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AN ANALYSIS AND SIMULATION OF R-R INTERVALS

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AN ANALYSIS AND SIMULATION OF R-R INTERVALS

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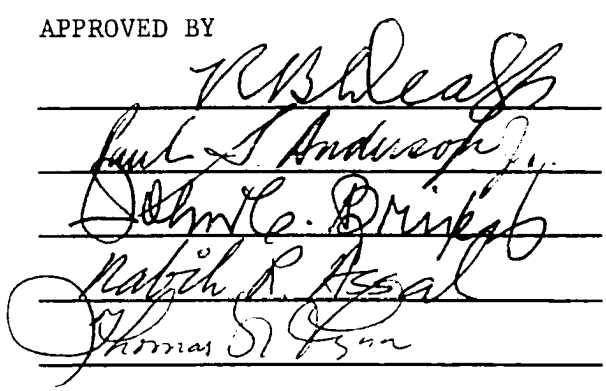

DISSERTATION COMMITTEE

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AN ANALYSIS AND SIMULATION OF R-R INTERVALS

CHAPTER I

INTRODUCTION AND REVIEW OF LITERATURE

In 1969 cardiovascular disease accounted for over 1,000,000 deaths, or approximately 55% of the total deaths in the United States. One-fourth of these victims were below 65 years of age. The American Heart Association reported that more than 27,000,000 Americans are living with some form of cardiovascular disease. A disease which is so widespread and not limited to just the aged must rank high as a major medical and public health problem, not only today but for the future. If progress is to be attained in reducing the number of deaths or controlling the development of this disease beyond which the individual is seriously handicapped, new methods must be developed to study the various components of the cardiovascular system in order to have a clearer understanding of mechanisms involved in the etiology and natural process of the disease.

An electrocardiogram (EKG or ECG) is the recording of electrical impulses that are associated with the contractions of the heart. It can reveal several types of heart abnormalities and specifically recent heart attacks can be confirmed by means of an EKG. However, the recording has limited value with respect to the prediction of an impending heart attack in a particular individual.

The normal EKG shows three waves or wave complexes known simply by the letters P, QRS, and T which are present in each beat. The tall spike, R wave, is usually the most conspicuous in the tracing. One characteristic of an EKG is the number of beats per minute which is called the heart rate while another way of looking at the same thing is the average time between beats. The time between two beats can be determined by measuring the time between the same reference point or wave for two consecutive beats. Since the R wave is the easiest to recognize, both by the physician and by the computer, it is chosen as the reference point for each beat. Hence comes the name R-R interval for the length of time between beats.

Various factors such as medications, heredity, and external stimuli may affect the variability or differences in the times between beats. It is difficult to distinguish small differences in R-R intervals when looking at a normal EKG; however, the unusual intervals can be observed easily. A small R-R interval is observed when there is an extrasystole or premature beat. These premature beats occur when the ventricle is stimulated during its relaxation phase and are followed by an unusually long relaxation phase called a compensatory pause.

Smaller differences or patterns in the R-R intervals may be present and consistent throughout a record but may not be detected by merely visually examining an EKG. Such differences or patterns may only be demonstrated by more precise measurements of the R-R intervals over many cycles or heart beats. With the use of a computer it would be possible to monitor individuals over an extended period in order to obtain the precise measurements which are needed to perform an extensive analyses of

R-R intervals.

Regardless of the fact that R-R intervals have been subjected to only limited analyses, considerable information is contained in R-R interval data. It contains information on the regularity of the heart beat and could be used to study trends in consecutive R-R intervals. For example, a particular record may have a grouping of three to five consecutive R-R intervals which are longer than the average R-R interval and then another grouping of three to five intervals shorter than the mean interval. This general pattern might continue for the entire record and be undetected unless precise measurements and detailed analyses are made of these trends.

The pattern or characteristics of the R-R interval data could be used in a patient monitoring situation where shifts in the pattern could be detected and correlated with clinical data. Particular patterns or trends may be characteristic of specific cardiac disorders. Arrhythmias may be detected by patient monitoring before they become clinically apparent or serious. Lown (1968) observed that although ventricular fibrillation develops suddenly, it is preceded by other rhythmic abnormalities in the heartbeat that may be present up to 72 hours before.

R-R intervals could be studied following the administration of certain drugs which are known to affect the regularity of the heart in an attempt to correlate characteristics of the R-R intervals with different medications and arrhythmias.

Although it would be desirable to keep the number of parameters describing R-R interval data as small and as simple as possible, parameters which describe the relationship of several consecutive R-R intervals should

be considered. Classical mathematical and engineering techniques from the theory of control systems and stochastic processes, such as Fourier and spectral analysis, are frequently used in the analysis of sequentially collected data. Cady, et al., (1961), Attinger (1964), and Taylor (1966) have utilized some of these techniques in their studies of the EKG.

The parameters describing R-R interval data could be incorporated into a model constructed for the purpose of generating a sequence of R-R intervals. The parameters with the corresponding model could be developed for a particular period of time or base period. R-R intervals obtained from using the model should not differ appreciably from those observed for the individual and then at some later time it could be determined whether the individual's pattern of variability of R-R intervals was different from his base pattern. These changes could be important in a patient monitoring situation and they might also be important and useful when evaluating medications for their effect on R-R interval patterns. In these instances one is looking for changes in the R-R interval data which is analogous to the technique of obtaining electrocardiograms before and after exercise and then making interpretations of the changes.

It was mentioned earlier that precise measurement of the R-R intervals was needed for more sophisticated analyses and for obtaining parameters describing R-R interval data. In developing models a large number of intervals are needed. In the past, R-R intervals were obtained by using calipers to measure the distance between R waves on an electrocardiogram; however, these measurements can now be made quickly and accurately by a digital computer. When using calipers the measured distance was converted to time units by taking into account the speed of the paper

passing through the recording machine.

The most common way to present R-R interval data is with a histogram. Sinborg, et al., (1966), stated monitoring techniques were available for the detection of arrhythmias, and that the electrocardiogram provided a means for an identification and qualitative description of the heart's electrical activity, and more important that the R-R interval histogram provided in addition a means for quantification of disorders of cardiac rhythm. Sinborg, et al., (1966), suggested preparation of histograms from records obtained over long periods of time as a technique to compare the responses of heart rate and rhythm to physiological and pharmacological interventions.

Horan and Kistler (1961) obtained histograms of R-R interval data from 47 records in 17 patients with atrial fibrillation. There were 442 to 1412 beats in each record. They observed bimodal frequency distributions of R-R intervals when the heart rate was in the range of 90 to 120 beats per minute. When the heart rates were less than 90 and greater then 120 beats per minute the frequency distributions were unimodal. In general the frequency of premature beats did not appear related to the average heart rate or shape of the R-R interval frequency distribution. One figure presented in the paper showed R-R interval histograms obtained from an individual while receiving no medication, and while receiving either digitalis or atropine. Differences in the shapes were noted and served as a technique to compare the patient's response to medication.

Horan and Kistler (1961) referenced the work of Arnoldi (1927) and Jordan (1954). Arnoldi made sequential comparisons in patients that had shown double peaks in their R-R interval distributions. He found a

tendency for grouping about the short "dominant" intervals at fast rates and about the long "dominant" intervals at slow rates. In longer records in nine of ten patients with atrial fibrillation Jordan failed to get multiple peaks. The single patient with a double peak had a much less pronounced double peak in the total record than in some segments of the record. Jordan then concluded that the dual peaks reported by Arnoldi were possibly artifacts resulting from small samples.

Kalbfleisch (1968) obtained sixty-five R-R interval histograms from eleven patients with normal (sinus) rhythm. The histograms covered recording times of fifteen to thirty minutes. Ten of the eleven patients had arteriosclerotic heart disease. Three of these ten had an acute myocardial infarction only hours previous to the period of the histogram while the remaining seven suffered myocardial infarctions in the more distant past. In general, the histograms took the shape of a normal frequency curve, however with an increase in heart rate the histograms tended to be leptokurtic and displayed a decrease in R-R interval variability.

Kalbfleisch mentioned the need to establish what a normal sinus rhythm histogram should look like and what affects everyday activities have on it. In addition, histogram shapes for different arrhythmias need to be established. He felt the histogram was not sufficient for diagnosing a type of arrhythmia and that in order to determine the type of arrhythmia the conventional electrocardiographic recording was still necessary whereas the histogram was only a means of displaying quantity of arrhythmias. Kalbfleisch recommended the use of histograms for quantification of drug effects on rate and rhythm. In a similar manner the course of an illness with regard to rate and rhythm could also be more

accurately followed with the use of R-R interval histograms.

A histogram of a set of data does not take into account the order in which the data was collected or the order in which the events occurred. Parameters describing R-R intervals should take into account the serial nature of the data. In working with R-R intervals, researchers were lead to consider two adjacent intervals. Moe and Abildskov (1964) considered the influence of long intervals on subsequent intervals. They used dogs in their experiments to study R-R intervals during periods of atrial fibrillation induced by electrical stimulation. They found that long intervals followed long intervals considerably more often than expected from random occurrence. With a rather limited sample they found a relatively high correlation between the duration of one interval and that of its successor, but no significant relationship persisted beyond the immediate successor.

Braunstein and Frank (1961) computed the autocorrelation function of what they defined to be the ventricular electrocardiogram. They worked with time to a specific R wave from an arbitrary reference time t_o and created a new sequence of binary data with a "one" indicating the presence of an R wave in an interval of a preselected partition. They obtained an autocorrelation of these data which showed a period approximately equal to the normal heart rate. These findings were consistent with those of Arnoldi (1927). Braunstein and Frank did not use the autocorrelation method on R-R interval data, although Moe and Abildskov (1964) suggested that autocorrelation be used to study the relationships between successive R-R intervals and also intervals farther removed. These studies showed the interest among researchers in obtaining information about R-R

interval data when the serial nature of the data was taken into account.

Electrocardiographic records consisting of 2000 successive R-R intervals were obtained from 24 patients with atrial fibrillation and studied by Goldstein and Barnett (1967). They obtained R-R interval distributions and frequency distributions of two adjacent intervals. Their patients had atrial fibrillation with different etiologies. They observed that patients with similar mean ventricular rates had similar histograms. They were not able to associate any particular histogram characteristic with an etiology or type of medication.

Burdick and Scarbrough (1968) discussed the relationship between "heart rate" and autocorrelation which they used as a measure of heart rate variability. Throughout their paper they used R-R interval data but referred to it as heart rate data. They felt the autocorrelation was a good measure to characterize R-R interval variability because it was unaffected by the mean R-R interval. They used eighteen normal male volunteers as subjects in conducting an experiment where each subject was observed and R-R interval data collected for a fifteen minute prestress, one minute stress, and fifteen minute post-stress period. The one minute stress period consisted of placing one foot in ice and water. Using regression analysis with the average R-R interval as the dependent variable and the autocorrelation as the independent variable they found a strong negative relationship between average R-R interval and autocorrelation of lag one. These results suggested that the average R-R interval should be considered as a factor in studying R-R interval variability.

A model for generating the intervals between consecutive R waves has been proposed by ten Hoopen (1966). He assumed that there was no

relationship between adjacent R-R intervals because, as he correctly stated, it complicated any analytical approach to consider them dependent. In his model a beat occurred as soon as a minimum number of basic miniature excitations reached the atrioventricular node. The intervals between basic excitations had a normal distribution. From time to time in an irregular fashion the process was interrupted in such a way that the amount of excitation accumulated since the last beat was set to zero and the process of summing miniature excitations started again. This method of generating a sequence of R-R intervals lead to an R-R interval distribution which was skewed because some of the intervals were very large.

Simons and Johnson (1965) discussed the possible relationships between respiration and heart rate. Other possible factors such as type of medication, particular situations thought to affect heart rate, familial history, and medical history could be investigated; however this study does not include an investigation of such cross-correlations.

The purpose of this study is to give methods to describe and use R-R interval data as well as to present and compare new techniques for simulating these data. Preliminary findings are presented which lead to new methods for simulating sequences of these intervals. Some of the methods or models include parameters describing the relationship among consecutive intervals. A total of ten methods are presented and comparisons made during two stages of sleep.

CHAPTER II

PRELIMINARY INVESTIGATION

A preliminary investigation was performed on R-R interval data from two subjects. The purpose of the investigation was to study the relationship of adjacent R-R intervals and those farther removed. For the first subject, Subject A, the data was separated into two records. The first with 140 R-R intervals during which five extrasystoles were present and the second with 160 R-R intervals when no extrasystoles were present. Plots of the data suggested that the data was more variable in the first record than the second, even when the short and compensatory long R-R intervals accompanying each extrasystole were ignored. R-R interval distributions for the two records are shown in Figures 1 and 2.

The average difference between successive intervals in both records was zero, indicating there was no overall linear trend in the length of the R-R intervals. The raw data was recorded to the nearest one hundred and twenty-fifth of a second. A measure of the variability of the R-R intervals in the two records was obtained. The sum of each difference squared and divided by the number summed yielded 25.71×10^{-4} in the first record and 3.43×10^{-4} in the second. In computations related to the first record, differences which involved the "short" or "long" R-R interval accompanying an extrasystole were omitted. Even with those omitted, there was an apparent difference in the variability of the R-R

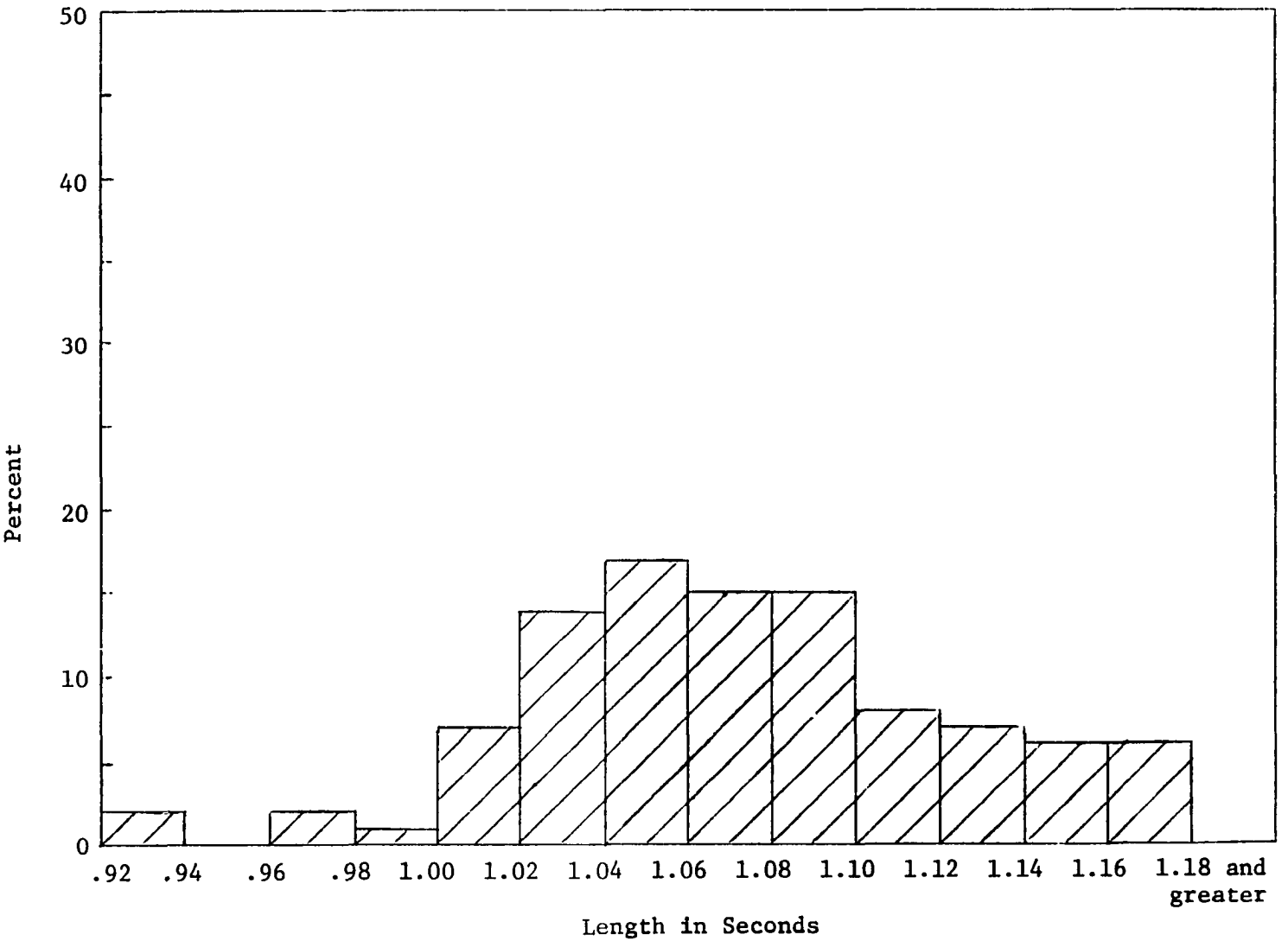

Figure 1--Histogram of R-R intervals for Record 1 of Subject A.

