A COMPLEMENTARY TECHNIQUE FOR DETERMINING THE LATENCY OF STEADY STATE EVOKED POTENTIALS

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Diane Van Dyke

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Name: Diane Myra Van Dyke

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Examining Committee:

Chairperson: Dr. P. Bakan

Dr. L. Diamond

Dr. P. Bakan

Dr. B. Beyerstein

Dr. A.H. Burr
External Examiner
Biological Sciences
Simon Fraser University

Date Approved: Dec 7 1983

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A Complementary Technique for Determining the Latency of Steady State Evoked Potentials

Author: (signature)

Diane M. Van Dyke
(name)

June 19/83
(date)

ABSTRACT

The steady state visual EP (evoked potential) is a measure of the brain response to a light flickering usually faster than 8 Hz. Such a flicker measure has been accomplished with sinusoidally modulated light stimuli and nonsinusoidal, pulsed, strobe stimuli.

EP latency is the time it takes for the EP to occur following a stimulation. This time period, or delay, is estimated in steady state sinusoidal stimulation from an analysis of the phase difference between the stimulus and a synchronous component in the EP. In the nonsinusoidal method, EP latency is estimated from an analysis of the time difference between stimulus and EP peak points.

This study will investigate an additional (complementary) latency technique, based upon Diamond's procedure. The stimulus was a red (square-wave) flickering light, and the presentation rate ranged from 30 to 9 cycles per second. The procedure employed regular as well as irregularly spaced flicker, and determined latency independently at specific interstimulus intervals (ISIs). Four subjects were tested.

The study has shown that one or more fundamental components in the EP appear over a wide range of frequencies. These results are not consistent with Regan's idea that separate EP fundamental components are evoked only within separate and distinct frequency ranges, and that each frequency range is associated with a different latency system. Therefore, this suggests that contrary

to Regan's theory there are not three latency systems set off by three frequency ranges, or channels. Rather there are a number of fundamental components in each steady state EP cycle at all flicker frequencies, and each component has a different latency.

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INTRODUCTION

Evoked potentials

Evoked potentials (EPs) are electrical events of the brain that occur immediately following the presentation of a stimulus. The stimulus can be either non-conceptual, such as a flash of light or a tone, or conceptual, such as a memory task. They are recorded at the scalp and represent electrical activity that is occurring at all levels of the nervous system, from the receptors to the association cortex (Picton et al, 1977). For this reason the EP waveform can be comprised of a number of integrated components, each with a specific latency. Because their amplitude is only one tenth that of the spontaneous EEG computers have now made it possible to summate a series of evoked waveforms and give an averaged evoked response.

Transient EPs

In any sensory modality EPs can be characterized as either transient or steady-state. This depends upon the stimulus presentation rate. Transient EPs are elicited by a brief, rapidly changing, stimulus. Regan (1977 a) describes the transient EP in terms of "giving the system a "kick" and then letting it settle down before kicking it again." According to Regan, a transient stimulus is presented at a rate of less than one per second. This slow rate ensures that the response to one stimulus is over before the response to the next one begins (Kinney et al, 1972). Transient EPs are described by a plot of EP amplitude (voltage) over time.

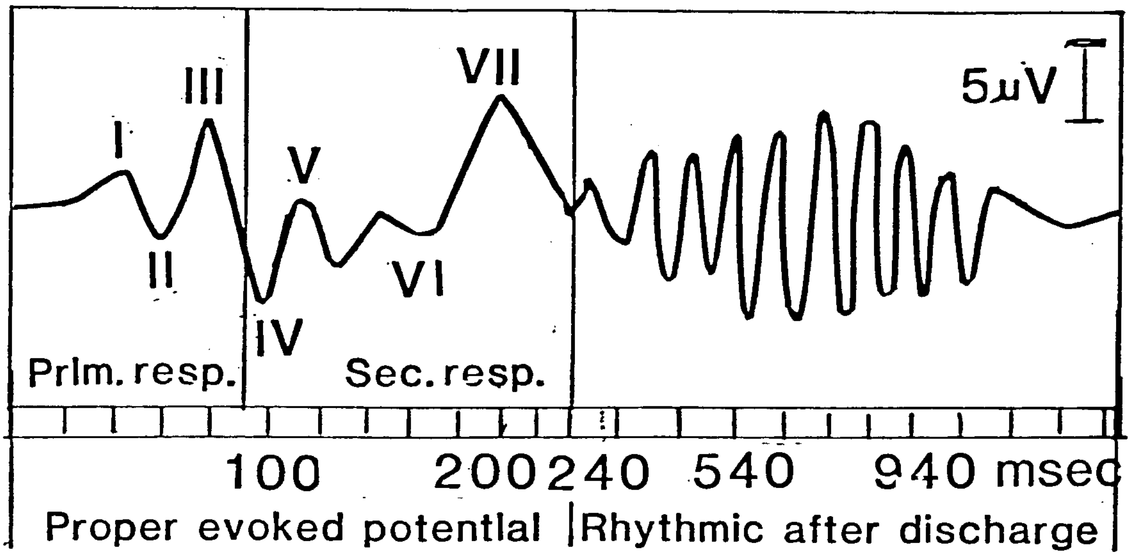
No unanimous agreement exists on the specifications for a standard waveform because large differences exist both within and between individuals in the population. However, it is possible to define a general form, even though a universal agreement on specific peaks and slopes does not exist. For example, in vision, a number of different methods for classifying the EP components are used (Ciganek, 1961; Gastaut & Regis, 1961), (see Figure 1).

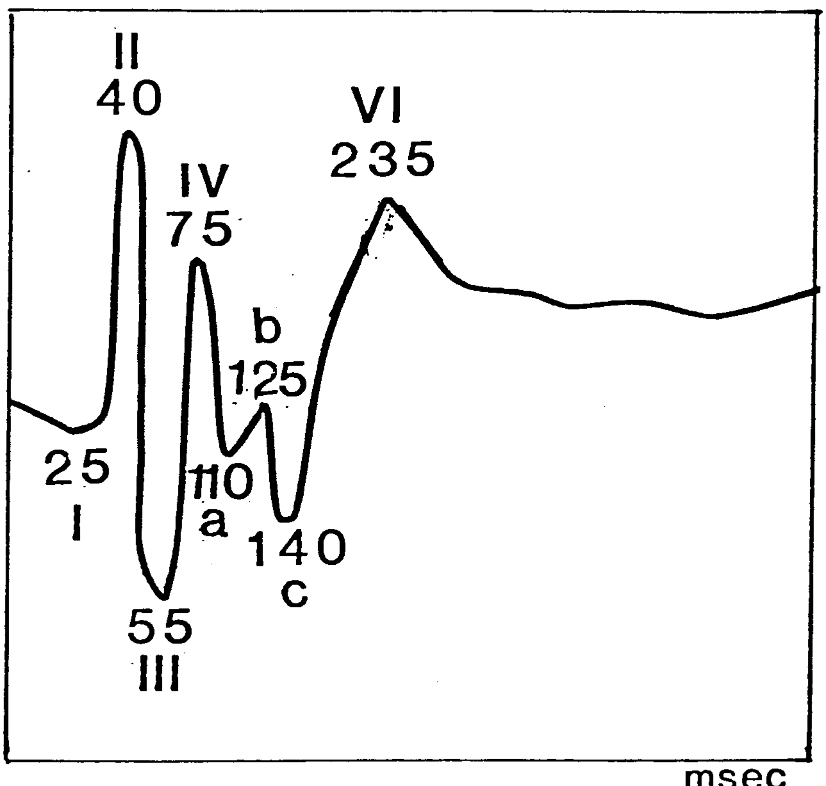
Sensory related EP structure. In all modalities transient sensory EPs are typically comprised of three distinct components. The first component constitutes a set of responses that occur within the first 50 msec after stimulation. These early responses are generally determined by the characteristics of the stimulus and are localized over the primary receiving areas of the cortex. Although they are relatively stable, a small degree of variability exists in their latency & amplitude. In vision, this component is referred to as the primary response (Ciganek, 1961). The second major component is usually large and bimodal (first going negative and then positive) and is recorded more diffusely over the scalp.

Figure 1.

