSE Hr/F9	Lower 95 % C.I.	Upper 95 % C.I.
1.00	-4	10	1.280	1.199	1.361	1.189	1.124	1.254
1.00	-4	20	1.477	1.363	1.590	1.351	1.261	1.441
1.00	-4	30	1.717	1.578	1.856	1.451	1.357	1.544
1.00	-4	50	1.814	1.660	1.968	1.556	1.446	1.666
1.00	-12	10	1.933	1.771	2.095	1.607	1.496	1.719
1.00	-12	20	2.050	1.890	2.210	1.732	1.609	1.856
1.00	-12	30	2.206	2.007	2.405	1.749	1.617	1.882
1.00	-12	50	2.472	2.252	2.691	1.889	1.749	2.030

Table: S4.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 4

initial value	N	BIAS FS-F7	Lower 95 % C.L	Upper 95 % C.L	prob. FS-F7 =0	M.S.E. FS-F7	Lower 95 % C.L	Upper 95 % C.L	prob. FS-F7 =0
-4	10	0.057	0.039	0.074	0.000	-0.056	-0.076	-0.037	0.000
-4	20	0.042	0.027	0.058	0.000	-0.038	-0.054	-0.022	0.000
-4	30	0.039	0.024	0.054	0.000	-0.034	-0.048	-0.019	0.000
-4	50	0.038	0.025	0.051	0.000	-0.032	-0.042	-0.021	0.000
-12	10	0.047	0.037	0.058	0.000	-0.034	-0.042	-0.027	0.000
-12	20	0.041	0.033	0.049	0.000	-0.022	-0.027	-0.018	0.000
-12	30	0.037	0.029	0.045	0.000	-0.017	-0.020	-0.013	0.000
-12	50	0.026	0.020	0.031	0.000	-0.009	-0.011	-0.007	0.000

Table S4.T6
COMPARISON OF 5 AND 7 TERM FOURIER T/P ESTIMATORS
MINIMUM M.S.E. OVER ALL SAMPLE SIZES TESTED

SIMULATION 4

initial value	Minimum * M.S.E.	5 Term M.S.E. ** LT H.M.	7 Term M.S.E. ** LT H.M.
-4	5	Y	Y
-12	5	Y	Y

* 5 - 5 Term fourier T/P estimator

7 - 7 Term fourier T/P estimator

E - 5 Term fourier M.S.E. = 7 Term fourier M.S.E.