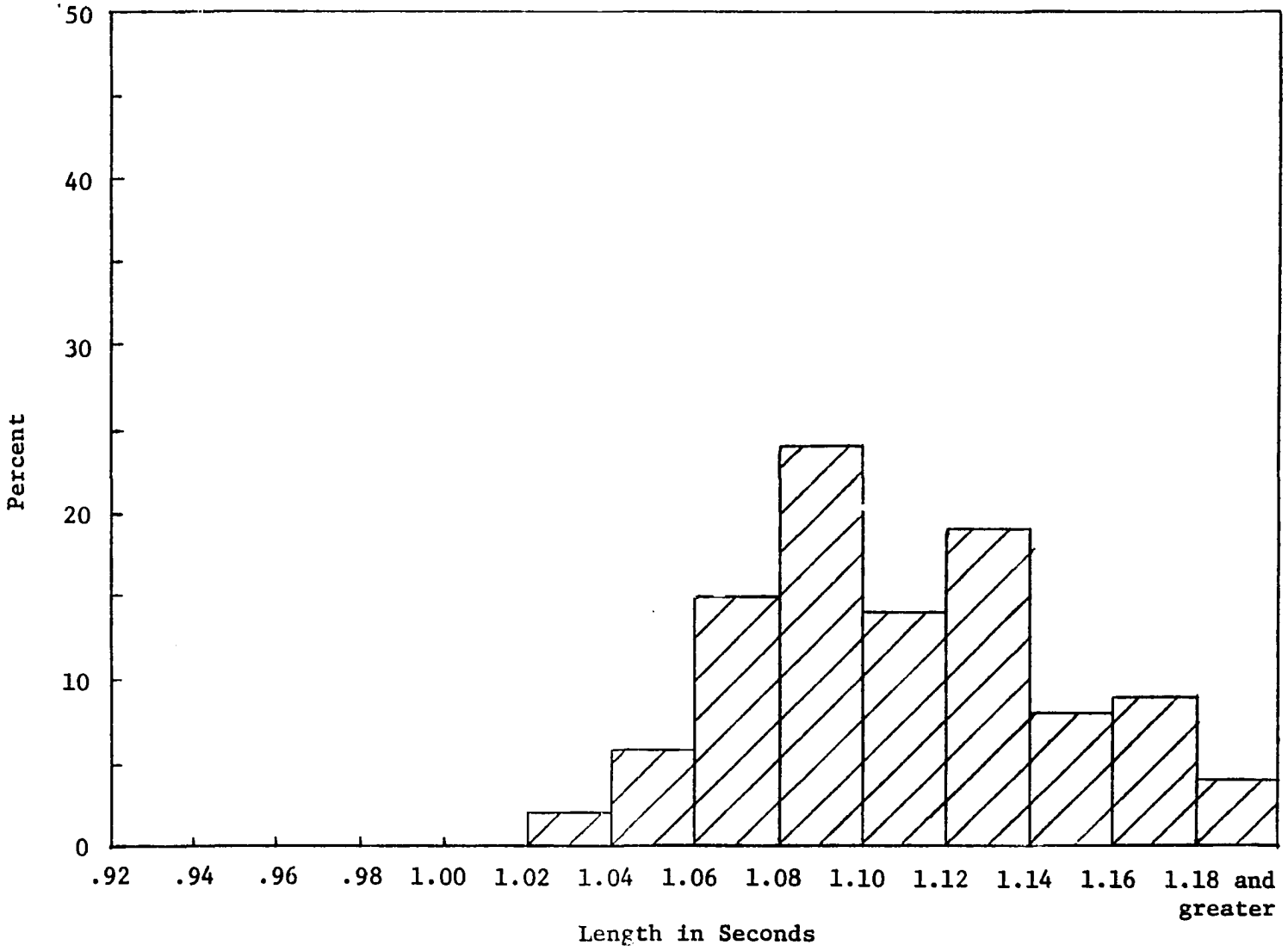

Figure 2--Histogram of R-R intervals for Record 2 of Subject A.

intervals during the time extrasystoles were present and when they were not present.

The R-R intervals of both records were divided into four types and the extrasystoles omitted. Type one consisted of intervals of length .90 to 1.02 seconds, type two consisted of intervals from 1.02 to 1.08 seconds, type three consisted of intervals from 1.08 to 1.14 seconds, and type four consisted of intervals greater than or equal to 1.14 seconds. Boundaries for the four types of intervals were chosen arbitrarily except that consideration was given to obtain sufficient numbers of R-R intervals of each type. There was no interval less than 1.02 seconds in the second record while the first record had 16 less than 1.02 seconds. The distributions of intervals from the two records and of intervals following the intervals of each type were obtained and compared using chi-squared tests. Statistical significance at the five percent level was determined. The distributions of R-R intervals from the two records were statistically significantly different (Figures 1 and 2). Distributions of the intervals following each type interval were obtained for each record and are shown in Figures 3 through 9. In the first record, the intervals following type one intervals (Figure 3) were significantly different from those following intervals in each of the other three types (Figures 4 through 6). The distributions of intervals following types two, three, and four intervals (Figures 4 through 6) were not significantly different. In the second record the intervals following interval types two, three, and four (Figures 7 through 9) were significantly different from each other. From these comparisons it could be inferred that the joint relationship of intervals between consecutive beats was different for Subject A when

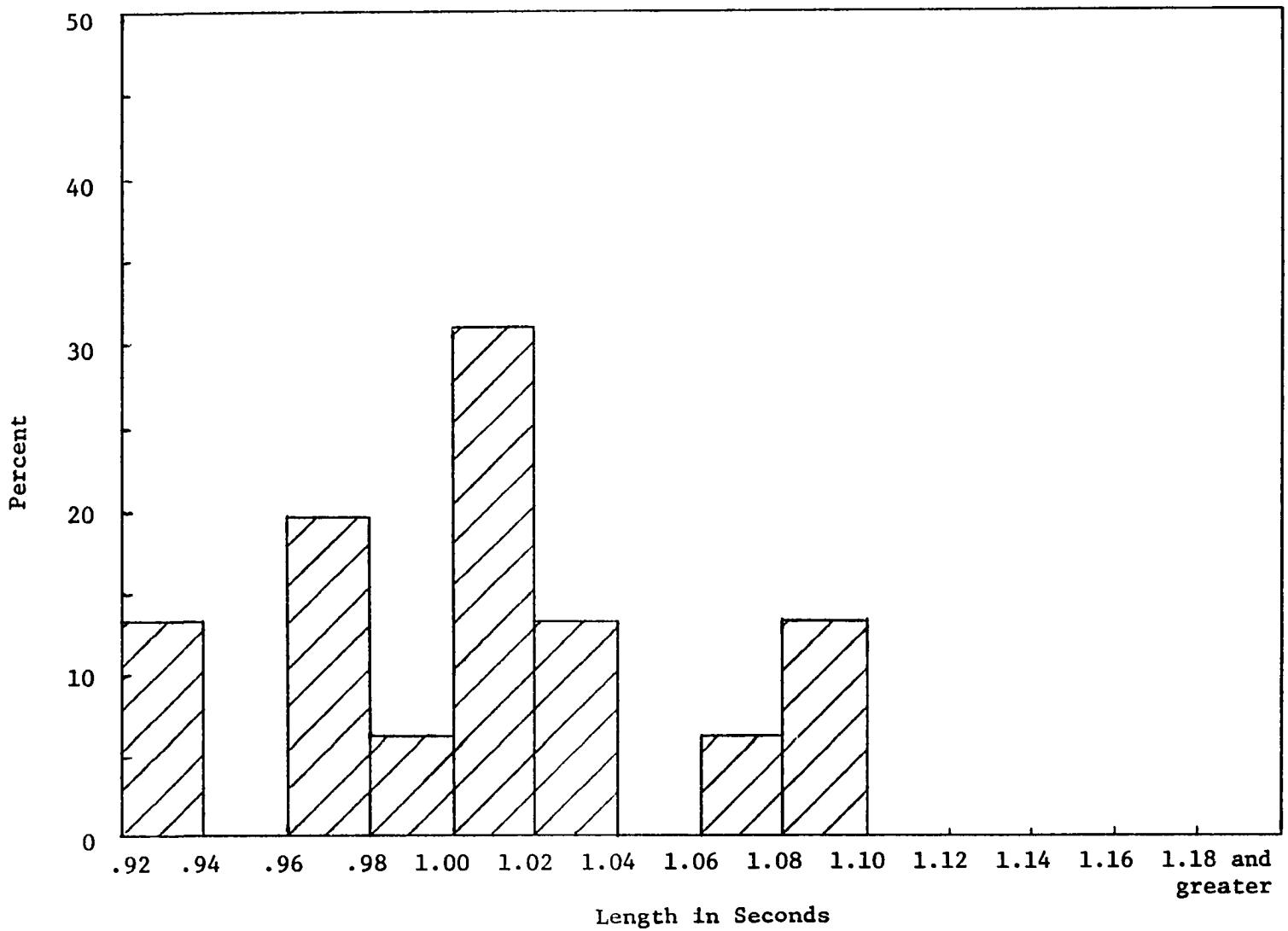

Figure 3--Histogram of first R-R intervals following type 1 R-R intervals for Record 1 of Subject A.

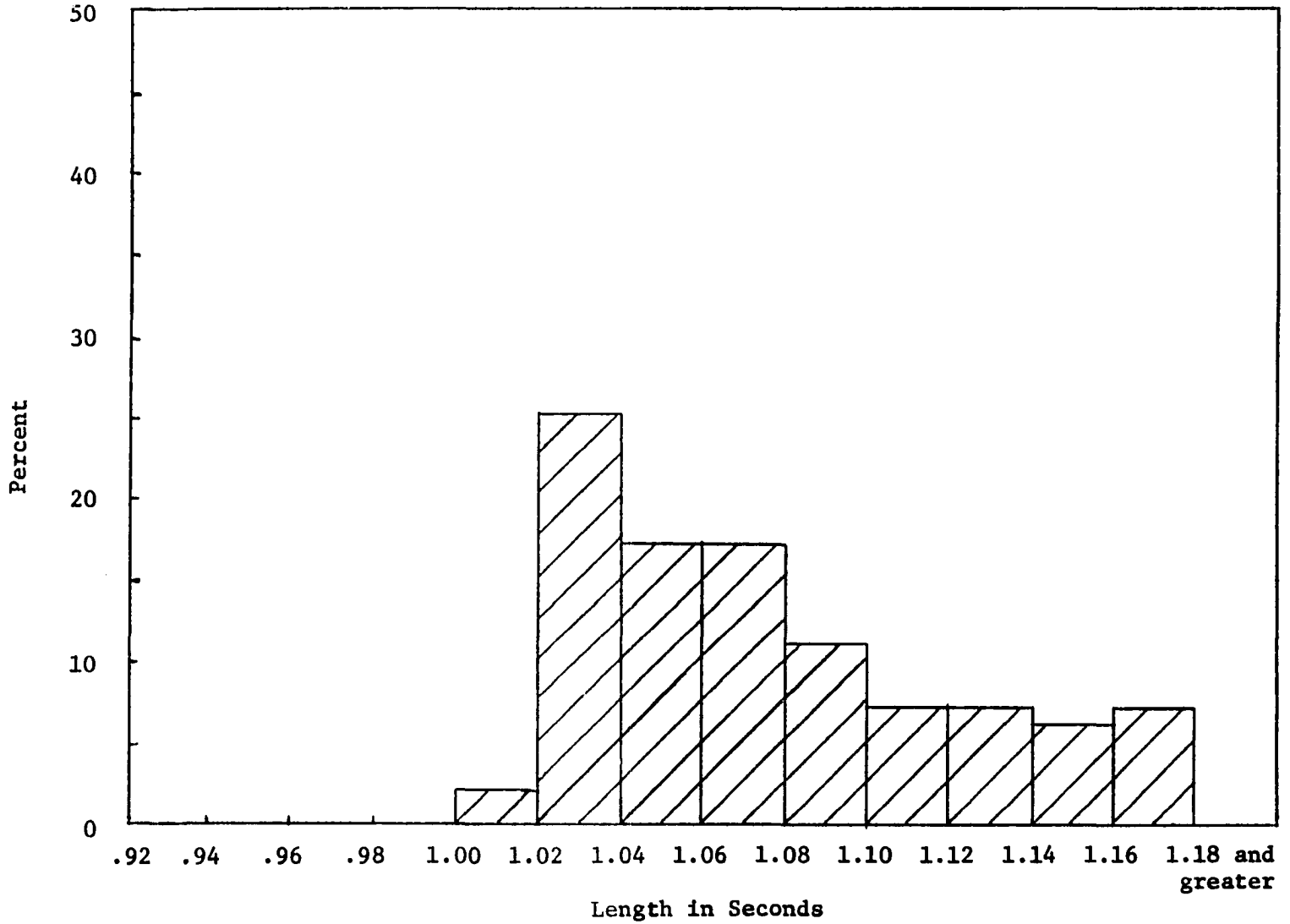

Figure 4--Histogram of first R-R intervals following type 2 R-R intervals for Record 1 of Subject A.