Two systems for describing transient visual evoked (VEP) waveforms in response to diffuse flashes. (a) The first system by Ciganek, divides the EP into three regions; a primary response (up to 90 msec), a secondary response (90-240 msec), and an after-discharge (greater than 240 msec). The waves are labelled sequentially, 1 through V11. (b) The second, described by Gastaut and Regis, (1965) numbers the waves sequentially along with their corresponding latencies. Negativity at Oz (occipital lobe, at the midline) is up.

a


I
II
III
IV
V
VI
VII
5µV
Prim. resp.
Sec. resp.
100
200
240
540
940 msec
Proper evoked potential
Rhythmic after discharge


II
40
IV
75
VI
235
b
125
25
I
110
a
140
c
55
III
msec

b

The latency of this component is approximately 90-100 msec. In vision, this component is referred to as the secondary response (Ciganek 1961). The third component, especially in vision, is the rhythmic after discharge which occurs approximately 250 msec after stimulation (Ciganek, 1961).

<u>Sensory and perceptual EP responses</u>.

In spite of overlapping components, transient EPs are arbi- divided on the basis of latency or amplitude, and are described as either early or late. In general, early EPs (up to 50 msec) are determined by or vary systematically with the physical parameters of the stimulus, and are relatively unaffected by psychological events. On the other hand, late EPs (approximately 200 msec or more) are associated with perceptual phenomena and sensitive to a wide variety of psychological variables.

Generally the understanding of EP components is inversely related to their latency. For instance, so much goes on in the nervous system after the presentation of a stimulus, that the longer the elapsed time (in msec) after the stimulus, the more difficult the analysis and interpretation become. This is because the longer latencies reflect higher levels of processing, in which several EP generators can be activated either simultaneously or in parallel fashion. Visual perception is a case in point. This involves form perception, luminance, colour, depth perception, and possibly other events, all occurring in parallel (Regan, 1977a). When a stimulus requires a perceptual decision, a late positive component occurs after approximately 250 msec (P300) (Donchin, in Regan, 1977a).

Steady-state EPs

In contrast to transient EPs, steady-state EPs are recorded in response to a repetitive stimulus which is presented at a rate faster than 3 Hz, according to Regan (1977 a) and 8 Hz, in Diamond's (1977 a; b) study. In steady-state the "system is shaken gently at a fixed rate" and the EP response that follows shows the same number of responses, per unit of time, as the stimulus rate (Kinney et al, 1972). Regan (1972) maintains that the effects of increasing the stimulus frequency results in the original shape of the EP waveform being replaced by a moderately deformed sinusoidal curve, "in which individual responses cannot be related to any particular flash." He describes the steady-state EP with two plots, amplitude (voltage) over frequency, and phase lag versus frequency: a frequency-domain analysis. Diamond (1977 b), how- however, does not describe the steady-state EP in the same manner. He describes it in terms of specific components plotted over time; a time-domain analysis. These two descriptive approaches result in two different methods of determining latency and are the major subject of discussion in this study.

EP LATENCY

Determining generator sites

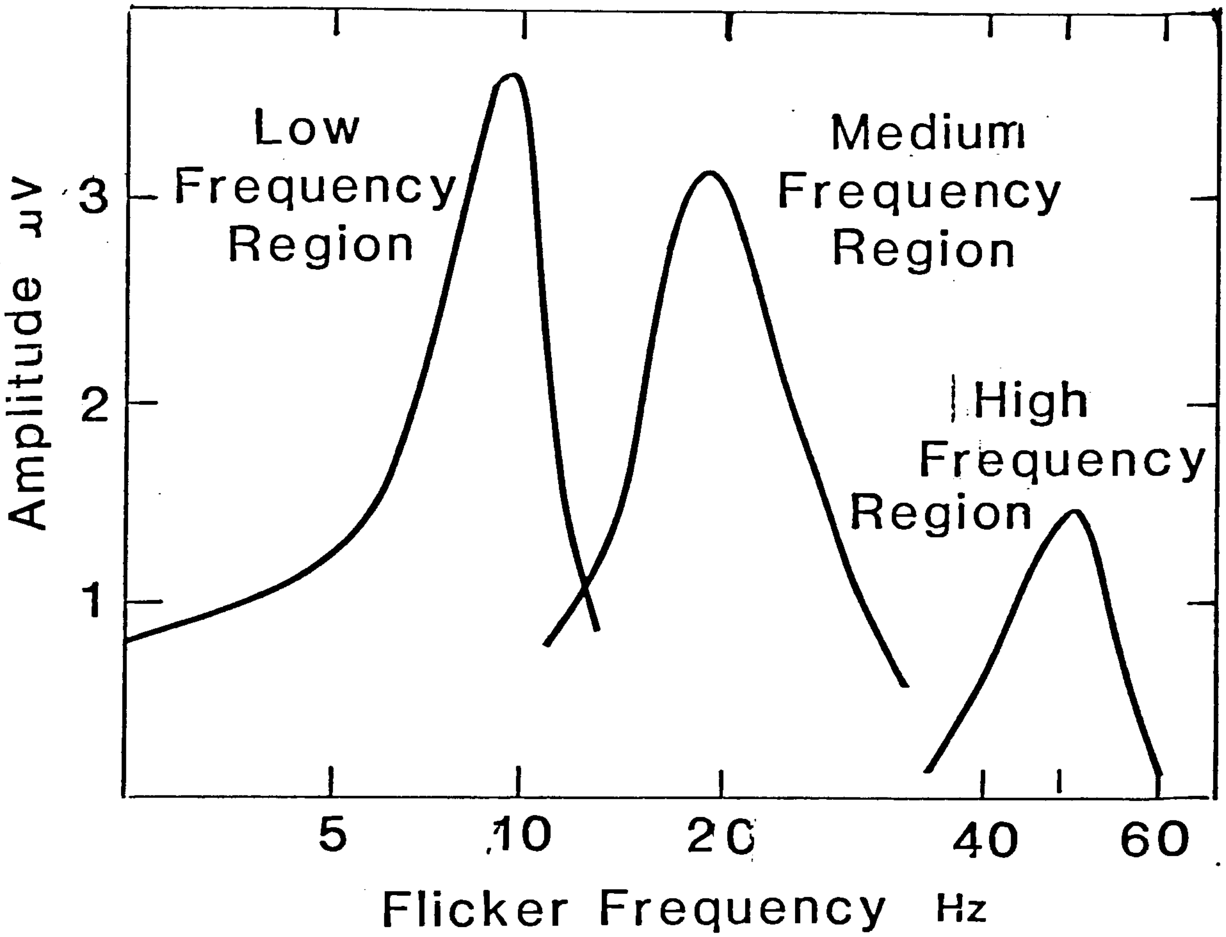
An extensive amount of research has focused on latency as a clue to distinguishing various EP components and hypothesizing their possible sites of origin (generaor sites) or functions. For example, Jewett, Romano & Williston (1978) demonstrated, in audition, that an EP component with a latency of 5 msec (the brainstem auditory evoked response, BAER) was generated in the brainstem, a non-cortical structure. In vision Regan (1972) and others have identified three frequency systems, by determining how the amplitude and latency of various visual evoked potential (VEP) components varied as a function of frequency. Regan maintains that these EPs are generated by different though overlapping cortical cells, thereby reflecting neural activity in 3 parallel channels which separate peripherally (Regan, 1977 a, see Figure 2).

Sensory functioning

Research has also been directed towards using latency as a measurement of normal sensory functioning from the receptors to the receiving areas of the brain. For example, the latency of

Figure 2

A plot of amplitude versus flicker frequency showing the effects of stimulus frequency on flicker EPs. Three frequency systems, a high-frequency (45-60 Hz), medium-frequency (13-25 Hz), and low-frequency (near alpha) are illustrated.



Low
Frequency
Region
Medium
Frequency
Region
High
Frequency
Region
Amplitude µV
3
2
1
5
10
20
40
60
Flicker Frequency Hz

the visual evoked potential (VEP) in patients with multiple sclerosis (MS) has been used as a diagnostic aid to confirm the presence of lesions in the visual pathway; lesions intefere with the speed of conduction in the afferent pathways which determines the latency. Regan (1977 a) has found that the latency of the medium frequency VEP is a reliable indicator of MS, more specifically the components with latencies between 60-200 msec. Since these components are extremely sensitive to patterned stimulation, it is thought that they reflect projections from foveal activity in the retina.