** Y: Yes

N: No

E: M.S.E's equal

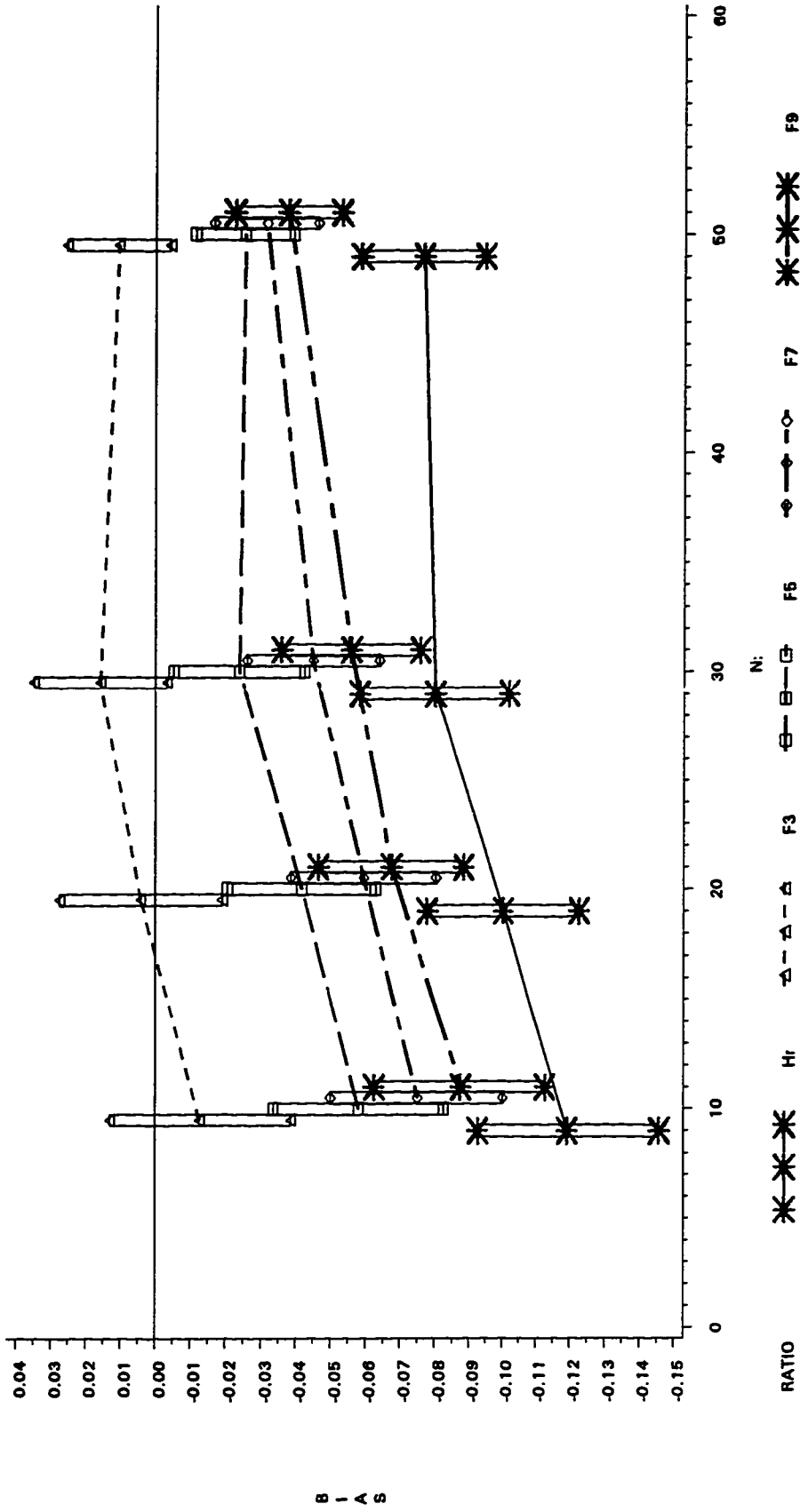


FIGURE: S5.F1: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 5