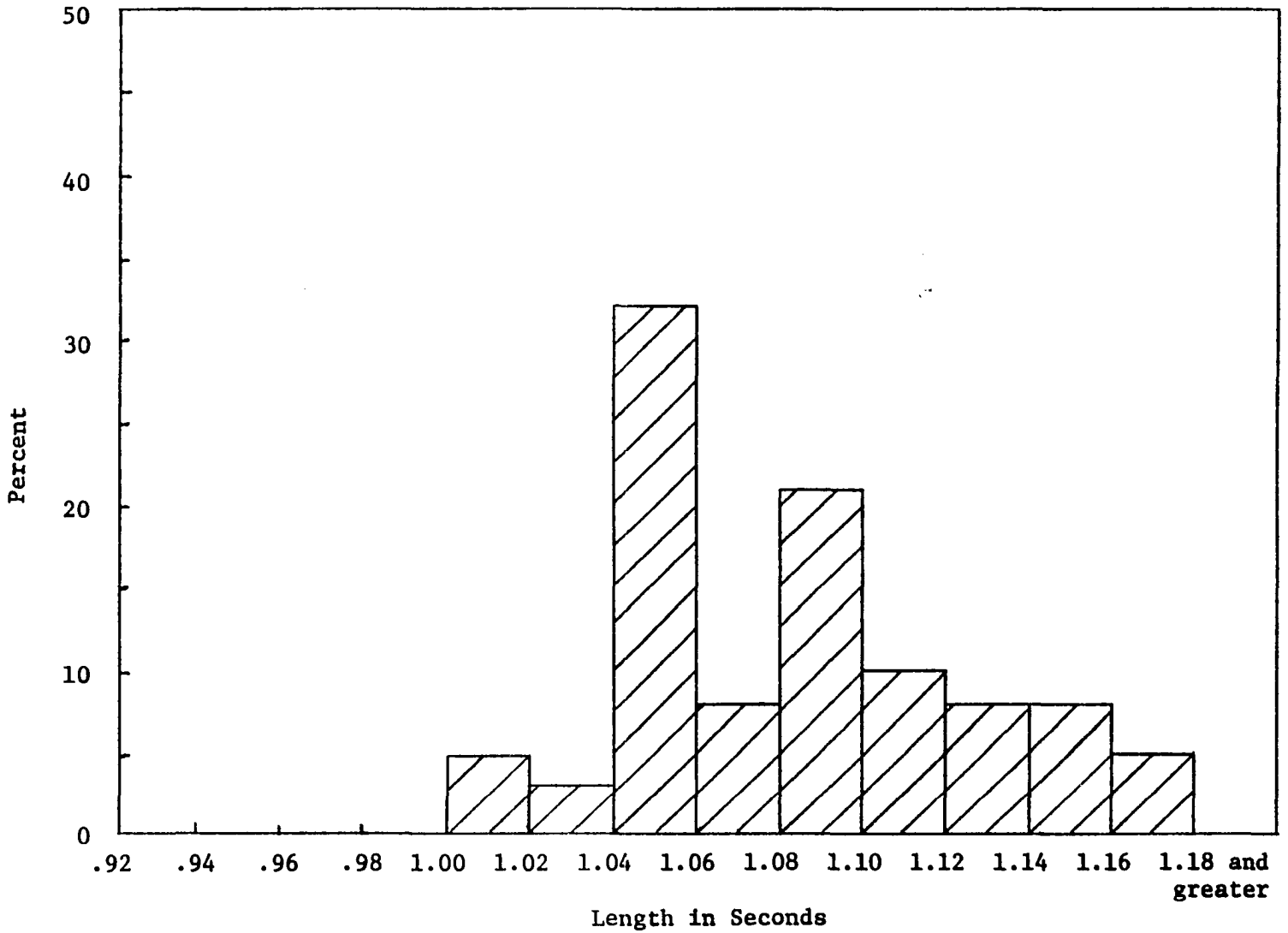

Figure 5--Histogram of first R-R intervals following type 3 R-R intervals for Record 1 of Subject A.

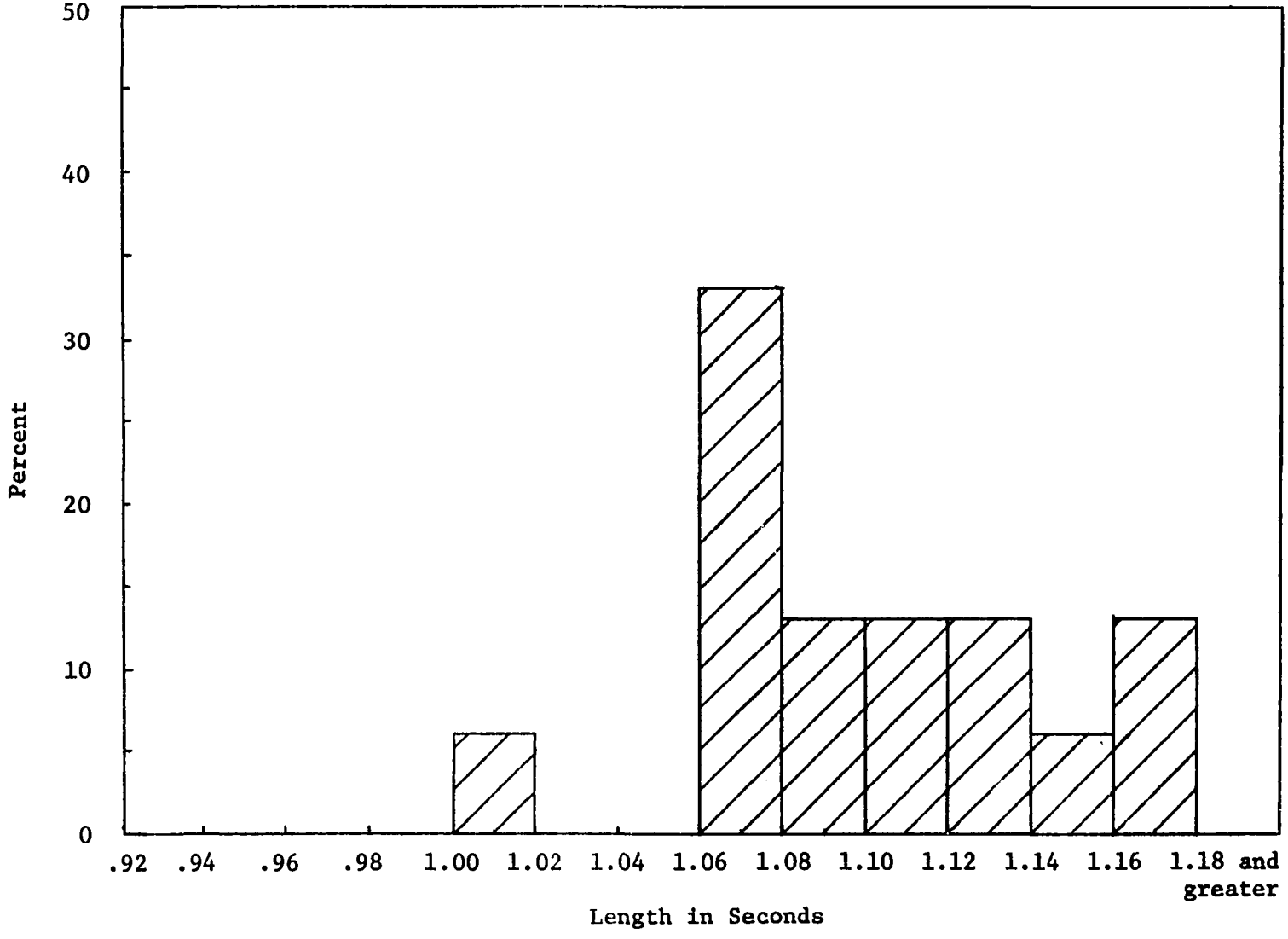

Figure 6--Histogram of first R-R intervals following type 4 R-R intervals for Record 1 of Subject A.

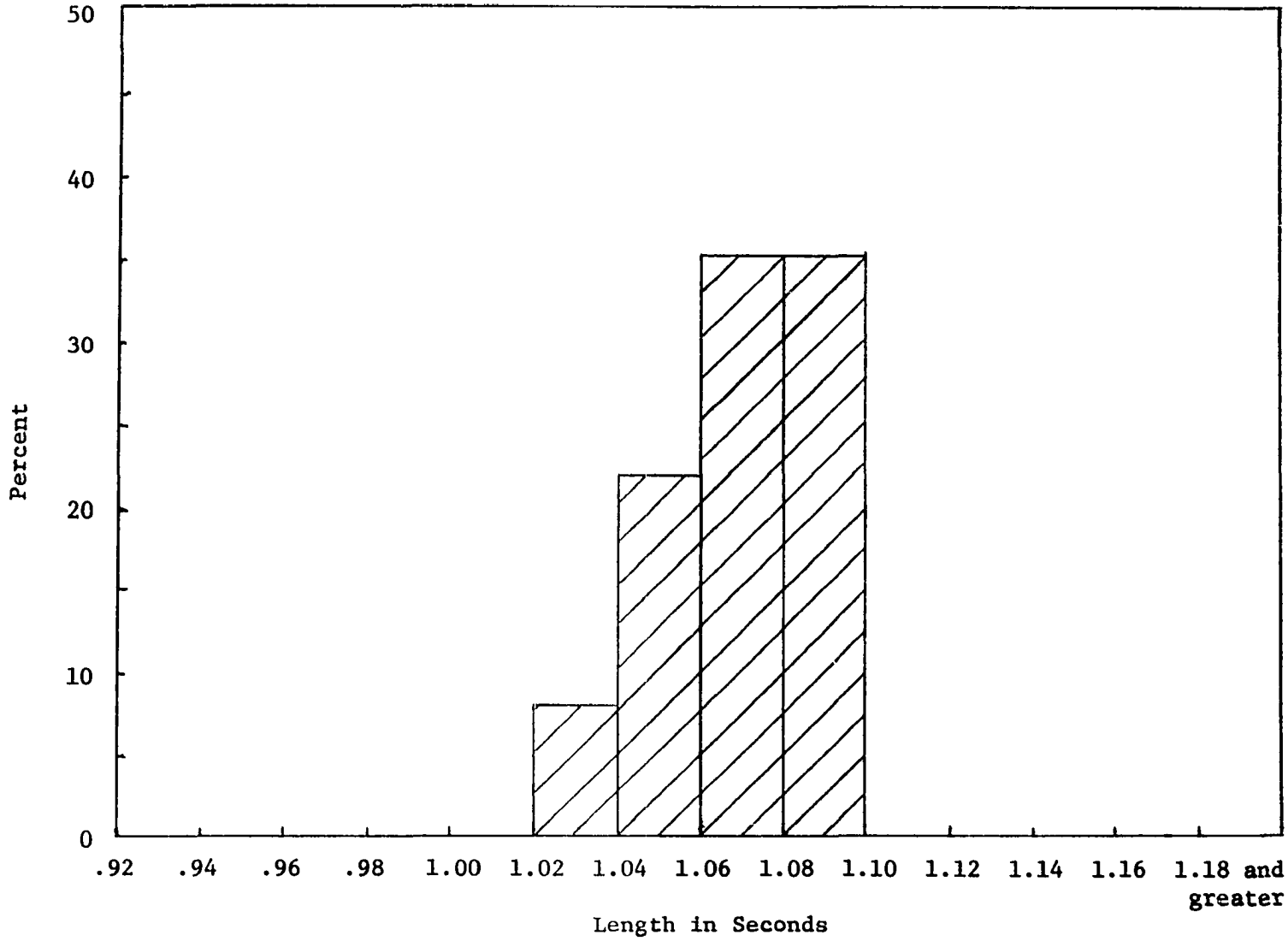

Figure 7--Histogram of first R-R intervals following type 2 R-R intervals for Record 2 of Subject A.

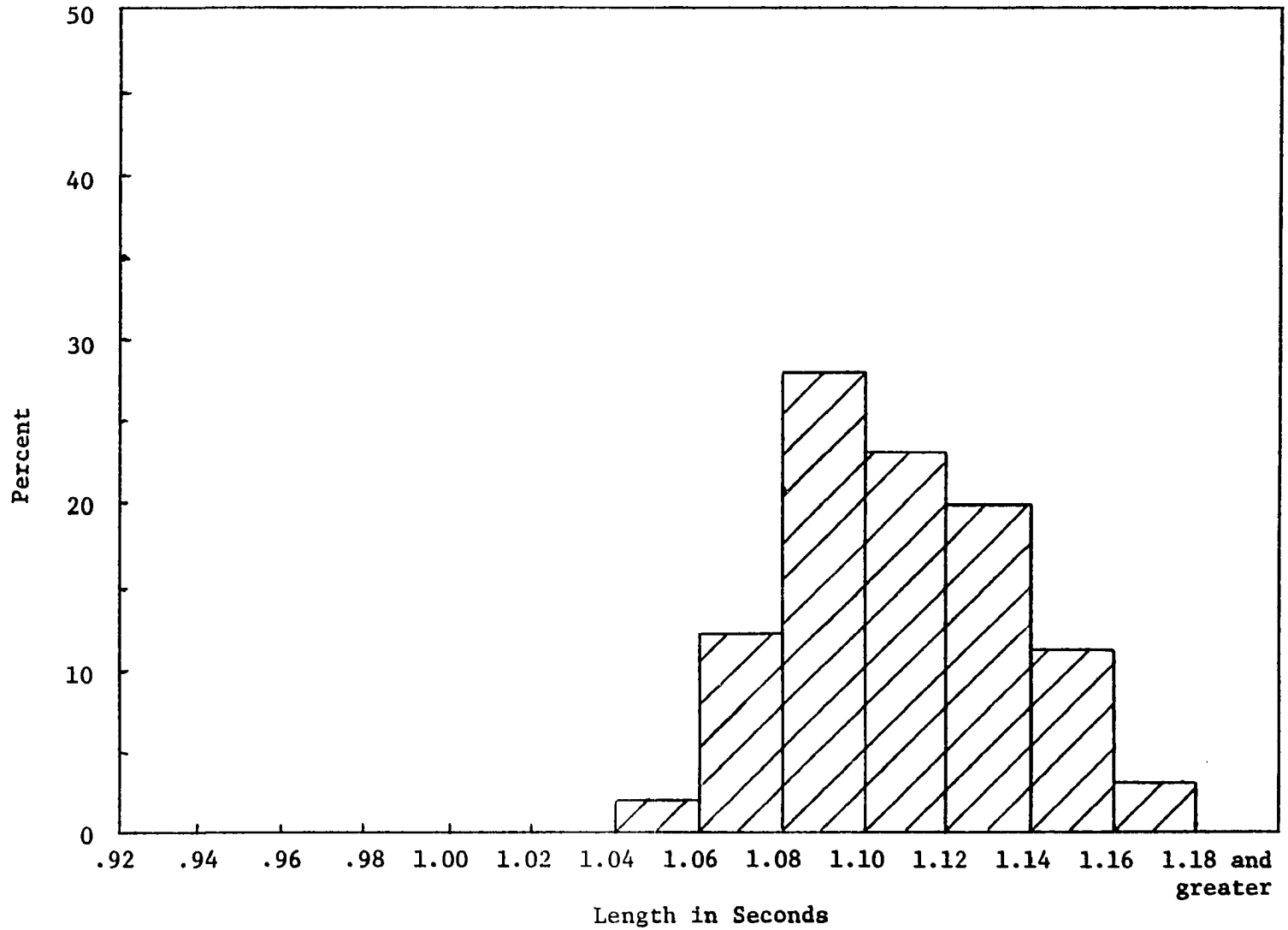

Figure 8--Histogram of first R-R intervals following type 3 R-R intervals for Record 2 of Subject A.