<u>Sensory threshold</u>

The correlation between latency and sensory thresholds has also been investigated extensively. In most cases, decreasing the intensity of a stimulus to threshold usually increases the latency of the EP components. According to Salamy et al (1978) this increase is probably related to the slower rise of presynaptic potentials of sensory cells at the lower intensities. However, in audition it has been shown by Salamy et al (1978), Wave V, of the BAER (with a latency of 5 msec) remains visible at threshold levels.

<u>Brain maturation</u>

Another major application of latency as a diagnostic tool is in studies on brain maturation. For example, with increasing age the peak latency of Wave V, of the BAER, decreases in time from birth to two years, reaching a low at age two and gradually increasing to age 65 (Salamy et al, 1978). The decrease in latency by age two results because as the axons become more myelinated and the synapses more efficient, conduction and transmission times become faster; therefore, the latencies of the components become shorter. In vision, Hrbek, Hrbkova, & Lenard (1969) maintain that the visual waveform remains fairly constant after age two, however between two and six there are further reductions in latency.

Intelligence

It has also been hypothesized that latency of the EP correlates with intelligence; in vision (Chalke & Ertl, 1965; Ertl & Schafer, 1969) and in audition (Callaway, 1975). In response to sensory stimulation, shorter latencies indicate higher levels of intelligence. However the attempts to relate intelligence to latency, as well as to other features of the EP, have met with varying degrees of criticism. One of the harshest critics is Vaughan, who states that "these attempts are based on nothing more substantial than the fact that brain processes underlie both intelligence and the EP" (in Regan, 1972, p.132).

Psychopathology

Investigating the latency of early sensory EPs has yielded a number of correlates of psychopathology (Shagass, 1977). An hypothesis has been proposed by Shagass, that disordered sensory processes might account for the perceptual distortions experienced by schizophrenic patients. It has been proposed that because these patients have an inadequate filtering system (i.e. subcortical mechanisms involved in regulating sensory input are underactivated), they should exhibit shorter EP latencies. Evidence has been found to support this, for example schizophrenic patients have shorter P45 latencies, as well as many amplitude differences, in comparison to normals (Shagass & Schwartz, 1963). And Vasconetto, Floris & Morocutti (1971) found shorter latencies in the N150 component.

Latency, therefore, apparently functions as an invaluable aid in the interpretation of evoked potentials. For this reason, new and more precise methods of determining latency are well justified.

Steady-state methods of determining EP latency: frequency-domain analysis

An essential part of Regan's method of determining the latency of steady-state EPs is based upon sine wave stimulation, Fourier Analysis and a number of assumptions related to these two procedures(e.g., phase-shift information).

Linear systems

One of the basic assumptions related to the use of sinusoidal stimulation is that the resulting EP waveform will be sinusoidal as well. This is a function of a linear system; a linear system is defined as a system in which the input passes through the system without any frequency distortions or related harmonics (Spekreijse, 1966). In determining the VEP response to sine wave stimulation, Regan relies upon a filtering process. For example, once the frequency of the stimulus is determined, it is a simple matter to filter out any activity not corresponding to the frequency of the stimulus, Note that some EP information (at other frequencies) may be sacrificed (Regan, 1977 a).

Non-linear systems

In vision, however, an obvious question needs to be answered. Is the visual system a linear system? If not, how reliable is Regan's analysis. In order to answer this question, Regan (1966) and others (Van der Tweel & Verduyn Lunel, 1965; Spekreijse, 1966) used variable rates of stimulation (5-60 Hz), and determined that the visual system was non-linear within different frequency ranges. (In a non-linear system a sinewave input produces something other than a sine wave output. Instead a distorted EP waveform is produced which is composed of the basic fundamental (F Hz) and related harmonics (2F Hz, 3F Hz, etc.), all multiples of the fundamental. The analysis now becomes one of splitting the waveform into its various component parts (Van der Tweel et al, 1965).

Fourier Analysis

Regan expresses the non-sinusoidal waveform in terms of a number of simple sine waves, each with its own amplitude and frequency. To do this he uses a number of bandpass filters, one set to determine the fundamental and the others the related harmonics. This technique is based upon Fourier Analysis; any periodic function, which indefinitely repeats itself, can be harmonically analysed, and thereby described as a linear sum of elementary sinusoidal terms, called Fourier components (in Schiffman, 1976, p. 39). Two parameters, relative amplitude and phase shift characterize Fourier components.

Phase difference

Regan's method of estimating latency measures the phase lag between the stimulus and a synchronous VEP component (Regan, 1972). The phase difference is usually expressed in degrees or radians and is calculated relative to the stimulus (see Figure 3A, B).

Slope

Regan, however, does not estimate latency by determining the phase lag at only one frequency; a number of frequencies are necessarily involved. A plot of the functional relationship between the phase lag and frequency is constructed and an estimate of the apparent latency is determined from the slope of the line. If the plot of the phase difference versus frequency is a straight line, (i.e., another function of a linear system is that the relationship between the input and output can be described by a linear equation) then the slope of the line is calculated and this gives an estimate of "apparent latency" (Regan, 1972).

$$\text{Apparent latency } (t) = \frac{1}{360} \quad \frac{d\phi}{df}$$

where t is latency in second; ϕ is phase lag in degrees, f the stimulus frequency in hertz, and

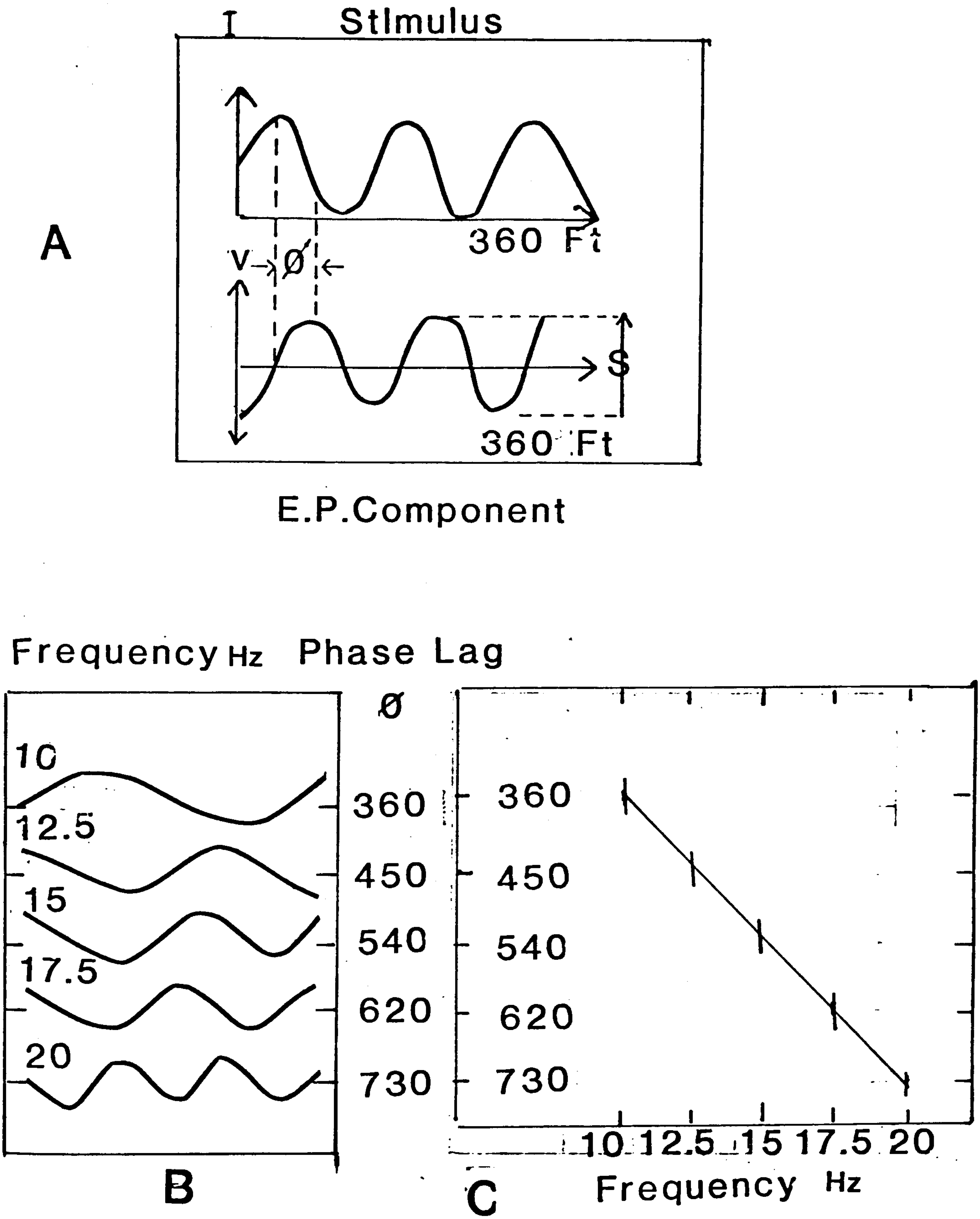
$$\frac{d\phi}{df}$$

the slope of the phase versus frequency plot.