CASE = 1

B I A S

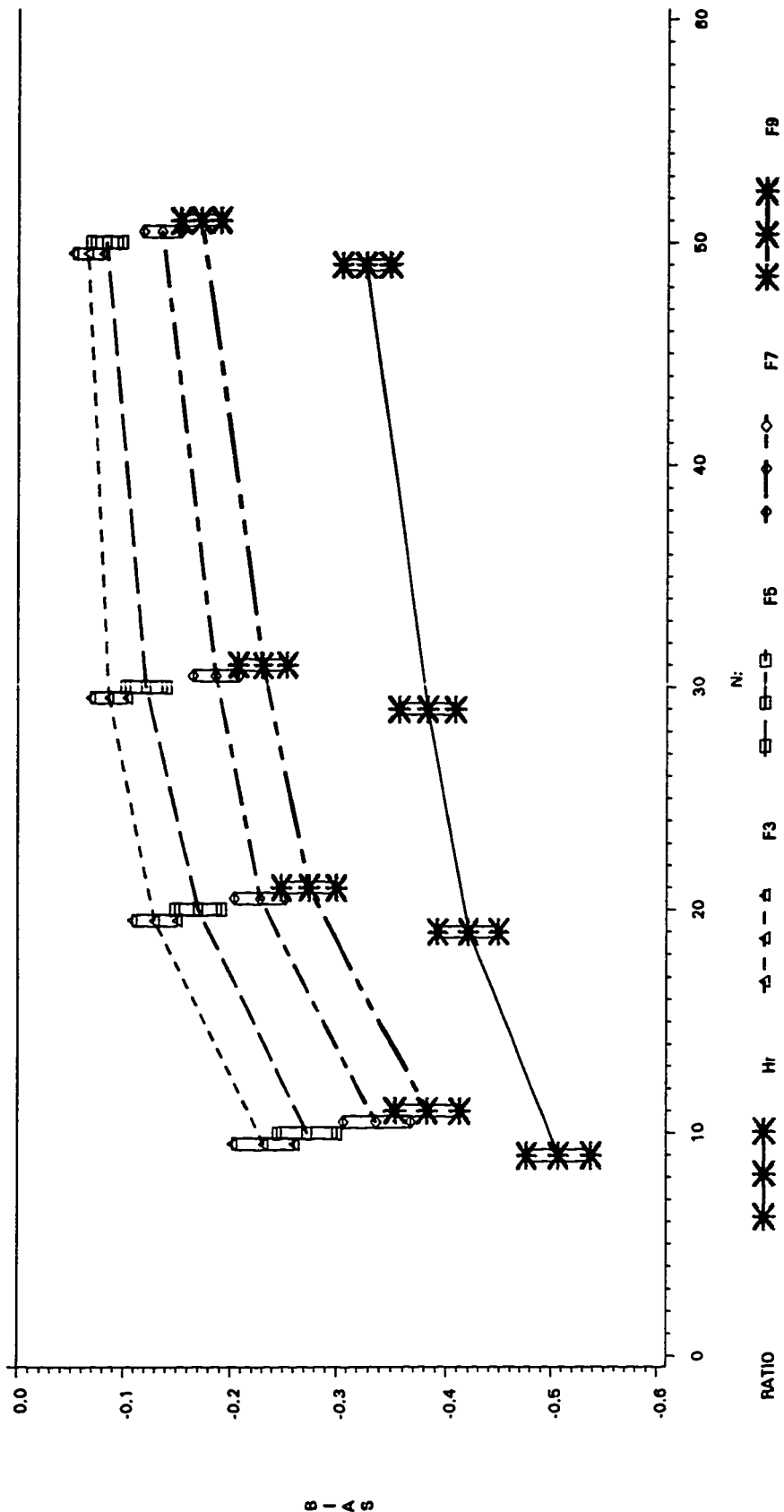
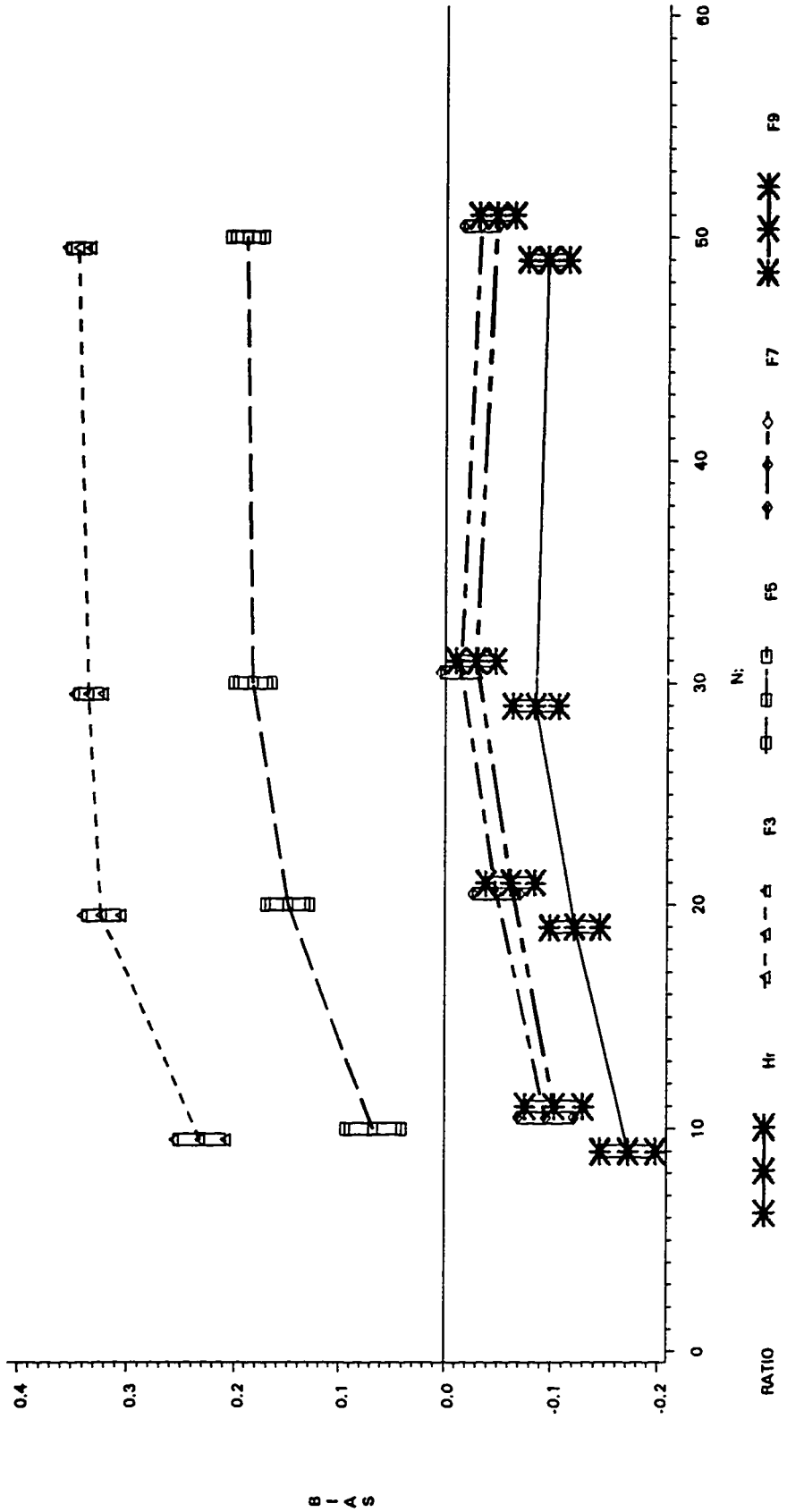
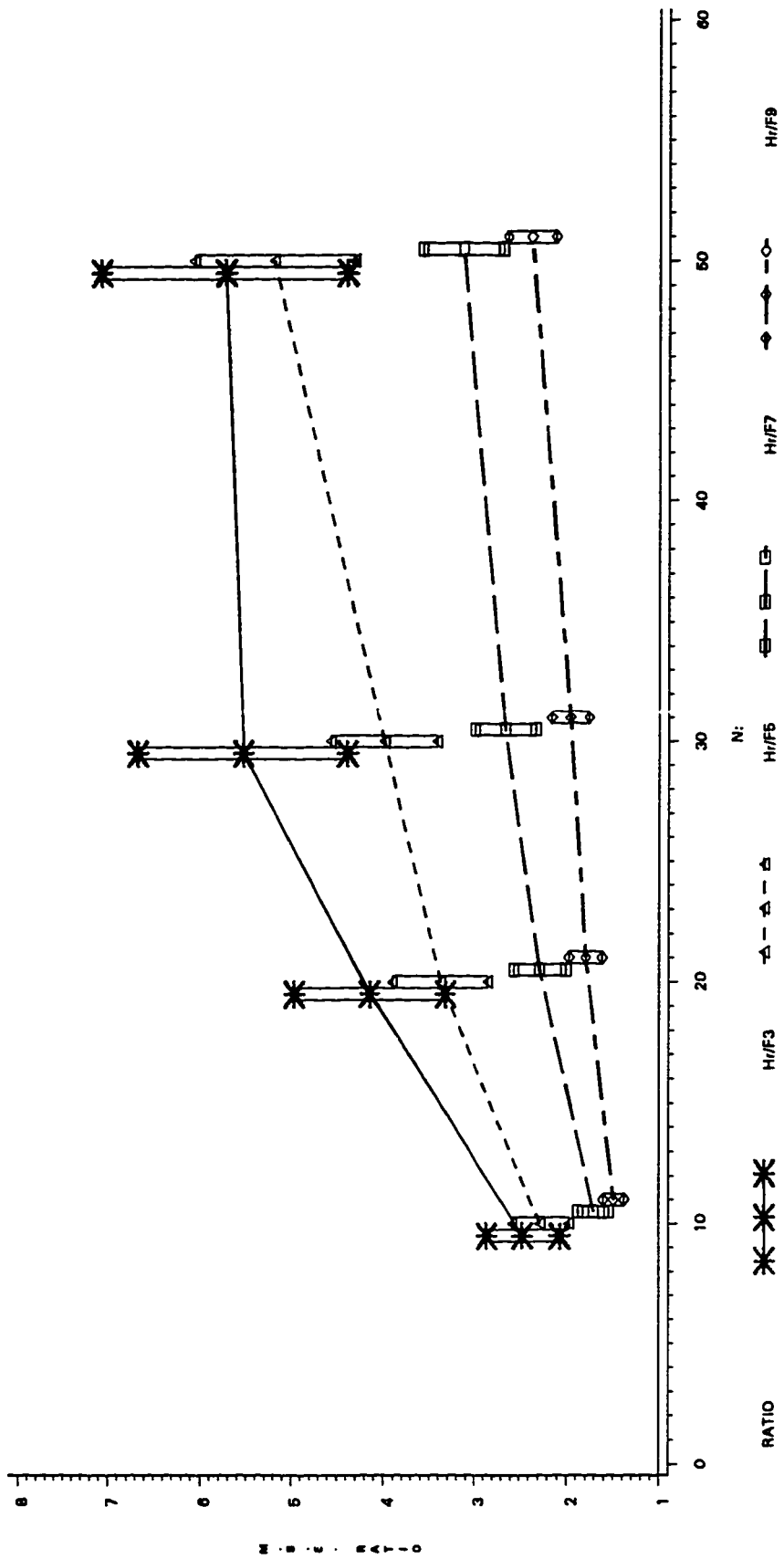