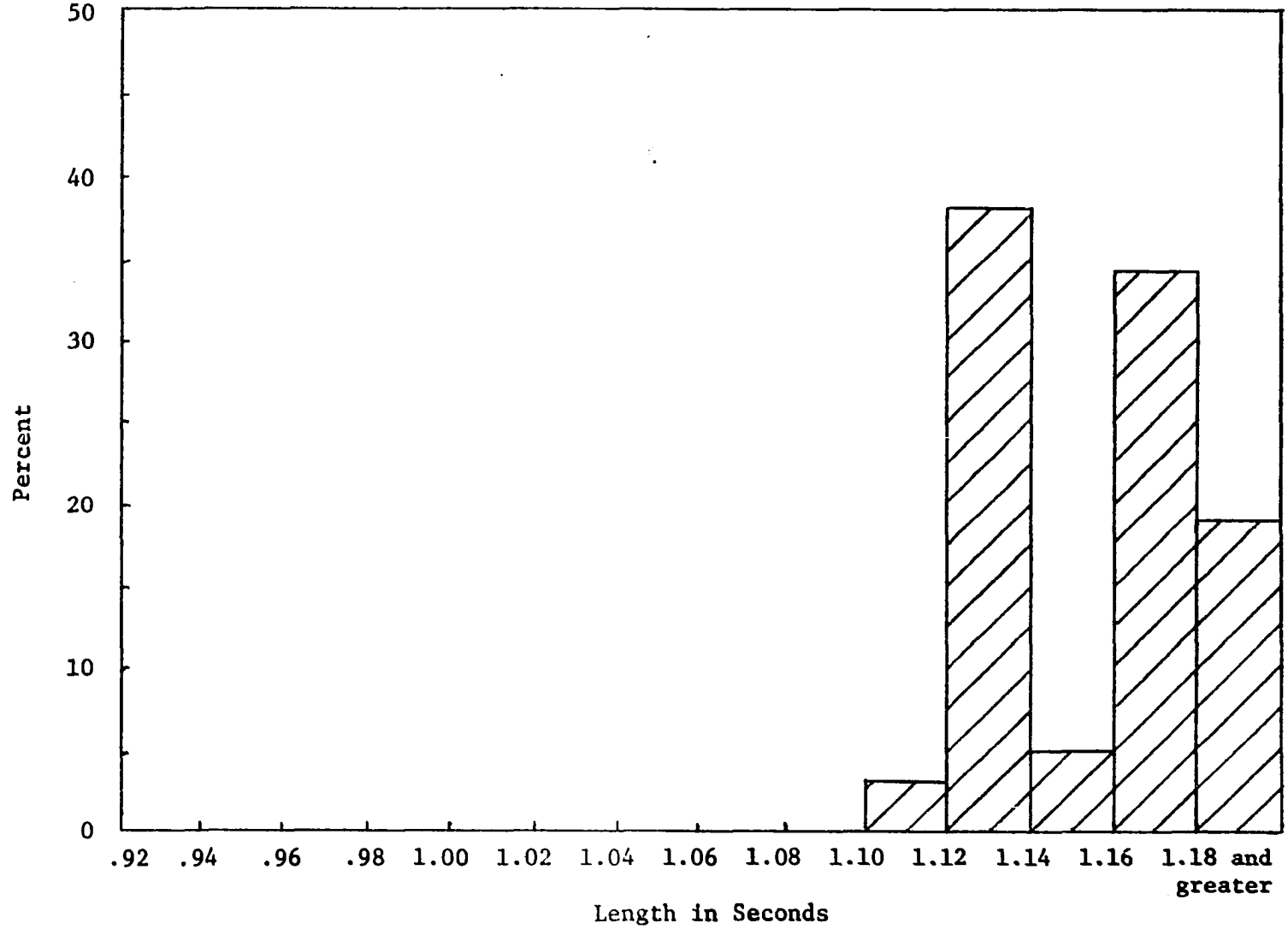

Figure 9--Histogram of first R-R intervals following type 4 R-R intervals for Record 2 of Subject A.

extrasystoles were present (Record 1) and when they were not present (Record 2). Also, the average squared difference between consecutive R-R intervals was markedly different, 25.71×10^{-4} for Record 1 and 3.43×10^{-4} for Record 2.

In addition to adjacent intervals, distributions were obtained for Subject A for the second intervals after intervals of the four types. In the first record the second intervals following type two intervals were significantly different from second intervals following types one, three, and four intervals. There were no significant differences of second intervals following types one, three, and four intervals. In the second record the second intervals following intervals of the three types present were significantly different from each other. In the second record distributions were compared for the third and fourth intervals following intervals of the three types. In both instances the three distributions were statistically significant from each other. Distributions of the fourth intervals following each type interval are shown in Figures 10 through 12. These findings were consistent with a statistical test that was performed to test the number of runs above and below the mean R-R interval. By the method given in Wilks (1962) the small number of runs were statistically significant at the one percent level. These findings also suggest that there is a relationship between consecutive intervals.

Intervals following type two intervals (Figures 4 and 7) were significantly different for the two records. Similar results for intervals following type three (Figures 5 and 8) and type four (Figures 6 and 9) intervals were found.

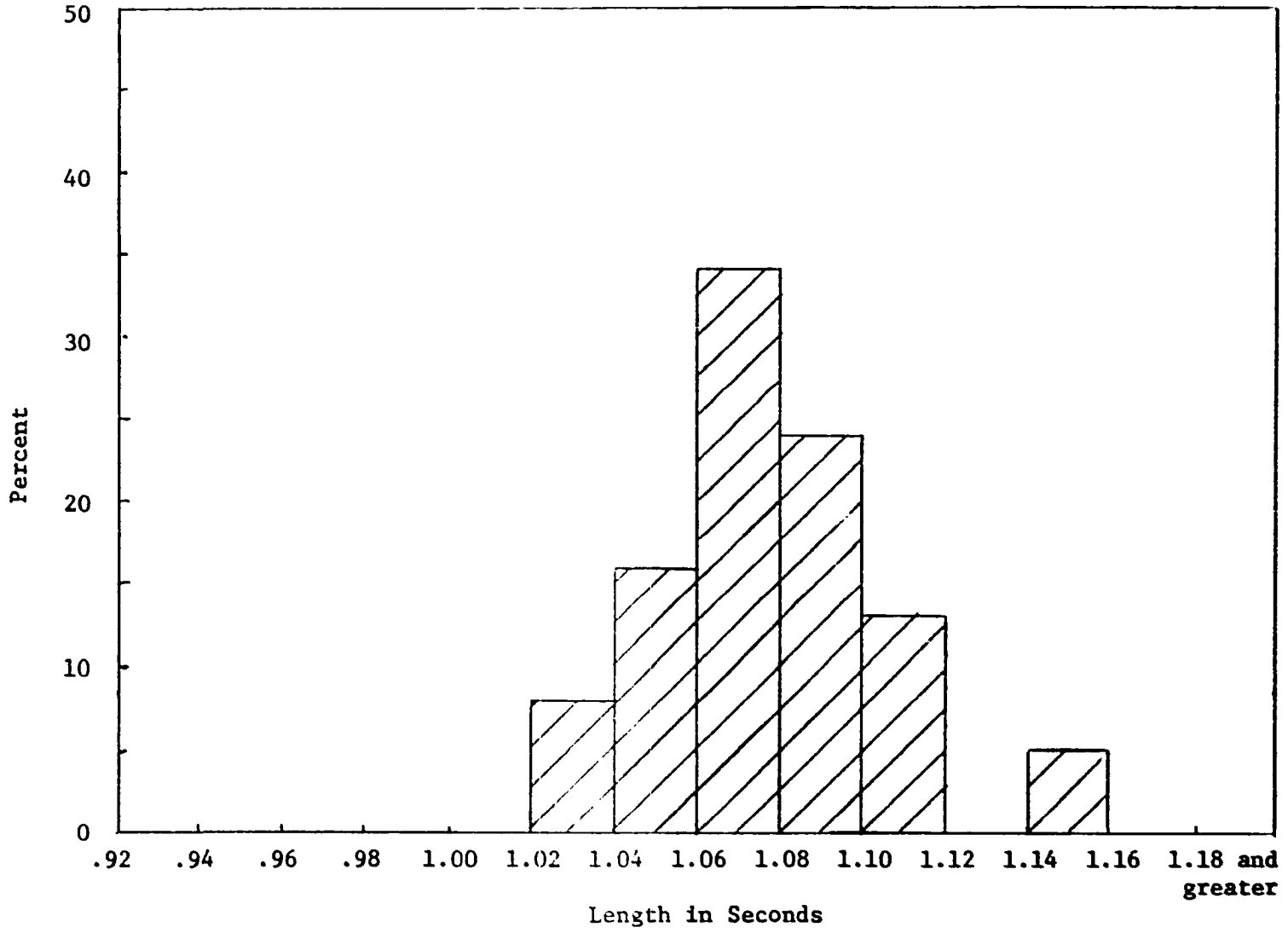

Figure 10--Histogram of fourth R-R intervals following type 2 R-R intervals for Record 2 of Subject A.

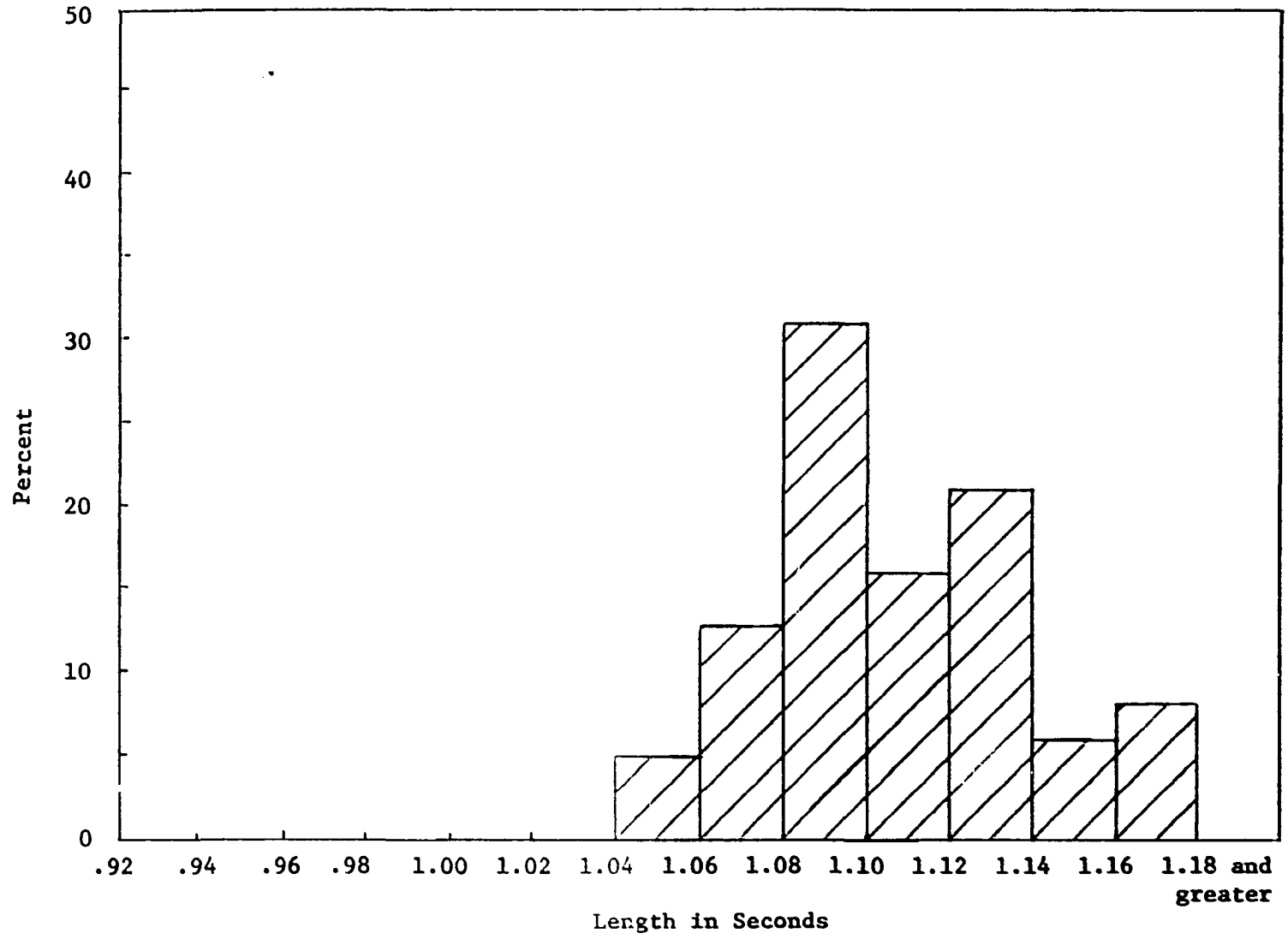

Figure 11--Histogram of fourth R-R intervals following type 3 R-R intervals for Record 2 of Subject A.

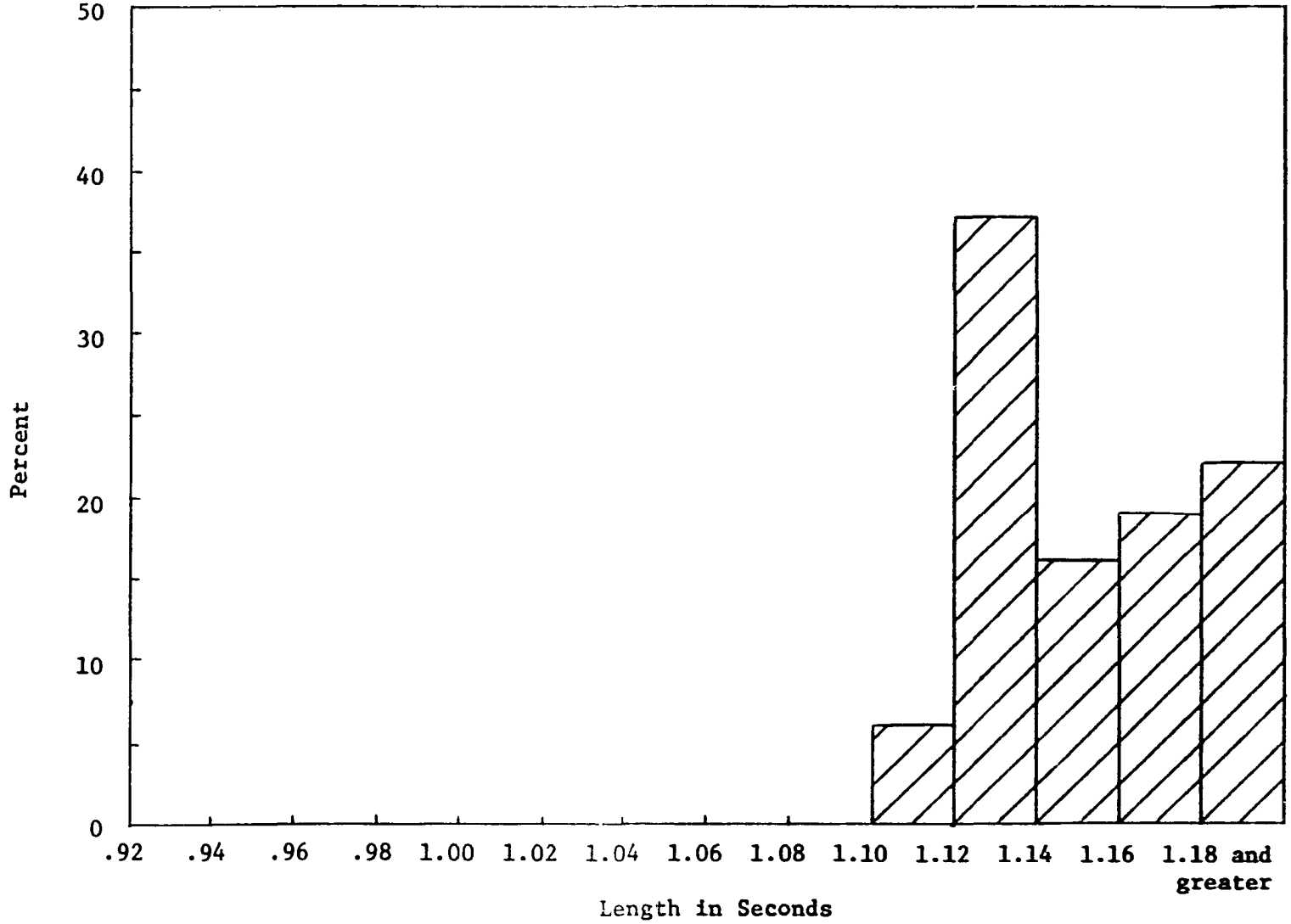

Figure 12--Histogram for fourth R-R intervals following type 4 R-R intervals for Record 2 of Subject A.