Using both amplitude and phase information, Regan and others determined three frequency specific systems in the visual system (see Figure 2) a low frequency system, up to 12 Hz, with maximum EP amplitude at 10 Hz and an apparent latency of approximately 120 msec; a medium frequency system that extends from 12 to 25 Hz, with maximum amplitude peak at 16 Hz, and an apparent latency of approximately 90 msec; and a high frequency system extending

Figure 3

(A) An illustration of phase lag (in degrees) between the stimulus and the evoked response. (B) illustrates how the phase lag of the evoked response increases as a function of increasing the stimulus frequency. (C) a plot of phase lag versus stimulus frequency, the slope gives a value of the delay in the system. According to Regan the phase lag of the evoked response is caused by a 100 msec delay in the retina-cortex system.


A
Stimulus
V
ø
360 Ft
S
360 Ft
E.P.Component
Frequency Hz
Phase Lag
ø
10
12.5
15
17.5
20
360
450
540
620
730
B
C
10
12.5
15
17.5
20
Frequency Hz

from 45-60 Hz with a maximum amplitude at 55.5 Hz, and a 60 msec apparent latency (Van der Tweel & Lunel, 1965; Regan, 1966; 1972; Spekreijse, 1966).

It was found that the relationship between phase lag and stimulus frequency was nearly a straight line, except at 10 Hz where there was a well defined step (see Figure 4). This corresponds to the maximum amplitude peak at 10 Hz and implies that the visual system's low frequency system may be non-linear. Responses in the low frequency system were also characterized by a second harmonic that was greater in amplitude than the fundamental. For instance, with a 5 Hz stimulus rate the largest EP component occurred at 10 Hz, the 2nd harmonic. This may be explained by assuming that the brain structures involved prefer a frequency around 10 Hz. In the high frequency system, it was also found that non-fundamental components were not exact multiples of the fundamental (Van der Tweel & Lunel, 1965) (see Figure 5).

Herein lies one of the weaknesses of this method. It is based upon a linear system which, in reality, often appears to be non-linear. Another weakness inherent in this method is the possibility that minor latency changes may exist within these three, relatively broad, frequency systems. According to Regan "properties of flicker EPs are fairly uniform within a single frequency region but are quite different (change abruptly) when frequency regions are crossed" (1966). However, in any one latency determination, since Regan's method requires more than one

Figure 4

(A) a plot of phase characteristics illustrating a well defined step occurring (in phase lag) at 10 Hz. (B) a plot of amplitude versus frequency with a maximum peak occurring at 10 Hz. These two plots define lthe visual system's low frequency response to flicker.

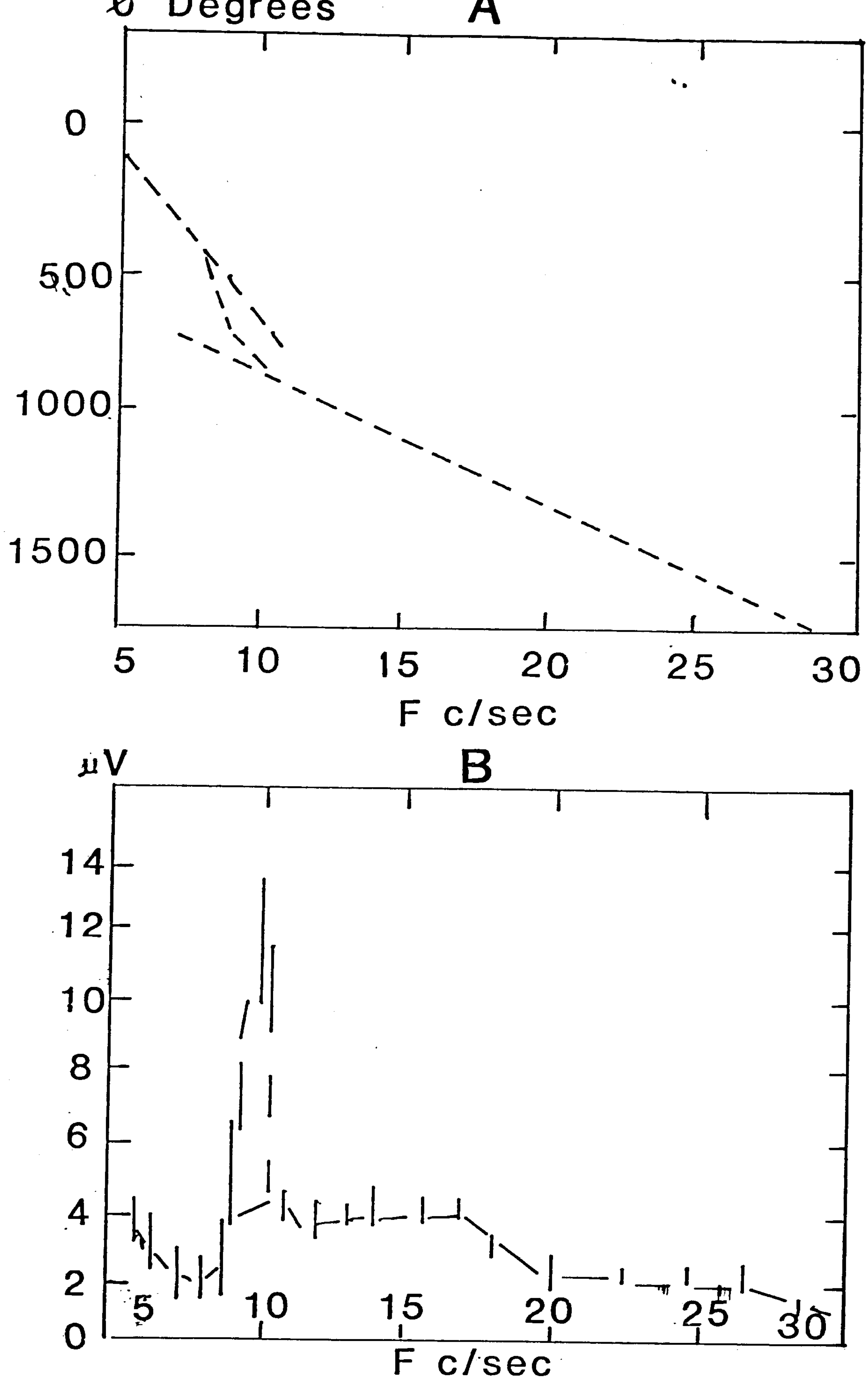
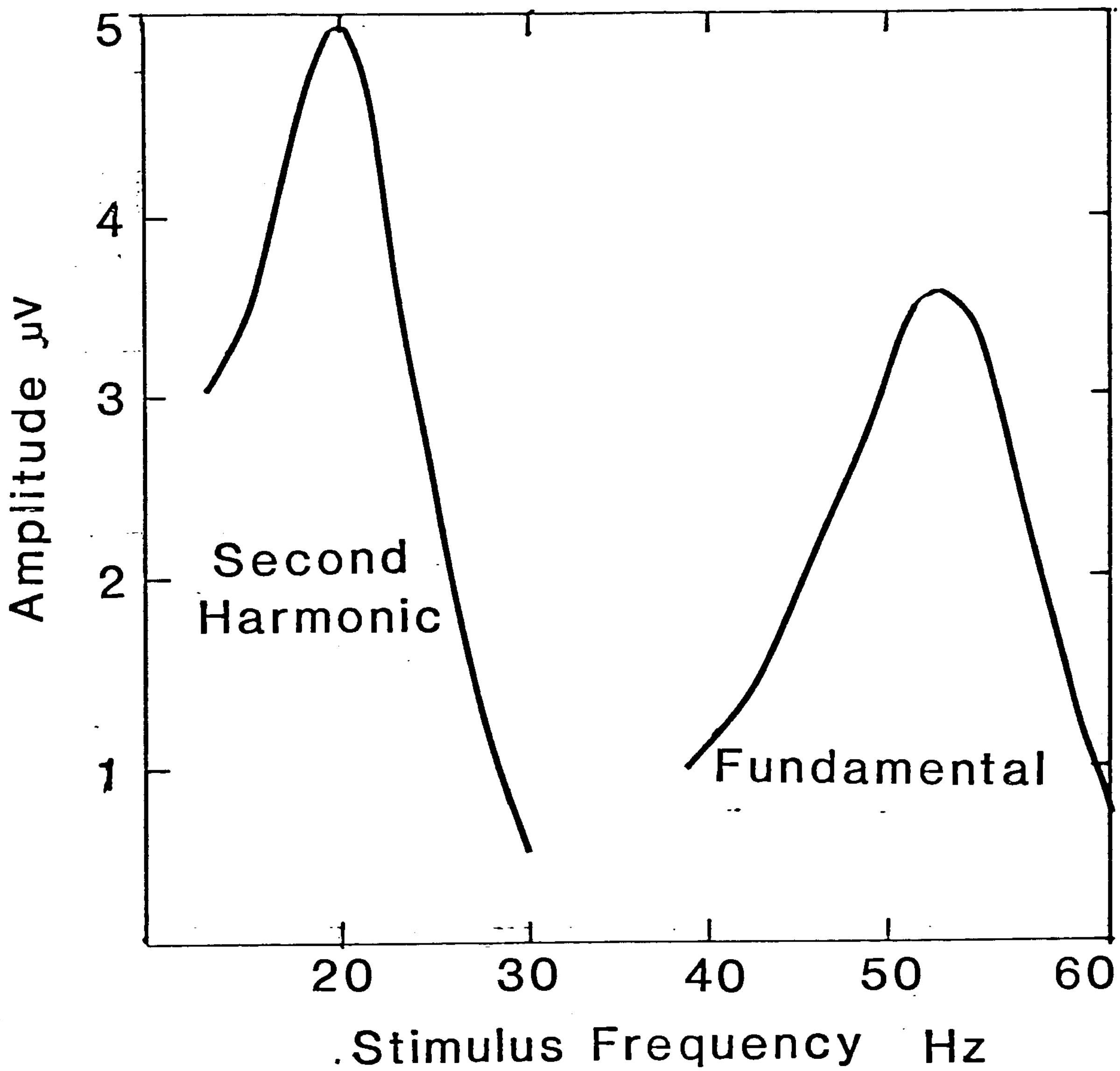