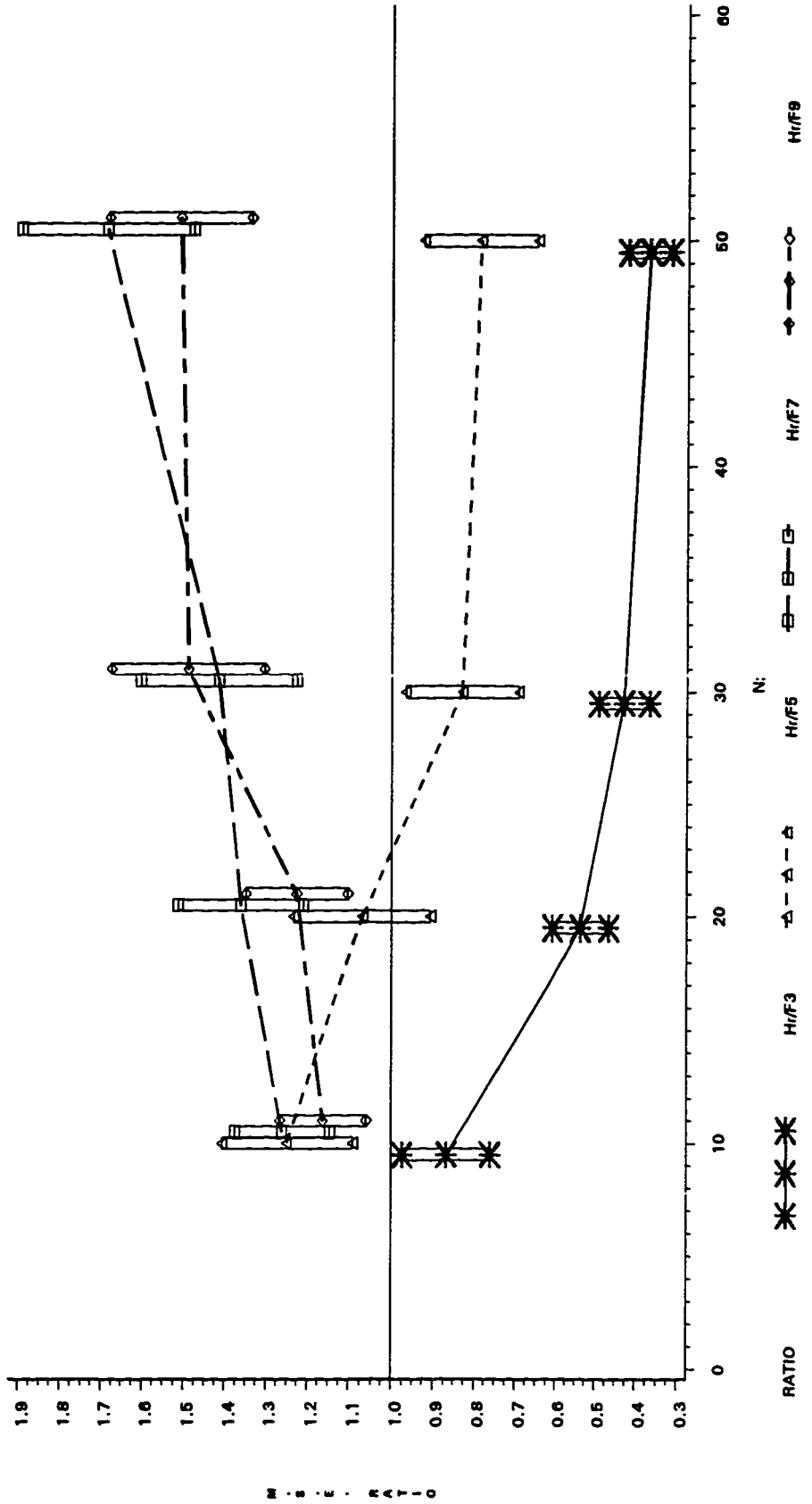
FIGURE: S5.F2: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 5
CASE = 2



**FIGURE: S5.F3: PLOT OF AVERAGE BIAS OF ESTIMATORS - SIMULATION 5
CASE = 3**



**FIGURE: S5.F5: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 5
CASE = 2**



**FIGURE: 55.F6: PLOT OF RATIOS OF M.S.E. OF ESTIMATORS - SIMULATION 5
CASE = 3**

Table: S5.T1
BIAS ESTIMATE
SIMULATION 5

curve	t/p actual	initial value	N	F3 bias	Lower 95 % C.I.	Upper 95 % C.I.	F5 bias	Lower 95 % C.I.	Upper 95 % C.I.
1	0.40	4	10	-0.013	-0.039	0.013	-0.058	-0.082	-0.034
	0.40	4	20	0.004	-0.019	0.027	-0.042	-0.063	-0.021
	0.40	4	30	0.016	-0.003	0.035	-0.024	-0.042	-0.005
	0.40	4	50	0.011	-0.004	0.025	-0.025	-0.039	-0.011
2	0.91	6	10	-0.231	-0.261	-0.202	-0.273	-0.301	-0.245
	0.91	6	20	-0.129	-0.150	-0.108	-0.170	-0.191	-0.148
	0.91	6	30	-0.086	-0.103	-0.069	-0.121	-0.141	-0.102
	0.91	6	50	-0.066	-0.080	-0.051	-0.083	-0.098	-0.069
2	0.49	4	10	0.232	0.208	0.257	0.067	0.040	0.094
	0.49	4	20	0.324	0.306	0.341	0.150	0.129	0.171
	0.49	4	30	0.335	0.322	0.348	0.183	0.165	0.201
	0.49	4	50	0.345	0.334	0.356	0.190	0.174	0.205