For a second subject, Subject B, 300 R-R intervals were divided into two records of 150 R-R intervals each. In the first record the patient had an apparent extrasystole, but there was no extrasystole present in the second record. The data in each record was divided into four types; less than .77 seconds, .77 to .79 seconds, .79 to .81 seconds, and .81 or greater seconds. The distributions of R-R intervals following intervals of the four types were all significantly different from each other. These results were obtained in both records. The average of the squared deviations between successive R-R intervals was 6.7×10^{-5} for record one and 5.2×10^{-5} for record two. The short and compensatory long R-R intervals accompanying the extrasystole were excluded from the computations. There was a statistically significant small number of runs above and below the mean R-R interval in both records.

Sequences of R-R intervals were generated for Subject A. The generated data summarized in Table 1 were obtained by using a random model and the assumption that two consecutive R-R intervals had a bivariate normal distribution. The values of the parameters used in the model were equal to those obtained from the observed data.

These preliminary analyses involving interval lengths and consecutive intervals showed that the joint relationship of consecutive intervals was worthy of further study and should be considered in developing simulation models for R-R interval data.

TABLE 1

PRELIMINARY RESULTS FOR ONE SUBJECT

SUBJECT A - OBSERVED R-R INTERVALS

	Mean	Variance	Correlation Between Consecutive R-R Intervals
Record 1	1.0636	.00965	-.138
Record 2	1.1084	.00142	.872

SUBJECT A - GENERATED R-R INTERVALS

	Mean	Variance	Correlation Between Consecutive R-R Intervals
Record 1	1.0608	.01087	-.142
Record 2	1.1023	.00174	.886

CHAPTER III

METHODS

R-R interval data from four individuals were utilized in evaluating ten different simulation methods. The data were obtained from the Department of Psychiatry at the University of Oklahoma Medical Center. Demographic information on the subjects is given in Table 2. For each subject, 400 R-R intervals were obtained during a period of slow wave sleep and another 400 were obtained during a stage of sleep when the subject was experiencing rapid eye movements (REM sleep). 800 R-R intervals were obtained from each subject on two different days.

Each record of 400 R-R intervals was divided into two sections consisting of the first 200 R-R intervals and the second 200 R-R intervals. Means and variances for each section are given in Table 3. The minimum and maximum R-R intervals as well as the range for each section are given in Table 4.

Ten different methods were used to generate series of R-R intervals. Five series corresponding to each section of data were generated using each method. The preliminary investigation presented in CHAPTER II indicated that in some cases there is a joint relationship between consecutive intervals. For this reason, eight of the ten simulation methods studied incorporated in one manner or another a joint relationship of consecutive intervals. The univariate and bivariate empirical and the

TABLE 2

STUDY SUBJECTS

Subject Number	Age	Sex	Date of Record	Patient* or Control†
1	46	M	11-10-67 11-11-67	Control
2	32	M	11-17-67 11-18-67	Control
3	54	M	3-23-68 3-24-68	Control
4	57	M	4-26-68 4-27-68	Patient

*Patient denotes subject suffered coronary insufficiency one to seven years before the test or recording.

†Control subjects had no previous clinical history of heart disease.

TABLE 3

R-R INTERVAL MEANS AND VARIANCES
(MEAN, VARIANCE)

SLOW WAVE SLEEP

	DAY 1		DAY 2	
Subject	Section 1	Section 2	Section 1	Section 2
1	(0.791, 0.00594)	(0.800, 0.00277)	(0.899, 0.00115)	(0.897, 0.00074)
2	(0.772, 0.00057)	(0.771, 0.00079)	(0.800, 0.00136)	(0.806, 0.00130)
3	(0.950, 0.00052)	(0.933, 0.00034)	(0.891, 0.00058)	(0.872, 0.00029)
4	(0.859, 0.00031)	(0.860, 0.00024)	(0.839, 0.00190)	(0.858, 0.00026)

REM SLEEP

	DAY 1		DAY 2	
Subject	Section 1	Section 2	Section 1	Section 2
1	(0.823, 0.00793)	(0.852, 0.00172)	(0.902, 0.00044)	(0.893, 0.00079)
2	(0.852, 0.00332)	(0.910, 0.00963)	(0.798, 0.00237)	(0.752, 0.00041)
3	(0.908, 0.00114)	(0.890, 0.00074)	(0.831, 0.00089)	(0.804, 0.00019)
4	(0.909, 0.00154)	(0.912, 0.00303)	(0.884, 0.00137)	(0.853, 0.00264)

TABLE 4

R-R INTERVAL RANGE DATA
(MINIMUM, MAXIMUM)
RANGE

SLOW WAVE SLEEP

Subject	DAY 1 Section 1	DAY 1 Section 2	DAY 2 Section 1	DAY 2 Section 2
1	(0.624, 0.976) 0.352	(0.696, 0.992) 0.296	(0.840, 1.064) 0.224	(0.840, 0.976) 0.136
2	(0.720, 0.848) 0.128	(0.704, 0.856) 0.152	(0.720, 0.944) 0.224	(0.728, 1.040) 0.312
3	(0.904, 1.016) 0.112	(0.888, 0.984) 0.096	(0.840, 0.960) 0.120	(0.840, 0.928) 0.088
4	(0.808, 0.920) 0.112	(0.824, 0.952) 0.128	(0.704, 0.928) 0.224	(0.800, 0.920) 0.120

REM SLEEP

Subject	DAY 1 Section 1	DAY 1 Section 2	DAY 2 Section 1	DAY 2 Section 2
1	(0.640, 1.032) 0.392	(0.784, 1.016) 0.232	(0.856, 0.976) 0.120	(0.800, 0.976) 0.176
2	(0.720, 1.032) 0.312	(0.720, 1.384) 0.664	(0.720, 1.152) 0.432	(0.704, 0.800) 0.096
3	(0.856, 1.008) 0.152	(0.824, 0.976) 0.152	(0.776, 0.912) 0.136	(0.768, 0.840) 0.072
4	(0.816, 1.064) 0.248	(0.768, 1.088) 0.320	(0.760, 0.960) 0.200	(0.696, 0.952) 0.256

univariate and multivariate normal distributions were inherent in these methods. The normal distributions were chosen because they are applicable to a wide variety of data. For the convenience of the reader the methods are listed in Table 5.

In describing the simulation methods, x_t is used to denote the t^{th} observed R-R interval of a record while y_{jt} is used to denote the generated R-R interval corresponding to the t^{th} observed interval and j^{th} trial.

A sum of squared deviations of lag ℓ is defined by

$$\sum_{t=1}^{200-\ell} (x_t - y_{j\ t+\ell})^2$$

for trial j. It is a measure of the closeness of the generated to the observed data. The sums of squared deviations were adjusted in order to correspond to 200 differences between observed and generated data and the minimum sums of squared deviations for lags zero through nineteen were used for comparisons of the methods without adjustment. For the methods with adjustment the sums of squared deviations with lag zero were used. The Wilcoxen Matched Pairs Signed Ranks test was used for comparisons between two methods while the Friedman Two-Way Analysis of Variance test using ranks was used for comparisons among three methods. A description of these tests is given in Siegel (1956). Separate comparisons of the simulation methods were made for two types of sleep.

A Fourier series with thirty-five pairs of terms was fit to each Section 1 and Section 2 data. Sums of squared deviations between the Fourier series and the observed data were computed. These computations were made because Fourier series analysis is frequently used to analyze

TABLE 5

LIST OF SIMULATION METHODS

Number		Method
1	UVN	Univariate Normal
2	UVE	Univariate Empirical
3	BVE	Bivariate Empirical
4	BVEA	Bivariate Empirical with Adjustment
5	BVN	Bivariate Normal
6	BVNA	Bivariate Normal with Adjustment
7	TVN	Trivariate Normal
8	TVNA	Trivariate Normal with Adjustment
9	QVN	Quadravariate Normal
10	QVNA	Quadravariate Normal with Adjustment

time series data such as consecutive R-R intervals; however, in this study the Fourier series fit and associated sum of squared deviations will only serve as a reference value and no direct comparisons will be made with the simulation methods.

A description of the methods used to simulate R-R interval data follows.

Method 1: Univariate Normal (UVN)

In this method the mean ($\bar{x}$) and the variance (s^2) was computed for Section 1 for each day and then a sequence of random variables was drawn from a normal distribution having the same mean and variance. This procedure was used to generate a series of R-R intervals. Their values were given by

$y_{jt} = g_{1jt}(\bar{x}, s^2)$, t=1, 2, ..., 200 and j=1, 2, 3, 4, 5, where $g_{1jt}(\bar{x}, s^2)$ is used to denote that y_{jt} depended on a normal distribution with parameters $\bar{x}$ and s^2.

$$\bar{x} = \frac{1}{200}\sum_{t=1}^{200} x_t \quad \text{and} \quad s^2 = \frac{1}{199}\sum_{t=1}^{200}(x_t - \bar{x})^2$$

After a sequence of 200 R-R intervals was drawn, the quantities

$$G_{1j} = \min_{\ell=0,1,\ldots,19} \frac{200}{200-\ell}\sum_{t=1}^{200-\ell}[x_t - g_{1j\ t+\ell}(\bar{x}, s^2)]^2, \quad j=1,2,3,4,5,$$

were computed, where the G_{1j} is used to denote the sum of squared deviations for Section 1, method 1, and trial j.

For each Section 1 there were five trials of each method. The means of the trials are denoted by $\bar{G}_1$ for method 1. Corresponding to each Section 2 of the data another set of intervals was generated by

$$y_{jt} = g_{1jt}(\bar{x}, s^2), \quad t=201, 202, \ldots, 400 \text{ and } j=1,2,3,4,5.$$

The parameters, $\bar{x}$ and s^2, were not recomputed using the Section 2 data. Instead they remained the same as those that were used for generating R-R intervals corresponding to the Section 1 data.

The sums of squared deviations

$$H_{1j} = \min_{\ell=0,1,\ldots,19} \frac{200}{200-\ell} \sum_{t=201}^{400-\ell} [x_t - g_{1j\ t+\ell}(\bar{x},s^2)]^2, \quad j=1,2,3,4,5$$

were computed. Each H_{1j} is used to denote the sum of squared deviations for the second section of data for method 1 and trial j. The average of the five trials, $\bar{H}_1$, was used for comparative purposes.

Method 2: Univariate Empirical (UVE)

In this method an empirical distribution of R-R intervals was obtained for each Section 1 of the data. Observations were drawn at random from the distribution in order to generate a sequence of 200 R-R intervals. Then R-R intervals were generated by

$$y_{jt} = g_{2jt}(x_1,x_2,\ldots,x_{200}), \quad t=1,2,\ldots,200 \text{ and } j=1,2,3,4,5,$$

where $g_{2jt}(x_1,x_2,\ldots,x_{200})$ is used to denote that y_{jt} was drawn from a distribution obtained from a sample of 200 R-R intervals.

The quantities

$$G_{2j} = \min_{\ell=0,1,\ldots,19} \frac{200}{200-\ell} \sum_{t=1}^{200-\ell} [x_t - g_{2j\ t+\ell}(x_1,x_2,\ldots,200)]^2, \quad j=1,2,3,4,5,$$

were computed for five trials for each Section 1 of the data. Their mean is denoted by $\bar{G}_2$. Corresponding to each Section 2 of the data another set of intervals was generated by

$$y_{jt} = g_{2jt}(x_1,x_2,\ldots,x_{200}), \quad t=201,202,\ldots,400 \text{ and } j=1,2,3,4,5.$$

The sums of squared deviations

$$H_{2j} = \min_{\ell=0,1,\ldots,19} \frac{200}{200-\ell} \sum_{t=201}^{400-\ell} [x_t - g_{2j\ t+\ell}(x_1,x_2,\ldots,x_{200})]^2, j=1,2,3,4,5$$

and the mean of the five trials, $\bar{H}_2$, was computed for each Section 2 of the data.

Method 3: Bivariate Empirical (BVE)

The two previous methods do not consider a possible joint relationship between consecutive R-R intervals. For this simulation method the joint empirical distribution of adjacent R-R intervals was obtained. Then the R-R intervals were generated by the following process;

$$y_{jt} = g_{3jt}(y_{j\ t-1},x_1,x_2,\ldots,x_{200}),\ t=2,3,\ldots,200,\ \text{and}\ j=1,2,3,4,5,$$

$$y_{j1} = x_1,$$

where $g_{3jt}(y_{j\ t-1},x_1,x_2,\ldots,x_{200})$ is used to denote that y_{jt} was drawn from a distribution which depended on $y_{j\ t-1}$ and the distribution of the x_t's which followed an interval of length $y_{j\ t-1}$.

The quantities

$$G_{3j} = \min_{\ell=0,1,\ldots,19} \frac{200}{199-\ell} \sum_{t=2}^{200-\ell} [x_t - g_{3j\ t+\ell}(y_{j\ t+\ell-1},x_1,x_2,\ldots,x_{200})]^2,$$

$$j = 1,2,3,4,5,$$

were computed for five trials of each Section 1 of the data and the mean was $\bar{G}_3$. Another set of R-R intervals was generated by

$$y_{jt} = g_{3jt}(y_{j\ t-1},x_1,x_2,\ldots,x_{200}),\ t=202,203,\ldots,400,\ j=1,2,3,4,5,$$

where $y_{j201} = x_{201}$.

The quantities

$$H_{3j} = \min_{\ell=0,1,\ldots,19} \frac{200}{199-\ell} \sum_{t=202}^{400-\ell} [x_t - g_{3j\ t+\ell}(y_{j\ t+\ell-1},x_1x_2,\ldots,x_{200})]^2,$$

$$j = 1,2,3,4,5,$$

for each Section 2 data were also computed for five trials as well as the mean, $\bar{H}_3$.

Method 4: Bivariate Empirical with Adjustment (BVEA)

The BVE and BVEA method both used the same bivariate empirical distribution. The methods differed in the manner used to generate the sequence of R-R intervals. In the BVEA method each interval was generated assuming that the previous R-R interval was known. That is, each newly generated R-R interval came from the distribution of R-R intervals which followed the interval of observed length, while for the BVE method each succeeding R-R interval was drawn from the distribution of R-R intervals which followed an R-R interval of the same length as the previously generated interval. For this method R-R intervals were simulated in the following manner by

$y_{jt} = g_{4jt}(x_{t-1},x_1,x_2,\ldots,x_{200})$, t=2,3,...,200, j=1,2,3,4,5 where $g_{4jt}(x_{t-1},x_1,x_2,\ldots,x_{200})$ is used to denote that y_{jt} was drawn from a distribution which depended on x_{t-1} and the distribution of x_t's which followed an interval of length x_{t-1}.

The quantities

$$G_{4j} = \frac{200}{199} \sum_{t=2}^{200} [x_t - g_{4jt}(x_{t-1},x_1,x_2,\ldots,x_{200})]^2 \text{ , } j=1,2,3,4,5,$$

were computed for five trials for each Section 1 of the data. The arithmetic average, $\bar{G}_4$, was then computed. R-R intervals were then generated corresponding to Section 2 data, where

$y_{jt} = g_{4jt}(x_{t-1},x_1,x_2,\ldots,x_{200})$, t=202,...,400, and j=1,2,3,4,5.

The sums of squared deviations

$$H_{4j} = \frac{200}{199} \sum_{t=202}^{400} [x_t - g_{4jt}(x_{t-1}, x_1, x_2, \ldots, x_{200})]^2, \quad j=1,2,3,4,5,$$

were computed. Their average value was $\bar{H}_4$ for the five trials.