φ Degrees
A
0
500
1000
1500
5
10
15
20
25
30
F c/sec
μV
B
14
12
10
8
6
4
2
0
5
10
15
20
25
30
F c/sec

Figure 5

Amplitude versus stimulation frequency (Hz) for fundamental and second harmonic in the high frequency range. Note that the amplitude of the 2nd harmonic is greater than that of the fundamental and is not an exact multiple of the fundamental.


5
4
3
2
1
Amplitude µV
Second
Harmonic
Fundamental
20
30
40
50
60
Stimulus Frequency Hz

stimulus frequency his method cannot measure regular or constant latency changes that may occur from one specific frequency to to another. The purpose of the present investigation is to determine possible latency changes between specific frequencies, thereby more accurately testing Regan's hypothesis of three frequency regions.

Time-domain analysis

Another method of determining the latency of steady-state EPs has been defined by Diamond (1977 a; b). This method does not require any of the assumptions inherent in the linear model. For example, it does not require stimulus - EP linearity and, in fact, has shown, contrary to Regan's hypothesis (1972), that an individual response cycle can be associated with a particular stimulus cycle (Diamond, 1979).

Diamond's method calculates latency from the time difference between identifiable reference points (e.g. peak points) in the stimulus and VEP cycles. This method is based upon the assumption that an association exists between the stimulus and EP cycle. Therefore, this measure requires only that for a constant set of experimental conditions EP latency is constant, and the reference points chosen in the stimulus and EP cycles are consistently identifiable at the same approximate time points within each cycle (Diamond, 1977 a; b).

Graphic illustration

This method is graphically presented in Figure 6 (a). The EP curves on the right side are artificial but analogous to averaged EP responses that would normally occur in response to a flickering light stimulus. It can be seen, in Figure 6 (a) that each EP cycle, on the right side, is associated with a specific flash on the left side, at different ISI intervals. (Diamond, in distinction to Regan, calculates latency in terms of ISI, the inverse of frequency. The stimulus-EP latency (t) is determined by identifying which EP cycle is associated with which particular flash.

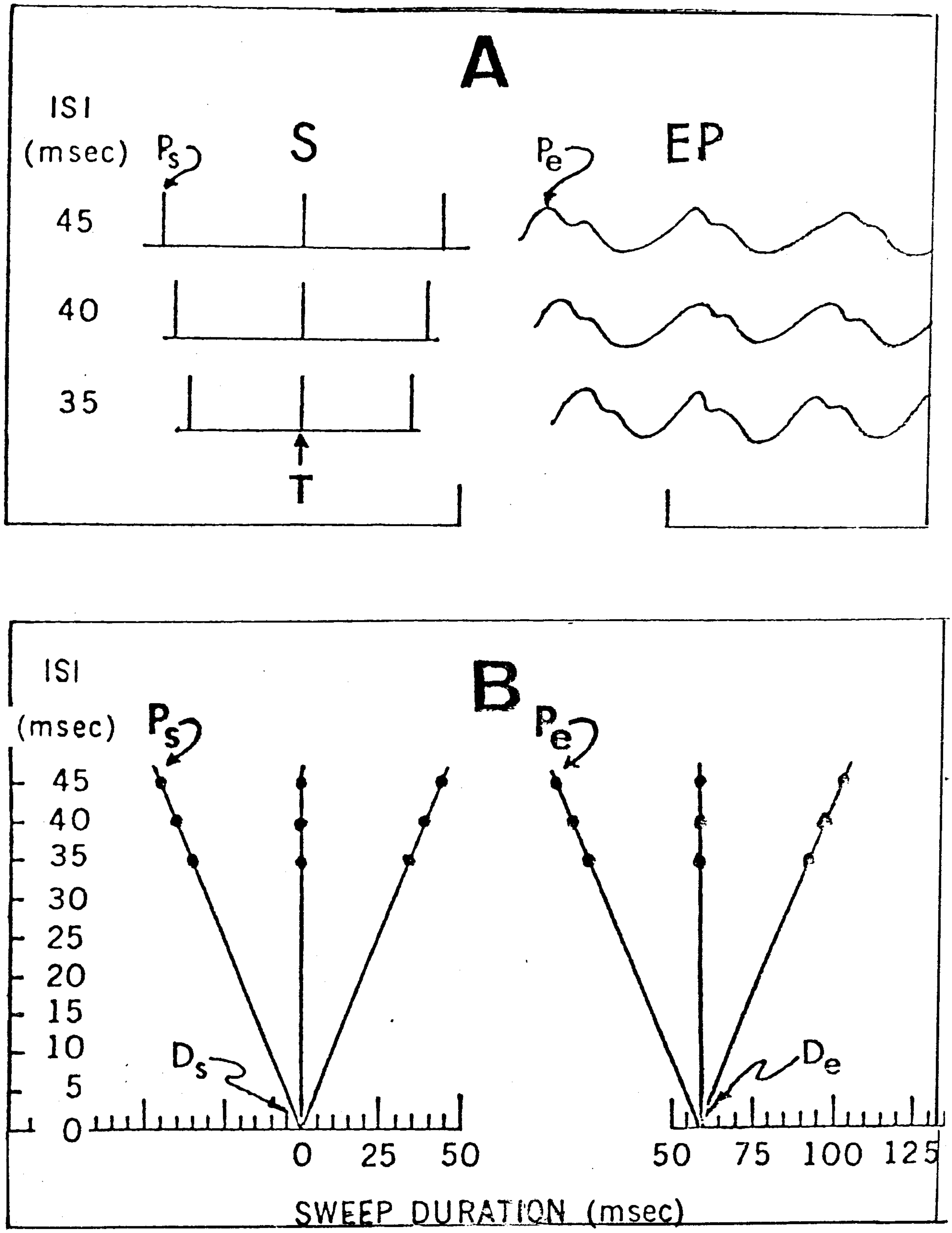
In order to calculate latency (t) a plot of the stimulus and EP peak reference points P_s and P_e is necessary, (see Figure 6 (b)). As illustrated, when regression lines are drawn through both the stimulus and EP peak reference points, they converge to to two intercept values D_s and D_e on the sweep duration axis, to to where mathematically, the ISI becomes zero. This is because D_s represents the "average" stimulus at zero ISI and D_e the "average" EP peak at zero ISI. Therefore the difference $D_e - D_s$ equals the delay or latency from the stimulus to the EP.