case	t/p act.	initial value	N	F7 bias	Lower 95 % C.I.	Upper 95 % C.I.	F9 bias	Lower r 95 % C.I.	Upper 95 % C.I.	Hr	Lower 95 % C.I.	Upper 95 % C.I.
1	0.40	4	10	-0.075	-0.100	-0.050	-0.088	-0.113	-0.062	-0.119	-0.146	-0.093
	0.40	4	20	-0.059	-0.080	-0.039	-0.067	-0.088	-0.047	-0.100	-0.123	-0.078
	0.40	4	30	-0.045	-0.064	-0.026	-0.056	-0.076	-0.036	-0.080	-0.102	-0.058
	0.40	4	50	-0.031	-0.046	-0.017	-0.038	-0.053	-0.023	-0.077	-0.095	-0.059
2	0.91	6	10	-0.337	-0.367	-0.307	-0.383	-0.412	-0.353	-0.507	-0.538	-0.476
	0.91	6	20	-0.228	-0.252	-0.203	-0.274	-0.300	-0.248	-0.420	-0.449	-0.392
	0.91	6	30	-0.186	-0.207	-0.165	-0.230	-0.254	-0.207	-0.382	-0.408	-0.356
	0.91	6	50	-0.136	-0.153	-0.118	-0.172	-0.191	-0.153	-0.326	-0.348	-0.305
3	0.49	4	10	-0.095	-0.121	-0.069	-0.103	-0.130	-0.076	-0.172	-0.198	-0.146
	0.49	4	20	-0.049	-0.071	-0.027	-0.062	-0.085	-0.039	-0.122	-0.146	-0.098
	0.49	4	30	-0.015	-0.034	0.004	-0.029	-0.048	-0.010	-0.085	-0.107	-0.064
	0.49	4	50	-0.032	-0.049	-0.016	-0.048	-0.065	-0.031	-0.096	-0.115	-0.077

Table: S5.T2
BIAS DIFFERENCE BETWEEN FOURIER ESTIMATE AND HOURLY
MEAN
SIMULATION 5

case	t/p act.	initial value	N	F3-Hr	Lower 95% C.I.	Upper 95% C.I.	prob. F3-Hr =0	F5- Hr	Lower 95% C.I.	Upper 95% C.I.	prob. F5-Hr =0
1	0.40	-4	10	0.107	0.082	0.131	0.000	0.061	0.041	0.082	0.000
	0.40	-4	20	0.104	0.083	0.126	0.000	0.059	0.041	0.076	0.000
	0.40	-4	30	0.096	0.077	0.115	0.000	0.056	0.040	0.073	0.000
	0.40	-4	50	0.087	0.072	0.103	0.000	0.051	0.038	0.065	0.000
2	0.91	-6	10	0.276	0.242	0.310	0.000	0.235	0.205	0.265	0.000
	0.91	-6	20	0.291	0.262	0.321	0.000	0.251	0.225	0.277	0.000
	0.91	-6	30	0.296	0.270	0.323	0.000	0.261	0.239	0.284	0.000
	0.91	-6	50	0.261	0.239	0.283	0.000	0.243	0.223	0.263	0.000
3	0.49	-4	10	0.405	0.376	0.433	0.000	0.240	0.216	0.263	0.000
	0.49	-4	20	0.446	0.420	0.471	0.000	0.272	0.250	0.294	0.000
	0.49	-4	30	0.420	0.398	0.443	0.000	0.269	0.249	0.288	0.000
	0.49	-4	50	0.441	0.422	0.460	0.000	0.286	0.269	0.302	0.000

case	t/p actu al	initia l value	N	F7-Hr	Lower 95% C.I.	Upper 95% C.I.	prob. F7-Hr =0	F9-Hr	Lower 95% C.I.	Upper 95% C.I.	prob. F9-Hr =0
1	0.40	-4	10	0.044	0.025	0.063	0.000	0.032	0.015	0.048	0.001
	0.40	-4	20	0.041	0.026	0.056	0.000	0.033	0.018	0.047	0.000
	0.40	-4	30	0.035	0.021	0.050	0.000	0.024	0.011	0.037	0.000
	0.40	-4	50	0.045	0.032	0.058	0.000	0.039	0.027	0.050	0.000
2	0.91	-6	10	0.170	0.144	0.196	0.000	0.125	0.102	0.147	0.000
	0.91	-6	20	0.193	0.169	0.217	0.000	0.146	0.125	0.168	0.000
	0.91	-6	30	0.196	0.175	0.217	0.000	0.152	0.133	0.171	0.000
	0.91	-6	50	0.191	0.172	0.209	0.000	0.154	0.137	0.172	0.000
3	0.49	-4	10	0.077	0.057	0.097	0.000	0.069	0.051	0.087	0.000
	0.49	-4	20	0.073	0.056	0.090	0.000	0.060	0.043	0.076	0.000
	0.49	-4	30	0.070	0.054	0.087	0.000	0.056	0.041	0.071	0.000
	0.49	-4	50	0.064	0.050	0.077	0.000	0.048	0.036	0.060	0.000

Table: S5.T3
RATIO OF MEAN SQUARE ERRORS
MSE HOURLY / MSE FOURIER
SIMULATION 5

curve	t/p actual	initial value	N	MSE Hr/F3	Lower 95 % C.I.	Upper 95 % C.I.	MSE Hr/F5	Lower 95 % C.I.	Upper 95 % C.I.
1	0.40	-4	10	1.256	1.107	1.406	1.338	1.192	1.483
	0.40	-4	20	1.102	0.947	1.256	1.284	1.134	1.434
	0.40	-4	30	1.472	1.265	1.678	1.535	1.342	1.728
	0.40	-4	50	1.727	1.458	1.995	1.919	1.659	2.179
2	0.91	-6	10	2.462	2.068	2.857	2.275	1.976	2.575
	0.91	-6	20	4.143	3.321	4.965	3.377	2.848	3.905
	0.91	-6	30	5.525	4.383	6.668	3.989	3.415	4.562
	0.91	-6	50	5.724	4.382	7.066	5.187	4.313	6.061
3	0.49	-4	10	0.867	0.760	0.973	1.249	1.091	1.406
	0.49	-4	20	0.536	0.465	0.606	1.070	0.906	1.233
	0.49	-4	30	0.428	0.366	0.490	0.829	0.692	0.967
	0.49	-4	50	0.367	0.315	0.418	0.786	0.647	0.924