Method 5: Bivariate Normal (BVN)

For this method it was assumed that two consecutive R-R intervals had a bivariate normal distribution. Each pair of the form

$$(x_t, x_{t+1}), \quad t = 1,2,\ldots,199,$$

was used to estimate the parameters of the distribution. Likewise, it was assumed that pairs of the form

$$(y_{jt}, y_{j\,t+1}), \quad t = 1,2,\ldots,199, \quad j = 1,2,3,4,5,$$

had the same bivariate normal distribution. A method of this nature where sample moments are equated to moments of a theoretical distribution is commonly referred to as a method of moments. The R-R intervals were generated in the following manner:

$$y_{jt} = g_{5jt}(y_{j\,t-1}, \bar{x}, s^2, r_1), \quad t=2,3,\ldots,200 \text{ and } j=1,2,3,4,5,$$

$$y_{j1} = x_1,$$

$$r_1 = \frac{\sum_{t=1}^{199} (x_t - \bar{x}_1)(x_{t+1} - \bar{x}_2)}{\left[\sum_{t=1}^{199} (x_t - \bar{x}_1)^2 \sum_{t=1}^{199} (x_{t+1} - \bar{x}_2)^2\right]^{1/2}},$$

$$\bar{x}_1 = \frac{\sum_{t=1}^{199} x_t}{199},$$

$$\bar{x}_2 = \frac{\sum_{t=1}^{199} x_{t+1}}{199} = \frac{\sum_{t=2}^{200} x_t}{199},$$

$$s^2 = \frac{\sum_{t=1}^{200} (x_t - \bar{x})^2}{199} ,$$

where $g_{5jt}(y_{t-1}, \bar{x}, s^2, r_1)$ is used to denote that y_{jt} was drawn from a distribution which depended on the previously generated R-R interval, $y_{j\ t-1}$, as well as $\bar{x}$, s^2 and r_1. The mean was $\bar{x} + r_1(y_{j\ t-1} - \bar{x})$ and variance, $s^2(1 - r_1^2)$. The univariate normal with mean and variance given above arose from the bivariate normal assumption and the fact that the previously generated R-R interval was known.

The quantities

$$G_{5j} = \min_{\ell=0,1,\ldots,19} \frac{200}{199-\ell} \sum_{t=2}^{200-\ell} [x_t - g_{5j\ t+\ell}(y_{j\ t+\ell-1}, \bar{x}, s^2, r_1)]^2 ,$$

$$j = 1,2,3,4,5,$$

were computed for each of five trials and the arithmetic mean was $\bar{G}_5$. Sequences of R-R intervals corresponding to Section 2 data were generated by

$$y_{jt} = g_{5jt}(y_{j\ t-1}, \bar{x}, s^2, r_1), \quad t = 202,203,\ldots,400 \text{ and } j = 1,2,3,4,5,$$

$$y_{j201} = x_{201}.$$

The sums of squared deviations

$$H_{5j} = \min_{\ell=0,1,\ldots,19} \frac{200}{199-\ell} \sum_{t=202}^{400-\ell} [x_t - g_{5j\ t+\ell}(y_{j\ t+\ell-1}, \bar{x}, s^2, r_1)]^2,$$

$$j = 1,2,3,4,5,$$

for this method were obtained and averaged. Their average was $\bar{H}_5$.

Method 6: Bivariate Normal with Adjustment (BVNA)

The BVN and BVNA were similar and required the same assumptions about the pairs (x_t, x_{t+1}). The difference in the methods was in the

generation process. For the BVNA method x_{t-1} was substituted for $y_{j\ t-1}$. That is, each R-R interval was generated assuming the previous R-R interval had been observed, and

$$y_{jt} = g_{6jt}(x_{t-1}, \bar{x}, s^2, r_1) \quad t = 2,3,\ldots,200 \text{ and } j = 1,2,3,4,5,$$

where $\bar{x}$, s^2, and r_1 are defined in the description of the BVN method. $g_{6jt}(x_{t-1}, \bar{x}, s^2, r_1)$ denotes that each generated interval depended on the observed preceding interval, x_{t-1}, as well as $\bar{x}$, s^2, and r_1. As before, the quantities

$$G_{6j} = \frac{200}{199} \sum_{t=2}^{200} [x_t - g_{6jt}(x_{t-1}, \bar{x}, s^2, r_1)]^2, \quad j=1,2,3,4,5,$$

were computed for five trials for each Section 1. Their mean was $\bar{G}_6$. Another set of R-R intervals was generated which corresponded to the Section 2 data. A set was generated for each of five trials by

$$y_{jt} = g_{6jt}(x_{t-1}, \bar{x}, s^2, r_1) \quad t = 202,203,\ldots,400 \text{ and } j = 1,2,3,4,5,$$

$$y_{j201} = x_{201}.$$

The sums of squared deviations

$$H_{6j} = \frac{200}{199} \sum_{t=202}^{400} [x_t - g_{6jt}(x_{t-1}, \bar{x}, s^2, r_1)]^2, \quad j = 1,2,3,4,5,$$

were computed for each trial. Their arithmetic mean was $\bar{H}_6$.

Method 7: Trivariate Normal (TVN)

Generating by the TVN and TVNA methods assumed that three consecutive R-R intervals had a trivariate normal distribution. Each new interval was generated given the values of the two previously generated R-R intervals. It was generated by

$$y_{jt} = g_{7jt}(y_{j\ t-1}, y_{j\ t-2}, \bar{x}, s^2, r_1, r_2), \quad t=3,4,\ldots,200, \text{ and } j=1,2,3,4,5,$$

$$y_{j1} = x_1,$$

$$y_{j2} = x_2,$$

$$r_2 = \frac{\sum_{t=1}^{198} (x_t - \bar{x}_3)(x_{t+2} - \bar{x}_4)}{\left[\sum_{t=1}^{198} (x_t - \bar{x}_3)^2 \sum_{t=1}^{198} (x_{t+2} - \bar{x}_4)^2\right]^{1/2}} .$$

$$\bar{x}_3 = \sum_{t=1}^{198} x_t/198 ,$$

$$\bar{x}_4 = \sum_{t=1}^{198} x_{t+2}/198 = \sum_{t=3}^{200} x_t/198 ,$$

where $g_{7jt}(y_{j\ t-1}, y_{j\ t-2}, \bar{x}, s^2, r_1, r_2)$ denotes that y_{jt} was drawn from a distribution which depended on the previous two generated R-R intervals, as well as $\bar{x}$, s^2, r_1 and r_2. In the description of the BVN method, $\bar{x}$, s^2 and r_1 were defined.

The quantities

$$G_{7j} = \min_{\ell=0,1,\ldots,19} \frac{200}{198-\ell} \sum_{t=3}^{200-\ell} [x_t - g_{7j\ t+\ell}(y_{j\ t+\ell-2}, y_{j\ t+\ell-1}, \bar{x}, s^2, r_1, r_2)]^2,$$

$j = 1,2,3,4,5,$

were computed for each of the five trials and the arithmetic mean was $\bar{G}_7$. Sequences of R-R intervals were generated to correspond to the Section 2 data. They were generated in the following manner by

$y_{jt} = g_{7jt}(y_{j\ t-1}, y_{j\ t-2}, \bar{x}, s^2, r_1, r_2)$, $t=203,204,\ldots,400$, and
$j = 1,2,3,4,5.$

$$y_{j201} = x_{201} ,$$

$$y_{j202} = x_{202} .$$

The sums of squared deviations

$$H_{7j} = \min_{\ell=0,1,\ldots,19} \frac{200}{198-\ell} \sum_{t=203}^{400-\ell} [x_t - g_{7j\ t+\ell}(y_{j\ t+\ell-2}, y_{j\ t+\ell-1}, \bar{x}, s^2, r_1, r_2)]^2,$$

$j = 1,2,3,4,5,$

were computed for five trials. Their mean was $\bar{H}_7$.

Method 8: Trivariate Normal with Adjustment (TVNA)

This method is similar to the TVN method except that each new interval was generated given the values of the two previously observed R-R intervals.

$y_{jt} = g_{8jt}(x_{t-1}, x_{t-2}, \bar{x}, s^2, r_1, r_2)$ for $t=3,4,\ldots,200$, and $j=1,2,3,4,5$, where $g_{8jt}(x_{t-1}, x_{t-2}, \bar{x}, s^2, r_1, r_2)$ denotes that y_{jt} was drawn from a distribution which depended on the previous two observed R-R intervals, $\bar{x}$, s^2, r_1 and r_2. These parameters were defined earlier. The quantities

$$G_{8j} = \frac{200}{198} \sum_{t=3}^{200} [x_t - g_{8jt}(x_{t-1}, x_{t-2}, \bar{x}, s^2, r_1, r_2)]^2, \quad j=1,2,3,4,5,$$

were computed for five trials on each Section 1 of the data. The mean of the trials for each Section 1 was $\bar{G}_8$. Corresponding to the Section 2 data R-R intervals were generated by

$y_{jt} = g_{8jt}(x_{t-1}, x_{t-2}, \bar{x}, s^2, r_1, r_2)$ for $t=203,204,\ldots,400$ and $j = 1,2,3,4,5.$

The sums of squared deviations

$$H_{8j} = \frac{200}{198} \sum_{t=203}^{400} [x_t - g_{8jt}(x_{t-1}, x_{t-2}, \bar{x}, s^2, r_1, r_2)]^2, \quad j = 1,2,3,4,5,$$

were computed for each of five trials. Their mean was $\bar{H}_8$.

Method 9: Quadravariate Normal (QVN)

In the QVN and QVNA methods it was assumed that four consecutive

R-R intervals had a quadravariate normal distribution. Each new interval was generated given the values of the three previously generated R-R intervals. It was generated by

$y_{jt} = g_{9jt}(y_{j\,t-1}, y_{j\,t-2}, y_{j\,t-3}, \bar{x}, s^2, r_1, r_2, r_3)'$ for $t = 4,5,\ldots,200$ and $j = 1,2,3,4,5,$

$y_{j1} = x_1,$

$y_{j2} = x_2,$

$y_{j3} = x_3,$

$$r_3 = \frac{\sum_{t=1}^{197} (x_t - \bar{x}_5)(x_{t+3} - \bar{x}_6)}{\left[\sum_{t=1}^{197} (x_t - \bar{x}_5)^2 \sum_{t=1}^{197} (x_{t+3} - \bar{x}_6)^2\right]^{1/2}}$$

$$\bar{x}_5 = \frac{\sum_{t=1}^{197} x_t}{197},$$

$$\bar{x}_6 = \frac{\sum_{t=1}^{197} x_{t+3}}{197} = \frac{\sum_{t=4}^{200} x_t}{197}$$

where $g_{9jt}(y_{j\,t-1}, y_{j\,t-2}, y_{j\,t-3}, \bar{x}, s^2, r_1, r_2, r_3)$ denotes that y_{jt} was drawn from a distribution which depended on the previous three generated R-R intervals, as well as $\bar{x}$, s^2, r_1, r_2, r_3. The parameters $\bar{x}$, s^2, r_1, r_2 were defined in the paragraphs describing other methods.

The quantities

$$G_{9j} = \min_{\ell=0,1,\ldots,19} \frac{200}{197-\ell} \sum_{t=4}^{200-\ell} [x_t - g_{9j\,t+\ell}(y_{j\,t+\ell-1}, y_{j\,t+\ell-2}, y_{j\,t+\ell-3}, \bar{x}, s^2, r_1, r_2, r_3)]^2, \quad j = 1,2,3,4,5,$$

were computed for each of five trials and the arithmetic mean was $\bar{G}_9$ for the Section 1 data. The following sets of data were generated to correspond to the Section 2 data.

$$y_{jt} = g_{9jt}(y_{j\,t-1}, y_{j\,t-2}, y_{j\,t-3}, \bar{x}, s^2, r_1, r_2, r_3)$$

$$t = 204, 205, \ldots, 400 \text{ and } j = 1,2,3,4,5,$$

$$y_{j201} = x_{201},$$

$$y_{j202} = x_{202},$$

$$y_{j203} = x_{203}.$$

The sums of squared deviations

$$H_{9j} = \min_{\ell=0,1,\ldots,19} \frac{200}{197-\ell} \sum_{t=204}^{400-\ell} [x_t - g_{9j\,t+\ell}(y_{j\,t+\ell-1}, y_{j\,t+\ell-2}, y_{j\,t+\ell-3}, \bar{x}, s^2, r_1, r_2, r_3)]^2, \; j = 1,2,3,4,5,$$

were computed for five trials. Their mean was $\bar{H}_9$.

Method 10: Quadravariate Normal with Adjustment (QVNA)

This method was similar to the QVN method except that each new interval was generated given the value of the three previously observed R-R intervals.

$$y_{jt} = g_{10jt}(x_{t-1}, x_{t-2}, x_{t-3}, \bar{x}, s^2, r_1, r_2, r_3)$$

$$t = 4, 5, \ldots, 200, \text{ and } j = 1,2,3,4,5,$$

where $g_{10jt}(x_{t-1}, x_{t-2}, x_{t-3}, \bar{x}, s^2, r_1, r_2, r_3)$ denotes that y_{jt} was drawn from a distribution which depended on the previous three observed R-R intervals, as well as $\bar{x}$, s^2, r_1, r_2, and r_3. The quantities

$$G_{10j} = \frac{200}{197} \sum_{t=4}^{200} [x_t - g_{10jt}(x_{t-3}, x_{t-2}, x_{t-1}, \bar{x}, s^2, r_1, r_2, r_3)]^2,$$

$$j = 1, 2, 3, 4, 5,$$

were computed for five trials on each Section 1 of data. The mean of the trials for each Section 1 data was $\bar{G}_{10}$ For the Section 2 data the sequences of intervals were generated by

$$y_{jt} = g_{10jt}(x_{t-1}, x_{t-2}, x_{t-3}, \bar{x}, s^2, r_1, r_2, r_3) ,$$
$$t = 204, 205, \ldots, 400 \text{ and } j = 1, 2, 3, 4, 5.$$

The sums of squared deviations

$$H_{10j} = \frac{200}{197} \sum_{t=204}^{400} [x_t - g_{10jt}(x_{t-1}, x_{t-2}, x_{t-3}, \bar{x}, s^2, r_1, r_2, r_3)]^2 ,$$

$$j = 1, 2, 3, 4, 5,$$

were computed for five trials. The mean of the trials was $\bar{H}_{10}$.

CHAPTER IV

ANALYSES AND RESULTS

Comparisons of the ten simulation methods, presented in CHAPTER III, were made using R-R interval data from four subjects, eight recording sessions, and two stages of sleep. Averaging the eight recording sessions for each method and section yielded the results in Table 6. Bar graphs displaying these data are shown in Figures 13 through 16. The initial set of comparisons of the simulation methods was made using only the data from each Section 1. For comparing two methods the Wilcoxen Matched Pairs Signed Ranks test was used and for comparisons among three methods the Friedman Two-Way Analysis of Variance test using ranks was used. Separate comparisons of the simulation methods were made for slow wave and REM sleep.

The UVN and UVE methods were not statistically significant at the .10 level for either stage of sleep. The UVN and BVN methods were significantly different at the .02 level for slow wave sleep and at the .10 level for REM sleep. The UVE and BVE methods were significantly different at the .01 level for REM sleep but not significantly different at the .10 level for slow wave sleep. The BVE and BVN methods were significantly different at the .10 level for slow wave sleep but were not significantly different for REM sleep. The BVEA and BVNA methods were not significantly different for either slow wave or REM sleep.