Latency calculation

Since latency is defined as the time-difference by which the EP lags the stimulus, then (t) equals $D_e - D_s$,where D_s=0. In

Figure 6.

An illustration of Diamond's time-difference latency calculation. (a) Artificial EP (on right) to repetitive stimulus (on left) repeated at three ISIs. T indicates the stimulus which triggers the averager at the zero point on the sweep duration axis. Sweep duration is the time window during which the averaging computer samples the EP. P_s & P_e are stimulus and EP reference points, respectively. (b) Plot of stimulus and EP peaks with regression lines placed through peak reference points converging to intercept the abscissa, D_s and D_e at ISI=0. EP latency=$D_e - D_s$.



A
ISI (msec)
P_s
S
P_e
EP
45
40
35
T
B
ISI (msec)
P_s
P_e
45
40
35
30
25
20
15
10
5
0
D_s
D_e
0
25
50
50
75
100
125
SWEEP DURATION (msec)

The latency (t) = D_e is calculated by least squares as the average intercept of the EP regression lines (see Figure 6 (b)).

Assumption

Diamond's (1977 a; b) straight-line regression solution assumes a constant EP latency over the ISI range studied and for the reference points chosen. In a manner similar to Regan's apparent latency method, (1966) this method does not take into account the possibility that minor latency shifts may occur within the three frequency systems. Both methods require more than one stimulus frequency for a specific latency determination. For example, the latency of the VEP response to three different ISI values (e.g. 35, 40, 45 msec) in Diamond's latency method, would produce a latency which represents an average over the ISI range. However, the latency may actually shift within the ISI region (35-45 msec), but the method cannot measure such a shift.

The steady state latency method to be investigated in this study overcomes this problem. It is based upon the assumption that there exists an association between a particular stimulus and a particular EP response cycle in the steady state EP. The latency will be determined independently at specific ISI values (rather than over a range of ISI values). This will be done for a wide range of ISI values that encompass the three frequency systems identified by Regan (1972) and others (Van der Tweel & Lunel, 1965; Spekreijse, 1966). This study will also determine if the latencies resulting from this new procedure are consistant with the three frequency systems defined and measured by Regan (1972, p.75) and comparable to Diamond's (1977 a) results.

METHOD

Subjects

Observations were made on four subjects, two males and two females, ranging in age from 27 to 58 years; all had normal or corrected vision and viewed a flickering light, presented stereoscopically. Subjects sat relaxed, in a dimly lit room, in front of a stereoscope. The viewing height of the stereoscope was individually adjusted for each subject and subjects were instructed to place their faces as close to the stereoscope as possible so that the scope rested confortably across the bridge of the nose. Since luminance was not a variable and viewing through artificial pupils was found to be more difficult, subjects viewed licker through natural pupils.

Apparatus

Visual evoked potentials were taken from the scalp with a Beckman electrode on the midline over the occipital cortex, 2.5 cm above the inion, with a reference electrode clipped to the right earlobe and a ground electrode clipped to the left earlobe. Electrode impedance never exceeded 4000 Ohms. Scalp potentials, amplified by a Schonander (EEG), were averaged from 32 sweeps of an averaging computer (Fabritek 1070). The total of 32 sweeps were obtained from two consecutive sets of 16 sweeps, each set was peceded by a 35 msec adaptation period. The sweep time was set at two values, 225 msec at the shorter ISIs (up to 61 msec), and 400 msec at the longer values (66-121 msec ISI). Signals below 3 dB and above 700 Hz were attenuated by 3 dB amplifier filters at the EEG input stage.

The visual apparatus included a Keystone stereoscope (model 3100). Identical stimulation was presented independently to each eye. The visual path to each eye consisted of two LED panels, each containing 16 lights arranged in a rectangle, and a rectangular transluscent diffusing screen in front of each panel. The rectangular screens were binocularly viewed through two 5.3 diopter lens. This resulted in a 7.6 x 10 degree rectangle, as measured in visual angle. The stereoscope was enclosed in a dark compartment to eliminate light stimulation other than that from the rectangular targets.

The LED was manufactured by Monsanto (model #7). Its wavelength was 685 nm and was selected for a number of reasons. First, it has been shown (Nilsson, 1978) that red light stimulation is effective in diagnosing multiple sclerosis (MS). And secondly, the LED has sharp on and off gradients - a rise or fall time of less than 50 usec. This enables the use of narrow square wave light pulse stimulation.

The LEDs were driven by 5 volt square wave pulses of 5 msec duration and 100 percent modulation depth. These pulses were generated by a Wavetek function generator (Model 184) and sequenced by an interval programming device. The luminance of each rectangular stimulus was calibrated by a Spectra (Pritchard) photometer. The pulse duration was calibrated by an MTI (45,A) photocell feeding into an oscilloscope monitor.

Since the subjects' visual sensitivity can change with stimulation over time, a regular stimulation-adaptation cycle was established during data collection. First, the binocular rectangular field was held steady for 35 sec of adaptation, then it was flickered during the trial time, and the EP measure was taken. After the EP measure, the field was made steady again for 35 sec adaptation after which flicker was again presented and another EP measure taken. Four such adaptation-flicker cycles were presented, followed by a 5 minute rest period. The brightness of the targets during steady light adaptation was equivalent to the apparent brightness of the flicker at 31 msec ISI. The luminance of each flash for all ISI values was 14 Ft-L; that of the adapting light was 0.6 ft-L .

Procedure

The procedure was designed to test a new measure of steady state VEP latency using flicker. The flicker was varied from 31 to 121 msec ISI in steps of 5 msec at the shorter ISIs (31-81 msec) and in steps of 10 msec for the longer ISIs (91-121 msec). At each ISI value four flicker conditions were measured.

This new method analyzed both synchronous and asynchronous flicker stimulation (as in Diamond, 1979). For asynchronous stimulation the time interval between successive flashes was alternated. For example, starting with the first flash, if successive flashes were designated A,B,A, . . . and so forth, the time interval AB (between A and B) was 28 msec, the next time interval between BA, 31 msec, the next between AB, 28 msec, and so on. For synchronous stimulation AB equalled BA. Note that at each basic ISI value the time interval between BA was held constant throughout all four conditions. This is illustrated in Figure 7 (a) and (b).

At each basic ISI value (from 31 to 121 msec) one synchronous ISI value was presented and three asynchronous ISI values were presented in which only AB varied. For example, at 31 msec basic ISI, AB was set at 28, 31 (synchronous), 36, and 41 msec, in successive averaging trials. BA was held constant at 31 msec for the four conditions. Therefore, at AB=31 msec, the stimulus was synchronous and at the other values, asynchronous.