curve	t/p actual	initial value	N	MSE Hr/F7	Lower 95 % C.I.	Upper 95 % C.I.	MSE Hr/F9	Lower 95 % C.I.	Upper 95 % C.I.
1	0.40	-4	10	1.236	1.110	1.362	1.193	1.092	1.294
	0.40	-4	20	1.271	1.143	1.398	1.239	1.128	1.351
	0.40	-4	30	1.428	1.271	1.585	1.258	1.145	1.372
	0.40	-4	50	1.660	1.443	1.877	1.538	1.367	1.709
2	0.91	-6	10	1.711	1.545	1.878	1.494	1.380	1.607
	0.91	-6	20	2.283	2.009	2.558	1.797	1.617	1.976
	0.91	-6	30	2.657	2.325	2.989	1.959	1.760	2.159
	0.91	-6	50	3.128	2.684	3.573	2.372	2.115	2.629
3	0.49	-4	10	1.261	1.145	1.376	1.163	1.060	1.265
	0.49	-4	20	1.362	1.209	1.514	1.226	1.103	1.348
	0.49	-4	30	1.414	1.225	1.603	1.489	1.305	1.674
	0.49	-4	50	1.685	1.478	1.893	1.508	1.336	1.681

Table: S5.T4
MEAN SQUARE ERROR DIFFERENCE
BETWEEN FOURIER ESTIMATE AND HOURLY MEAN
SIMULATION 5

curve	t/p act.	initial value	N	F3-Hr	Lower 95 % C.L	Upper 95 % C.L	prob. F3-Hr =0	F5-Hr	Lower 95% C.L	Upper 95% C.L	prob. F5-Hr =0
1	0.40	-4	10	-0.18	-0.27	-0.09	0.000	-0.22	-0.30	-0.14	0.000
	0.40	-4	20	-0.06	-0.14	0.002	0.005	-0.14	-0.20	-0.07	0.000
	0.40	-4	30	-0.18	-0.24	-0.11	0.000	-0.20	-0.25	-0.14	0.000
	0.40	-4	50	-0.17	-0.21	-0.12	0.000	-0.19	-0.23	-0.15	0.000
2	0.91	-6	10	-0.211	-0.242	-0.180	0.000	-0.199	-0.227	-0.171	0.000
	0.91	-6	20	-0.198	-0.223	-0.172	0.000	-0.184	-0.207	-0.161	0.000
	0.91	-6	30	-0.177	-0.198	-0.156	0.000	-0.162	-0.180	-0.143	0.000
	0.91	-6	50	-0.128	-0.143	-0.113	0.000	-0.125	-0.139	-0.111	0.000
3	0.49	-4	10	0.015	0.002	0.028	0.014	-0.020	-0.031	-0.009	0.001
	0.49	-4	20	0.063	0.051	0.075	0.000	-0.005	-0.015	0.006	0.942
	0.49	-4	30	0.075	0.064	0.086	0.000	0.011	0.001	0.022	0.006
	0.49	-4	50	0.084	0.074	0.093	0.000	0.013	0.004	0.023	0.001

curve	t/p act.	initial value	N	F7- Hr	Lower 95% C.L	Upper 95% C.L	prob. F7-Hr =0	F9-Hr	Lower 95 % C.L	Upper 95 % C.L	prob. F9-Hr =0
1	0.40	-4	10	-0.17	-0.25	-0.09	0.000	-0.14	-0.21	-0.07	0.000
	0.40	-4	20	-0.13	-0.19	-0.08	0.000	-0.12	-0.17	-0.07	0.000
	0.40	-4	30	-0.17	-0.22	-0.12	0.000	-0.11	-0.16	-0.07	0.001
	0.40	-4	50	-0.16	-0.20	-0.12	0.000	-0.14	-0.17	-0.10	0.000
2	0.91	-6	10	-0.148	-0.172	-0.123	0.000	-0.118	-0.139	-0.096	0.000
	0.91	-6	20	-0.147	-0.168	-0.126	0.000	-0.116	-0.135	-0.097	0.000
	0.91	-6	30	-0.135	-0.152	-0.117	0.000	-0.106	-0.122	-0.090	0.000
	0.91	-6	50	-0.105	-0.119	-0.092	0.000	-0.090	-0.102	-0.077	0.000
3	0.49	-4	10	-0.021	-0.029	-0.012	0.000	-0.014	-0.022	-0.006	0.000
	0.49	-4	20	-0.019	-0.026	-0.012	0.000	-0.013	-0.020	-0.007	0.000
	0.49	-4	30	-0.016	-0.023	-0.010	0.000	-0.018	-0.024	-0.012	0.000
	0.49	-4	50	-0.020	-0.025	-0.015	0.000	-0.016	-0.021	-0.012	0.000

Table: S5.T5
BIAS AND M.S.E. DIFFERENCE
BETWEEN 5 AND 7 TERM FOURIER T/P ESTIMATORS
SIMULATION 5

case	N	BIAS F5-F7	Lower 95 % C.I	Upper 95 % C.I	prob. F5-F7 =0	M.S.E . F5-F7	Lower 95 % C.I	Upper 95 % C.I	prob. F5-F7 =0
1	10	0.017	0.005	0.029	0.043	-0.005	-0.010	-0.000	0.019
1	20	0.018	0.009	0.027	0.011	-0.001	-0.004	0.003	0.254
1	30	0.021	0.013	0.029	0.000	-0.003	-0.006	0.000	0.037
1	50	0.006	-0.000	0.013	0.209	-0.003	-0.005	-0.001	0.002
2	10	0.064	0.045	0.083	0.000	-0.052	-0.067	-0.036	0.000
2	20	0.058	0.043	0.073	0.000	-0.037	-0.047	-0.027	0.000
2	30	0.065	0.052	0.077	0.000	-0.027	-0.034	-0.020	0.000
2	50	0.052	0.042	0.063	0.000	-0.020	-0.025	-0.014	0.000
3	10	0.163	0.146	0.179	0.000	0.001	-0.008	0.009	0.907
3	20	0.199	0.185	0.213	0.000	0.015	0.006	0.023	0.000
3	30	0.198	0.186	0.211	0.000	0.028	0.020	0.036	0.000
3	50	0.222	0.211	0.232	0.000	0.033	0.026	0.040	0.000

Table S5.T6
COMPARISON OF 5 AND 7 TERM FOURIER T/P ESTIMATORS
MINIMUM M.S.E. OVER ALL SAMPLE SIZES TESTED

SIMULATION 5

Case	Minimum * M.S.E.	5 Term M.S.E. ** LT H.M.	7 Term M.S.E. ** LT H.M.
1	E	Y	Y
2	5	Y	Y
3	7	E	Y

* 5 - 5 Term fourier T/P estimator
 7 - 7 Term fourier T/P estimator
 E - 5 Term fourier M.S.E. = 7 Term fourier M.S.E.