TABLE 6

AVERAGE SUMS OF SQUARED DEVIATIONS

	SLOW WAVE SLEEP	
Methods	Section 1	Section 2
Fourier	0.05083	0.04079
1 UNV	0.57582	0.44621
2 UVE	0.56560	0.46308
3 BVE	0.54227	0.40894
4 BVEA	0.18514	0.26381
5 BVN	0.48431	0.43454
6 BVNA	0.20146	0.18962
7 TVN	0.46002	0.42532
8 TVNA	0.18534	0.17538
9 QVN	0.44980	0.42889
10 QVNA	0.15221	0.15612
	REM SLEEP	
Methods	Section 1	Section 2
Fourier	0.03798	0.06900
1 UVN	0.90268	1.07816
2 UVE	0.88686	1.11208
3 BVE	0.75537	1.05037
4 BVEA	0.17610	1.09872
5 BVN	0.79595	1.00673
6 BVNA	0.21311	0.31230
7 TVN	0.81340	1.04564
8 TVNA	0.21866	0.33009
9 QVN	0.70807	0.97530
10 QVNA	0.19636	0.30754

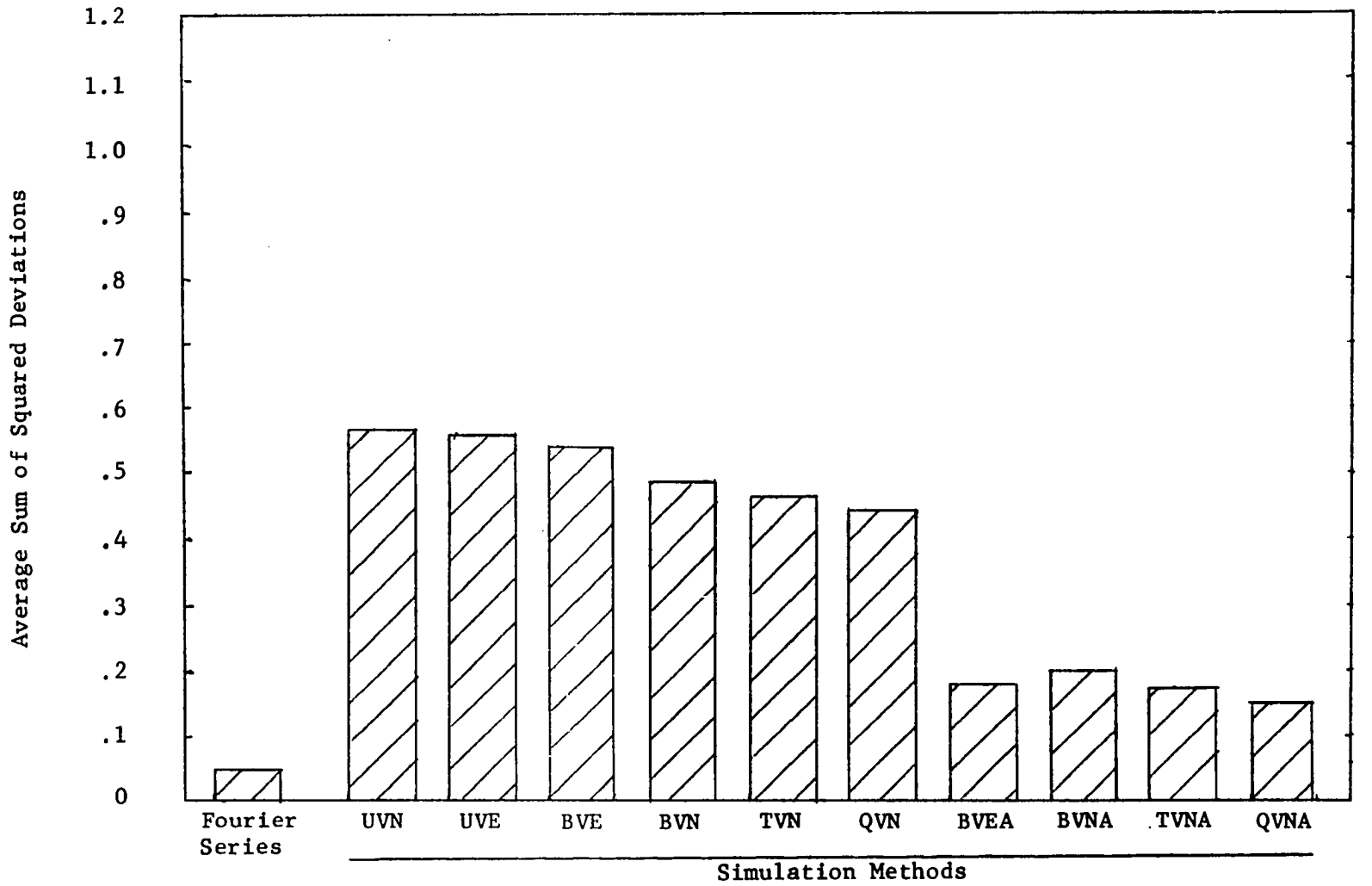

Figure 13 - Section 1 of slow wave sleep.

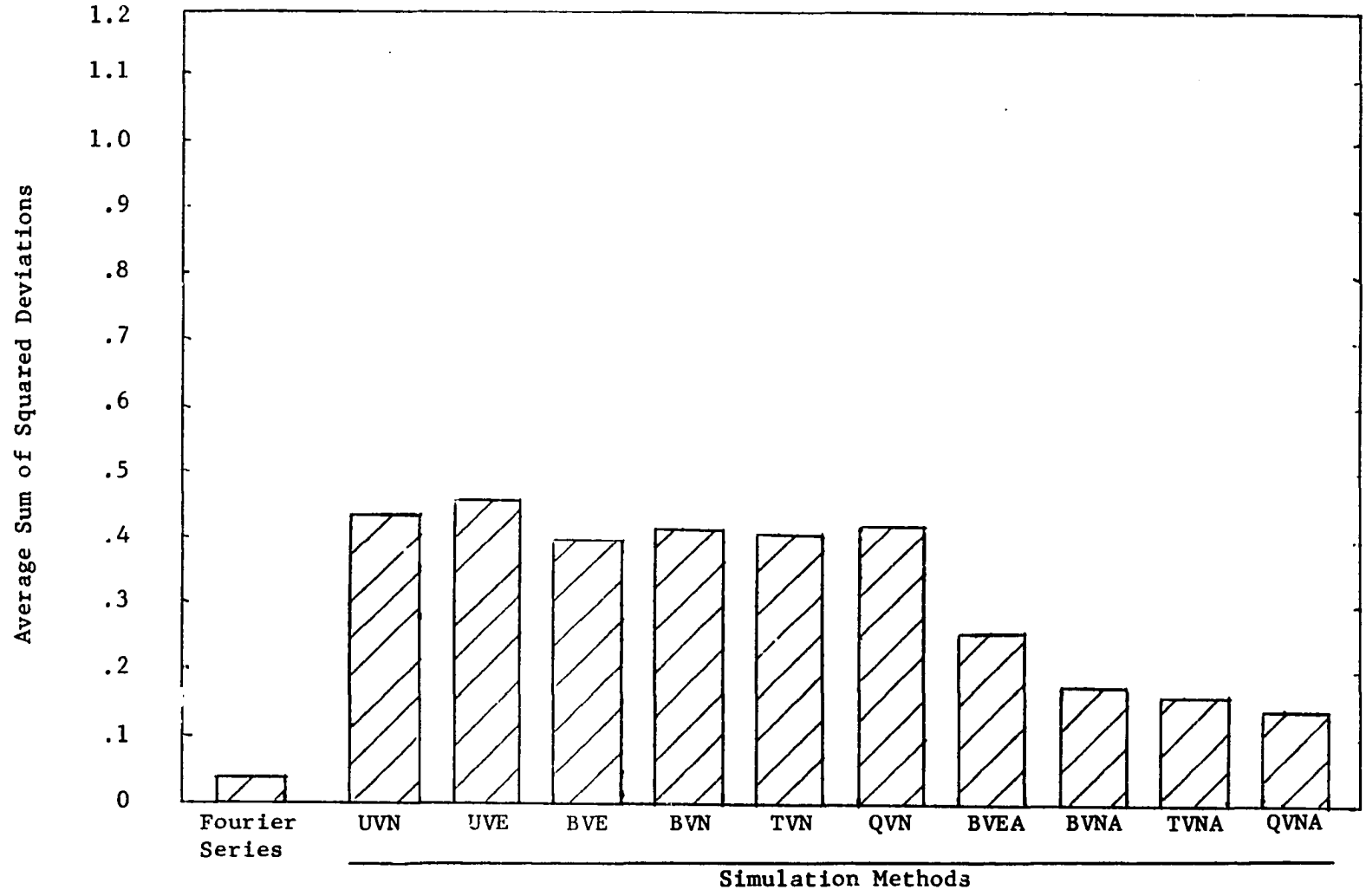

Figure 14 - Section 2 of slow wave sleep.

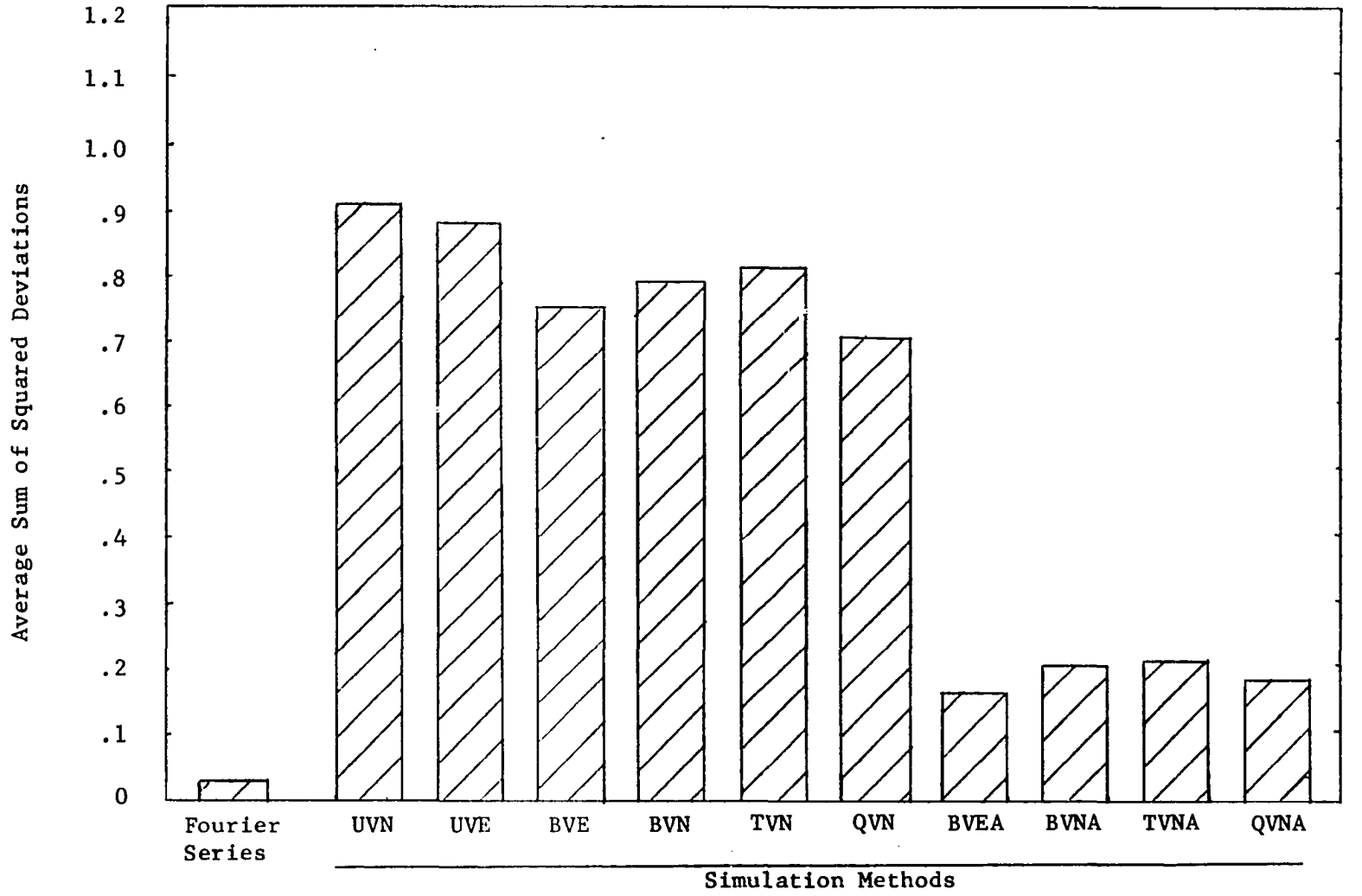

Figure 15 - Section 1 of REM sleep.

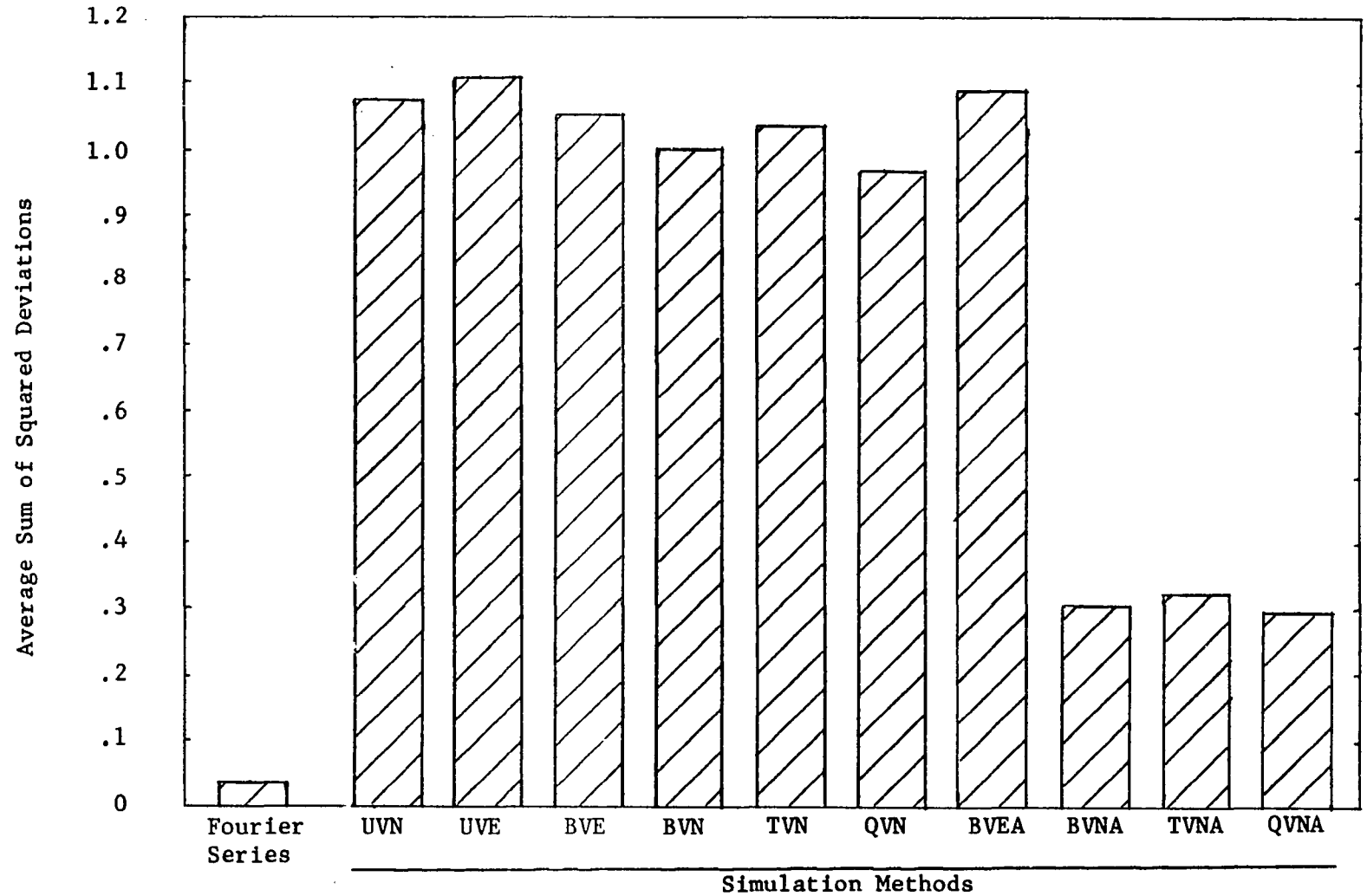

Figure 16 - Section 2 of REM sleep.