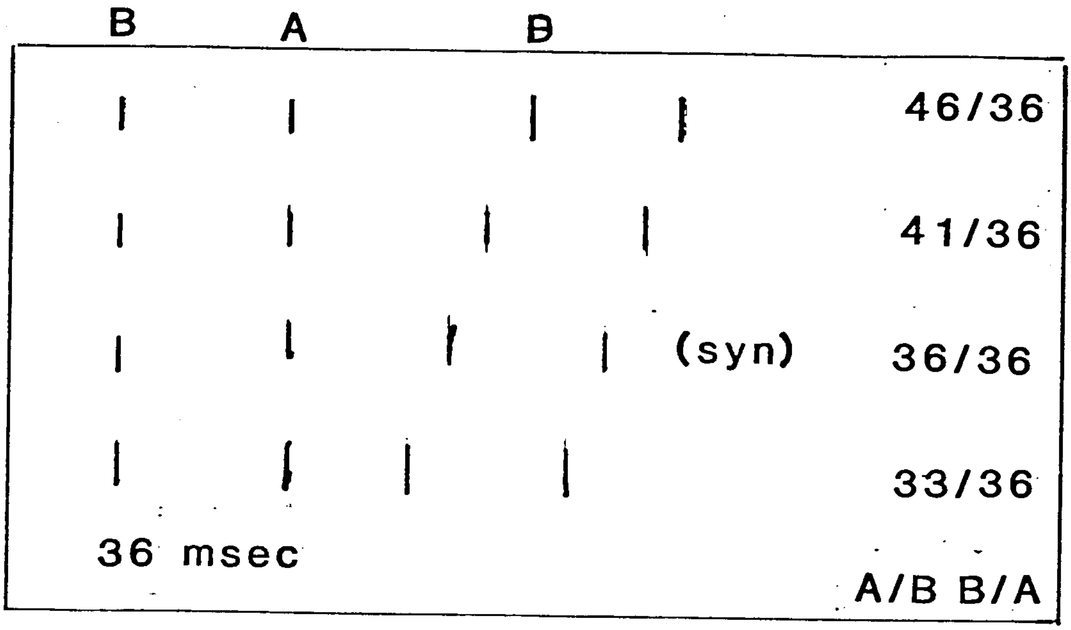
Of the two flashes only flash A was used to trigger the sweep of the signal averager. In this manner, a flash A is always located at zero on the sweep duration axis (see Figure 7b) and serves as a constant reference point in time.

If an association exists between the stimulus intervals and the evoked response (Diamond, 1979) the interval between an EP response to A and B should increase as the AB interval increases,

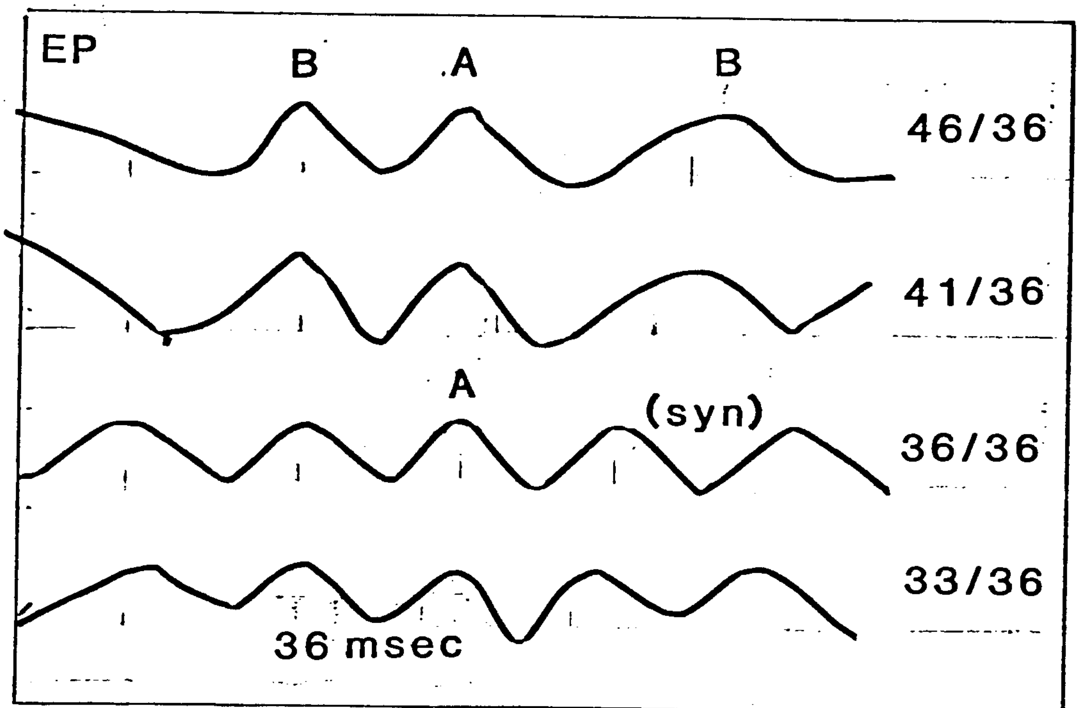
Figure 7

(a) An example of an asynchronous flicker procedure.

(b) Steady state response curves resulting from the asynchroous procedure. Positive is up.



a Flash Presentation



b Duration

and the interval between the EP response to B and A should remain constant. Therefore, the latency can be determined at a particular ISI value (e.g. 31 msec) without varying the ISI preceding the A flash as was done in the previous methods of Diamond (1979) and Regan (1972).

Measurement procedures: Computer Algorithms

Latency determination procedures generally require identifying peaks in the EP, and then applying a latency measurement procedure. Most steady state EP latency studies (e.g., Regan, 1972; Diamond, 1977 a) have been based upon the assumption that the latency of the EP does not change as a function of ISI, and thus may be calculated across all ISIs used in the study. The aim of this study was to develop a series of computer algorithms that would (1) identify peaks automatically, (2) investigate the possibility of peak variability, as a function of ISI, (3) investigate the possibility of peak variability, as a function of differentially filtering (smoothing) the EP curves, (4) calculate latencies, and then determine their impact upon traditional latency concepts and procedures. In order to compare the latency results, in this present study, to the latency results produced by Fourier analysis (Regan, 1972) it was necessary to filter out the high frequencies in the EP curve with a number 19 filter window. For a detailed description and illustration of these algorithm procedures, see Appendices A, B, and C.

RESULTS

The results of the two subjects presented here are representative of all subjcts unless otherwide stated.

Components generated as a function of ISI

The results in Figure 8 show that the number of components in the steady state EP, produced in response to each flash in a flicker train, varies as a function of ISI. For example, at the shorter ISIs (36 msec or less) the response is composed of a single component. At slightly longer ISIs (41 to 91 msec) a two component response is produced; and as the ISI continues to increase (101 to 121 msec) so do the number of components. However, minor individual difference did occur. For example, D.V.D., did not consistently produce additional components as a function of ISI, and at the longer ISIs, some subjects produced three instead of four component responses. However, all subjects showed the major phenomenon: as ISI is increased the number of components in the steady state EP increases.

Relationship between component amplitudes and ISI

Figure 9, reveals that amplitude variability between the components of the steady state EP results as a function of ISI.

Figure 8.

Steady state response curves to a red regularly spaced flickering light, for subject C.F. Curves are positive up. The number of components in the steady state EP decrease with shorter ISIs (faster rates of stimulus presentation); single component EPs occur at 31 msec ISI, double component EPs at 41 msec or greater, multiple component EPs at 101 msec ISI or greater. Filter window is 3 (see Appendix C). Vertical hash marks designate component peaks as determined by a peak detection computer program (see Appendix A).