** Y: Yes
 N: No
 E: M.S.E's equal

Table CV.T1

Covariance Matrix Used In Simulation

	1	2	3	4	5	6	7	8	9	10	11	12
1	152.90											
2	80.50	169.23										
3	60.50	89.05	194.21									
4	63.61	85.64	94.41	200.88								
5	63.34	79.74	65.31	88.10	172.45							
6	52.19	69.43	59.53	65.94	91.29	134.05						
7	41.49	44.59	60.87	77.16	57.67	58.15	164.90					
8	69.21	76.57	83.75	70.79	78.72	64.48	41.65	160.80				
9	65.56	90.72	95.29	81.14	92.76	73.22	41.92	122.48	193.73			
10	57.09	86.10	90.39	96.68	98.83	86.82	54.48	106.54	145.42	230.07		
11	57.19	57.50	92.56	78.85	78.94	49.74	44.63	67.84	73.27	101.09	151.75	
12	54.61	55.51	31.40	46.94	63.00	52.35	27.89	49.68	69.63	59.49	80.74	159.52
13	58.86	76.22	81.40	72.79	102.15	69.25	55.66	77.90	96.81	84.75	75.06	88.92
14	52.30	60.04	78.30	75.28	84.34	45.91	48.69	69.19	68.88	73.54	66.81	71.34
15	50.81	60.75	54.31	55.74	95.07	64.47	52.76	54.06	76.57	80.85	66.58	66.08
16	43.77	56.57	71.26	57.68	74.66	49.10	57.94	55.28	77.55	71.70	56.68	61.22
17	48.38	68.64	78.18	61.14	76.30	61.60	57.91	71.23	99.86	73.92	48.51	57.94
18	55.13	59.95	72.87	43.47	65.81	68.94	49.36	49.32	62.52	51.12	40.89	53.33
19	49.24	59.20	58.01	29.86	61.39	55.20	40.51	49.02	41.61	23.07	46.35	41.00
20	45.96	50.21	64.55	57.08	62.64	63.45	63.73	61.97	62.20	40.70	46.96	41.84
21	42.93	48.84	66.89	49.47	64.73	59.14	83.11	63.39	84.37	56.59	53.86	43.74
22	42.71	77.74	74.30	42.26	55.14	49.84	68.14	74.15	71.74	64.32	66.21	44.38
23	83.59	87.98	97.54	82.50	103.48	86.01	57.54	83.19	100.49	86.80	98.02	76.21
24	78.73	63.65	64.35	96.82	71.40	57.65	56.92	76.25	57.84	54.28	80.89	44.30

Table CV.T1

Covariance Matrix Used In Simulation

	13	14	15	16	17	18	19	20	21	22	23	24
13	176.71											
14	144.87	208.25										
15	96.63	114.66	190.10									
16	94.83	96.43	128.01	135.08								
17	99.20	114.15	118.95	114.01	171.72							
18	86.76	85.65	98.52	95.55	118.87	166.08						
19	69.75	73.04	92.97	87.77	88.74	104.54	135.26					
20	64.49	50.62	73.86	74.35	84.81	84.29	100.34	143.36				
21	63.81	37.86	72.63	76.24	101.06	91.02	79.75	112.22	204.94			
22	83.74	68.09	87.09	80.19	92.08	72.08	79.58	104.39	128.34	204.86		
23	97.49	85.93	90.49	83.37	94.74	90.45	86.30	90.60	90.36	119.13	194.00	
24	47.11	49.51	47.59	22.41	34.22	30.72	36.37	44.45	25.19	61.03	110.29	234.85

Chapter 4

Summary & Conclusions

In chapter 1 I derived the M.L.E. for the unknown parameters for the multivariate model:

$$X = D\beta A + e$$

for the situation where $e_i'e_i = \Sigma$ and $e_i'e_j = 0$ for $i=1,\dots,N$ and $i \neq j$

and:

$$\Sigma = \begin{bmatrix} \Sigma_D & \Sigma_O' \\ \Sigma_O & \Sigma_D \end{bmatrix} \quad \text{each submatrix is } p \times p.$$

This development is of value for estimation and testing purposes for various contrasts of the regression parameter β , with experimental designs of repeated measures when 2 series of measurements are taken on subjects of the study. The usual contrast of interest is the differences between the series of measurements, and the data is first transformed by taking paired differences between the two series of measurements for each subject and modeling those differences using standard multivariate techniques. A useful development involves extending the above model to include r ($r > 2$) series of measurements with the assumption of a covariance matrix with identical diagonal covariance matrices, and patterned off diagonal covariance matrices. One advantage of assuming a patterned covariance matrix with r series of measurements for each subject is the potential reduction in the necessary sample size to estimate the covariance matrix.

The primary result of this research is the usefulness of using a low order Fourier (or other orthogonal) expansion to model ABPM data for the purpose of computing the trough to peak (T/P) statistic versus computing the statistic based on time of day sample averages. Although the hourly average T/P statistic is asymptotically consistent for any proposed placebo adjusted drug response curve, a potentially severe price is paid in terms of mean square error. If the actual response curve can be modeled as a low order Fourier series, asymptotically the T/P statistic based on time of day averages has a variance considerably higher than for the T/P statistic based on the Fourier expansion. Further with finite sample sizes, the Monte - Carlo study results demonstrates that typically the T/P estimate based on the Fourier expansion has smaller mean square error for most of the drug response curves tested.