Methods with adjustment were compared with those not incorporating an adjustment. The comparisons were made in the following manner: BVE with BVEA, BVN with BVNA, TVN with TVNA, and QVN with QVNA. All of these comparisons showed the methods with adjustment to be significantly different at the .01 level from those without adjustment for both slow wave and REM sleep. In each case, the sum of squared deviations was less with the method incorporating the adjustment.

The BVN, TVN, and QVN methods were compared using the Friedman Two-Way Analysis of Variance. The three methods were not significantly different for either slow wave or REM sleep. The BVNA, TVNA, and QVNA methods were significantly different at the .001 level for slow wave sleep and at the .01 level for REM sleep. For slow wave sleep the sum of squared deviations, denoted by $\bar{G}_{10}$ for the QVNA method, was less than the sum of squared deviations for either the BVNA or TVNA methods, denoted by $\bar{G}_6$ and $\bar{G}_8$ respectively, for all eight records. For REM sleep, $\bar{G}_{10}$ was less than either $\bar{G}_6$ or $\bar{G}_8$ for seven of eight records. Results pertaining to Section 1 data are summarized in Table 7.

Only R-R interval data from Section 1 of each record were used as input for each simulation method. These parameters were then used to generate a sequence of R-R intervals corresponding to Section 2 of each record. The sum of squared deviations was obtained in a manner identical to that used for the Section 1 data and a similar set of comparisons among the methods was made. The UVN and UVE methods were not statistically significantly different at the .10 level for either stage of sleep. The UVN and BVN methods were significantly different at the .02 level for REM sleep but not significantly different at the .10 level for slow wave

TABLE 7

SECTION 1 RESULTS

Methods in Comparison		Significance Level (.10 or greater) Slow Wave Sleep	REM Sleep
UVN UVE	Univariate Normal Univariate Empirical	N.S.*	N.S.
UVE BVN	Univariate Normal Bivariate Normal	.02	.10
UVE BVE	Univariate Empirical Bivariate Empirical	N.S.	.01
BVE BVN	Bivariate Empirical Bivariate Normal	.10	N.S.
BVE BVEA	Bivariate Empirical Bivariate Empirical with Adjustment	.01	.01
BVN BVNA	Bivariate Normal Bivariate Normal with Adjustment	.01	.01
TVN TVNA	Trivariate Normal Trivariate Normal with Adjustment	.01	.01
QVN QVNA	Quadravariate Normal Quadravariate Normal with Adjustment	.01	.01
BVEA BVNA	Bivariate Empirical with Adjustment Bivariate Normal with Adjustment	N.S.	N.S.
BVN TVN QVN	Bivariate Normal Trivariate Normal Quadravariate Normal	N.S.	N.S.
BVNA TVNA QVNA	Bivariate Normal with Adjustment Trivariate Normal with Adjustment Quadravariate Normal with Adjustment	.001	.01

*Not Significant

sleep. The UVE and BVE methods were significantly different at the .05 level for slow wave sleep but were not different for REM sleep. The BVE and BVN methods were not significantly different for either slow wave or REM sleep. The BVEA and BVNA methods were significantly different at the .05 level for both slow wave and REM sleep.

In comparing the methods which incorporate an adjustment with those not incorporating an adjustment, the BVE method was not significantly different from the BVEA method. However, comparisons of BVN with BVNA, TVN with TVNA, and QVN with QVNA resulted in the methods with adjustment to be better than the analogous methods where no adjustment was utilized. These results held for both stages of sleep at the .02 level of significance.

The BVN, TVN, and QVN methods were not significantly different for either stage of sleep. However, the BVNA, TVNA, and QVNA methods were statistically significant at the .05 level for slow wave sleep and the .10 level for REM sleep. The results pertaining to Section 2 data are presented in Table 8.

Comparisons using the Wilcoxen Matched Pairs Signed Ranks test did not result in the bivariate distribution always being significantly better than the univariate distributions. However, it should be noted that in each of the comparisons of the univariate with bivariate normal and univariate with bivariate empirical simulation methods, the sum of squared deviations was smaller for the bivariate distributions for at least six of the eight records.

There were no significant differences between the Bivariate, Trivariate, and Quadravariate Normal Methods without Adjustment, but there were significant differences when there was an adjustment.

TABLE 8

SECTION 2 RESULTS

Methods in Comparison		Significance Level (.10 or greater) Slow Wave Sleep	REM Sleep
UVN UVE	Univariate Normal Univariate Empirical	N.S.*	N.S.
UVE BVN	Univariate Normal Bivariate Normal	N.S.	.02
UVE BVE	Univariate Empirical Bivariate Empirical	.05	N.S.
BVE BVN	Bivariate Empirical Bivariate Normal	N.S.	N.S.
BVE BVEA	Bivariate Empirical Bivariate Empirical with Adjustment	N.S.	N.S.
BVN BVNA	Bivariate Normal Bivariate Normal with Adjustment	.02	.02
TVN TVNA	Trivariate Normal Trivariate Normal with Adjustment	.02	.02
QVN QVNA	Quadravariate Normal Quadravariate Normal with Adjustment	.02	.02
BVEA BVNA	Bivariate Empirical with Adjustment Bivariate Normal with Adjustment	.05	.05
BVN TVN QVN	Bivariate Normal Trivariate Normal Quadravariate Normal	N.S.	N.S.
BVNA TVNA QVNA	Bivariate Normal with Adjustment Trivariate Normal with Adjustment Quadravariate Normal with Adjustment	.05	.10

*Not Significant

CHAPTER V

DISCUSSION

Results of the analyses of the simulation methods were reported in the previous chapter. In simulating R-R intervals the bivariate methods, both empirical and normal, yielded significantly smaller sums of squared deviations than the corresponding univariate methods for only one stage of sleep. For Section 1 data the Bivariate Normal Method was significantly closer (.02 level) to the observed data for slow wave sleep but not for REM sleep (.05 level). The Bivariate Empirical Method was significantly closer (.01 level) for REM sleep but not for slow wave sleep. Results from the univariate methods, normal and empirical, and the bivariate methods, normal and empirical, were not statistically significant (.05 level). For Section 2 data the opposite occurred. The Bivariate Empirical Method was significantly closer (.05 level) to the observed data than the Univariate Empirical Method for slow wave sleep but not for REM sleep. The Bivariate Normal Method was significantly closer (.02 level) to the observed data than the Univariate Normal for REM sleep but not for slow wave sleep. These inconsistent results might be attributed to only this particular set of data, differences in slow wave and REM sleep, the particular generation techniques, or some combination of these. Some undesirable properties of the bivariate empirical methods were discovered and will be discussed later in this chapter.

These results are also indicative of the need to apply the methods to a wide range of data in order to determine the best method for each situation or type of data. In this study the Quadravariate Normal Method with Adjustment was best for all eight records of slow wave sleep and seven of eight records of REM sleep in Section 1. For Section 2 it was best for six of eight records of slow wave sleep and five of eight for REM sleep.

Incorporating a joint distribution of three or four adjacent intervals did not necessarily improve the generation process for R-R intervals. It depended further on whether adjustments were made or not. There were no significant differences (.10 level) between the Bivariate, Trivariate, and Quadravariate Methods for both stages of sleep and both sections of data included in this study; however, the three methods with adjustment were significantly different (.10 level) for both stages of sleep and both sections of data. The methods with adjustment were better than the corresponding methods without adjustment. The one exception was the Bivariate Empirical Method which was not significantly different from the Bivariate Empirical Method with Adjustment in the new, Section 2, data. For the Section 1 data there was no significant difference between the Bivariate Empirical and the Bivariate Normal Methods with Adjustment. However, for the Section 2 data there were significant differences for both stages of sleep. The Bivariate Normal with Adjustment was the better method.

The results obtained from using the Bivariate Empirical Method with Adjustment might have been due to the manner in which the R-R intervals were generated for comparing with Section 2 data. When an

observed R-R interval was outside the range where previous data had been collected and a distribution established, a value equal to the arithmetic mean of the previous set of data was used for the observed value. Then the generation process continued. When this occurred the sum of squared deviations was inflated resulting in no improvement when an adjustment was incorporated. A similar situation was not encountered with the Bivariate Normal Method with Adjustment because there was an implied distribution of intervals following an interval of any length. Some of the complications accompanying the Bivariate Empirical Method with Adjustment, when used in new data, could be alleviated by using a much larger data base to establish the bivariate empirical distributions. This may not be desirable either because these deviations from a prior distribution based on a small data set from a short period of time might be more appropriate in characterizing the intraindividual R-R interval variability.

Although the sum of squared deviations between observed and generated data was used in this study to compare simulation methods and to investigate the relationship between R-R intervals in two stages of sleep, these studies could be expanded to other classes of subjects. There are two major areas where use of the sum of squared deviations could have merit. The first being as a discriminatory tool for cardiac disorders. The joint relationship of successive R-R intervals needs to be investigated in a wide range of subjects with various disorders of different intensity or progression. Relationships between R-R interval variability and anomalies may be found that would aid in the early detection and treatment of abnormalities before they become intractable.

A second area of application could be in patient monitoring where R-R interval data could be readily obtained. During a base period parameters could be obtained and used to estimate the joint distribution of successive R-R intervals. The sum of squared deviations would be a measure of whether the patient was varying significantly from his base pattern. The sum of squared deviations for a fixed increment of time or number of beats could be considered as a new variable and its distribution estimated. When an observed value deviated significantly from the expected, the patient's condition would be followed more closely or a change in treatment would be indicated.

Caceres et al. (1962), discuss the need to study the distribution of electrocardiographic variables in various populations to establish standards to characterize these populations. While the variables obtained in their work were characteristic of a particular beat, indices of variability incorporating several beats would also be useful. The sum of squared deviations could be used as this measure where it is computed for only ten consecutive beats. It could be considered as a variable describing the EKG in the same manner as other variables might describe it. The number of beats to include in computing a sum of squared deviations could be studied. Factors such as the amount of data available, precision required, and the type of irregularity to be detected would need to be considered in arriving at an optimal number of beats to include.

It may be beneficial to develop a dynamic model to simulate a sequence of R-R intervals. If new data were continually being monitored, it would be feasible to use this observed data to make modifications to

the parameters and models. However, this would require an on-line computer operation. Criteria would need to be established for an individual so that modifications in the model's sensitivity to an anomaly would not be affected.

Extensions of the empirical distribution method could be made in future studies. Trivariate and quadravariate empirical distributions could be obtained and then used to generate sequences of R-R intervals. From the data analyzed in the present study there is no strong indication to use or not use empirical distribution methods. Results of the Empirical Method in new data illustrate the need to obtain sufficient data to describe an empirical distribution. In methods incorporating an adjustment special consideration must be given to observed values which fall outside the range of the empirical distribution. In this study an observed value that fell outside the range was replaced by the mean value of the original distribution. In future studies it is planned to replace large values outside the range with the largest value observed in the original distribution and to replace small values outside the range with the smallest value observed in the original distribution. Empirical methods should be investigated where each new R-R interval observed is incorporated with previously observed intervals to make continuing modifications to the empirical distribution. Although application of these methods would require on-line computer operation, they could be tried and evaluated from serial data that has been recorded. Extensions of the Bivariate Empirical Method to the Trivariate and Quadravariate Methods would require a considerably larger data base.

It was mentioned in the preliminary results, CHAPTER II, that

there were differences in the relationships between successive beats during a period where extrasystoles were present and a period void of extrasystoles. Further research is indicated to study or correlate particular disorders with characteristics related to R-R interval data. In a patient monitoring situation arrhythmias may be detected before the clinical state becomes serious. The simulation methods given in CHAPTER III could be used in solving the problems of early detection of abnormalities in heartbeat.

CHAPTER VI

SUMMARY

This study gave a new manner in which to utilize and describe R-R interval data. Parameters incorporating several R-R intervals were obtained and used to characterize the R-R interval data; however, the same parameters could be used to characterize other serial data. Also, classically, Fourier analysis generally uses a much larger number of parameters and one of the principal objects of this investigation was to reduce the number of parameters to as small a number as feasible. In this study up to four successive R-R intervals were assumed to have multivariate distributions. Parameters describing the joint relationship were used to simulate the R-R intervals for an individual. Models presently used do not incorporate a joint relationship among several intervals. Because of advances in computer technology, simulation methods incorporating a multivariate approach such as those presented needed to be given further consideration.

A preliminary investigation of R-R interval data from two subjects yielded results indicating that there was a relationship among consecutive intervals and that it was different in the presence of extrasystoles. In this study ten methods were given which could be used to simulate R-R interval data. Eight of the methods incorporated, in one form or another, a joint relationship of two, three, or four consecutive

intervals. Data was obtained from four subjects, each on two different days, and for two stages of sleep. Parameters from the observed data were used as input to a simulation method, sequences of intervals were generated to correspond to each set of data, and the method was then applied to a new set of observed data for each subject. After a sequence of R-R intervals was generated, a sum of squared deviations between the observed and generated data was computed for each method and served as a basis for comparisons among the methods.

Some of the methods used assumed that the joint relationship among consecutive intervals was bivariate normal for two intervals, trivariate normal for three intervals and quadravariate normal for four intervals. For another method the bivariate empirical distribution between two consecutive intervals was obtained and used. In four of the simulation methods observed R-R intervals immediately preceding each generated interval were used. These were referred to as methods with adjustment. There were no differences between the Bivariate, Trivariate, and Quadravariate Normal Methods for either stage of sleep unless there were adjustments in which case the Quadravariate Normal Method was the best. Keeping the input parameters the same and adding an adjustment to a simulation method resulted in a significant reduction in the sums of squared deviations for all sections of data studied.

It was expected that using adjustments based on previous actual data as compared to using generated data would reduce, at least slightly, the sums of squared deviations but both methods must be studied in order to be able to model effectively a variety of clinical situations. Methods with adjustments could be used only in an on-line patient monitoring

situation. Moreover, the use of adjustments provides the means to obtain a more realistic measure of the accuracy of the data generated from a given set of parameters.

The Bivariate Normal Method was better than the Univariate Normal Method for slow wave sleep but not REM sleep while the Bivariate Empirical Method was better than the Univariate Empirical Method for REM sleep but not slow wave sleep. These results indicate the need to investigate the methods in a wide range of subjects and under different conditions.

As stated in the introduction the basic motivations for undertaking this study were two-fold. It is obvious that if a small set of numbers or parameters could characterize the data in some segment of sequentially generated data such as R-R intervals, electrocardiograms, electroencephalograms, or galvanic skin resistances, then these numbers would be valuable for the classification of patients in various disease states. The second type of application of the same sets of parameters would be their use in monitoring of patients in intensive care or in experimental studies. A continuous record of these numbers, computed from running segments of the data, along with the running measure of goodness of fit with simulated data, would be used to indicate changes in the patients condition and even serve as a predictor of more serious changes to come, such as ventricular fibrillation. This study found that at most five such parameters worked well for these purposes.

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