The Monte - Carlo study also demonstrated the basic weakness of all of the T/P statistics. Since each of the T/P statistics are based on the maximum value of either the time of day averages or the Fourier estimates of the time of day mean, the statistics are biased, and the nature of the bias is dependent on sample size and the nature of the underlying drug response. This seemingly precludes creating a confidence interval with the property of including the actual T/P ratio with a specified probability. Perhaps other statistics need to be developed that contain information concerning the range of drug effect over time that have better statistical properties.

The Monte - Carlo study also demonstrates that the above multivariate model is not very useful for modeling ABPM hourly data. In the above multivariate model if we have 2 series of 24 hourly ABPM readings the unknown covariance matrix is 48×48 and has 552 unknown parameters, not exactly a parsimonious

parameterization. Perhaps models with more structured covariance structures would be more useful. Models have been proposed for prediction and estimation of growth curves with special covariance structures [Lee, 1988], as a generalization of the growth curve model [Potthoff et al, 1964], which might be useful for fitting hourly subject ABPM averages. As noted earlier, ABPM data tend not to be equally spaced (leading to the creation of hourly averages for analysis) with occasional missing or bad values. Methods have been developed [R. Jones, 1990, 1991] to handle longitudinal data with ARMA serial correlation when the data is unequally spaced, which may be usefull for modeling ABPM data.

List of References

- Anderson, T. W. (1971). *The Statistical Analysis of Time Series*, John Wiley & Sons, New York.
- Becker, R. A., Chambers, J. M., Wilks, A. R. (1988). *The New S Language*, Wadsworth & Brooks/Cole, Pacific Grove, Cal.
- Crager, M.R. and Reitman, M.A. (1991). Running average analysis of clinical trial ambulatory blood pressure data. *Biometrics* 47, 129-137.
- Fujikoshi, Y., Kanada, T., Tanimura, N. (1990). The growth cure model with an autoregressive covariance structure. *Ann. Inst. Statist. Math.* 42, 533-542.
- Grizzle, J. E. and Allen, D. M. (1969). Analysis of growth and dose response curves. *Biometrics* 25, 357-381.
- Heptinstall, R.H. (1974). Relation of hypertension to changes in the arteries. *Prog. Cardiovasc. Dis.* 17, 25-29.
- Hollander, M. and Wolfe, D. A. (1973). *Nonparametric Statistical Methods*, John Wiley & Sons, New York.
- Johnson, R. A. and Wichern, D. W. (1988). *Applied Multivariate Statistical Analysis*, 2 nd. ed. Prentice Hall, Englewood Cliffs, New Jersey.
- Jones, R. H. and Ackerson L. M. (1990). Serial correlation in unequally spaced longitudinal data, *Biometrika* 77, 721-731.
- Jones, R. H. and Boadi-Boateng, F. (1991). Unequally spaced longitudinal data with AR(1) serial correlation. *Biometrics* 47, 161-175.
- Kannel, W.B. (1974). Role of blood pressure in cardiovascular morbidity and mortality. *Prog. Cardiovasc. Dis.* 17, 5-24.
- Khatri, C. G. (1966). A note on a MANOVA model applied to problems in growth curve. *Ann. Inst. Statist. Math* 25, 413-424.
- Lee, J. C. (1988). Prediction and estimation of growth curves with special covariance structures. *Journal of the American Statistical Association* 83, 432-440.

Marier, M.R., Jacob, R.G., Lehoczy, J.P., Shapiro, A.P. (1988). The statistical analysis of treatment effects in 24-hour ambulatory blood pressure recordings. *Stat. Med.* 7, 697.

Morrison, D. F., *Multivariate Statistical Methods* (1976), 2 nd. ed. McGraw-Hill, New York.

Potthoff, R.F. and Roy, S.N.(1964). A generalized multivariate analysis of variance model useful especially for growth curve problems. *Biometrika* 51, 313-326.

Rao, C. R. (1965). The theory of least squares when the parameters are stochastic and its application to the analysis of growth curves. *Biometrika* 52, 447-458.

Rao, C. R. (1973). *Linear Statistical Inference and Its Applications*, 2 nd. ed. John Wiley & Sons, New York.

Staessen, J., Fagard, R., Ljinen, P., Thijs, L., van Hoof, R. and Amery, A. (1991). Ambulatory blood pressure monitoring in clinical trials. *Jour. of Hypertension* 9, S13-S19.

Srivastava, M. S. and Khatri, C. G. (1979). *An Introduction to Multivariate Statistics*, North Holland, New York.

Streitberg, B., Meyer-Sabellek, W., Baumgart, P. (1989). Statistical analysis of circadian blood pressure recordings in controlled clinical trials. *Jour. of Hypertension* 7, S11-S17.

Streitberg, B. and Meyer-Sabellek (1991). Smoothing twenty-four-hour ambulatory blood pressure profiles: a comparison of alternative methods. *Jour. of Hypertension* 8, S21-S27.

White, W. B. (1991). Analysis of ambulatory blood pressure data in antihypertensive drug trials. *Jour. of Hypertension* 9, S27-S32.

Zachariah, P.K. and Krier, J.D. (1991). Clinical uses of ambulatory blood pressure monitoring. *Jour. of Hypertension* 9, S7-S11.

Name: ROBERT A. JONES

Education:

- Ph.D. Biostatistics, 1997, University of Washington.**
- B.S. Mathematics, 1973, University of Washington.**
- B.S. Molecular Biology, 1971, University of Washington.**

Publications:

- 1. Data Management for a Large Collaborative Clinical Trial, Kronmal, R.A., Davis, K., Fisher, L., Jones, R.A., Computers in Biological Research, July, 1980.**
- 2. A SAS Profitability Analysis System, Preceedings of the Seventh Annual SUGI Conference, 1982, pp 293-297.**
- 3. Tolerance Bounds for Log Gamma Regression Models, Jones, R.A., Scholz, F.W., Osseander, M.I., Shorack, G., Technometrics, May 1985, vol. 27, no. 2 pp 109-118.**
- 4. Statistical Process Control Methods, Preceedings of the Third Annual World Productivity Meeting, Singapore, 1988, pp 124-135.**