ISI VERSUS COMPONENT INCREASE

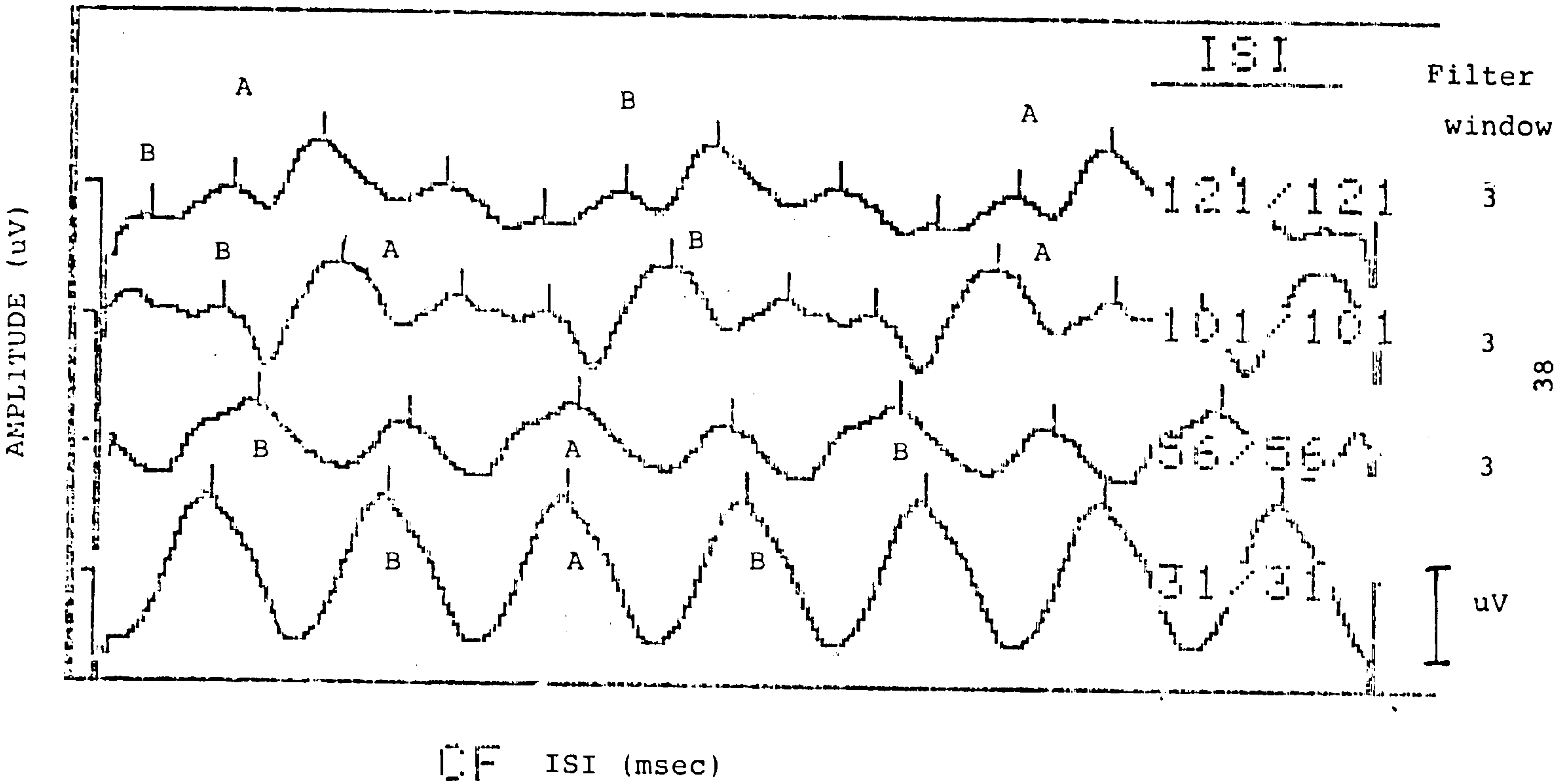
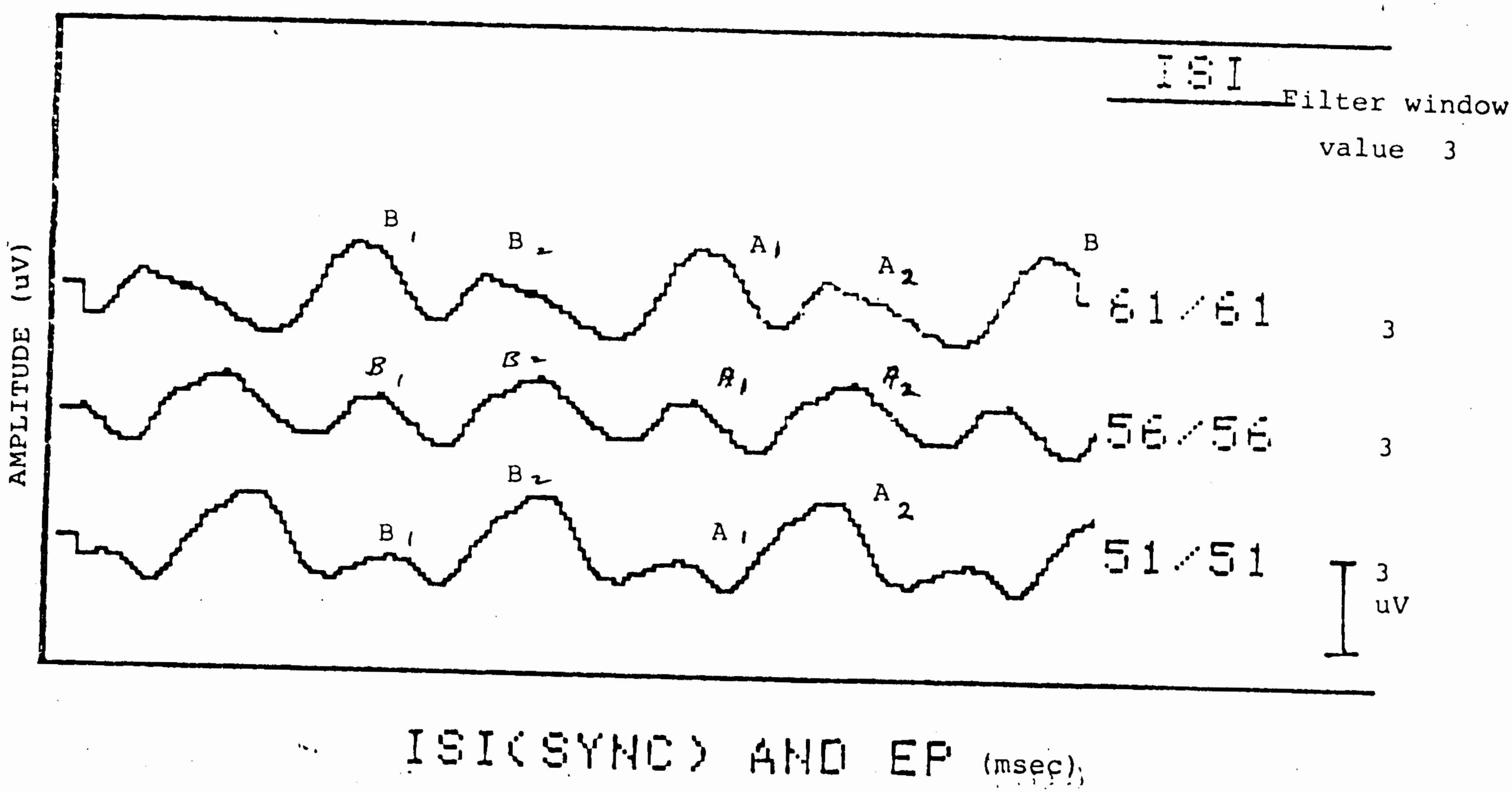


Figure 9.

Alterations in peak amplitudes between the components of steady state EP as a result of changes in ISI, (a) at 51 msec ISI, amplitude is larger in the early component, with a peak latency of 86 msec, (b) at 61 msec ISI, peak amplitudes reverse, the later component becomes larger with a peak value of 114 msec. Filter window is 3.

COMPONENT AMPLITUDE REVERSAL



As shown for C.F., a 51 msec ISI stimulus clearly evoked a two component response in which the amplitude of the first component was larger than the second, a large/small relationship. However, at 61 msec ISI, the respective amplitudes reversed with that of the second component becoming larger than the first, a small/large relationship.

<u>Filter effects on synchronous EP components</u>

The effects of filtering the steady state EP were analysed in a procedure that involved filtering out the high frequencies in the EP curve. Two filter values were used. The first, a low filter value (a minimum window value of 3; see appendix C) resulted in the retention of one or more components (peaks) in the response, and the second, a higher filter value (window value 19) reduced the number of components (peaks) in the EP response to one per cycle.

The rational for reducing the number of EP components to one was to produce a single fundamental EP response to the flickering light analogous to the fundamental component produced by Fourier analysis. Figures 10 and 11 illustrate these results.

The curves in Figures 12 to 15, in which the latency of a positive EP peak is plotted as a function of ISI, reveal that significant peak latency differences resulted from differentially filtering the data. The positive peak (or peaks) was

Figure 10.

Filter effects upon steady state response curves to red flicker, for subject C.F. Positive is up. Response is reduced to a single component EP. Filter window is either 3 or 19.

FILTER EFFECTS

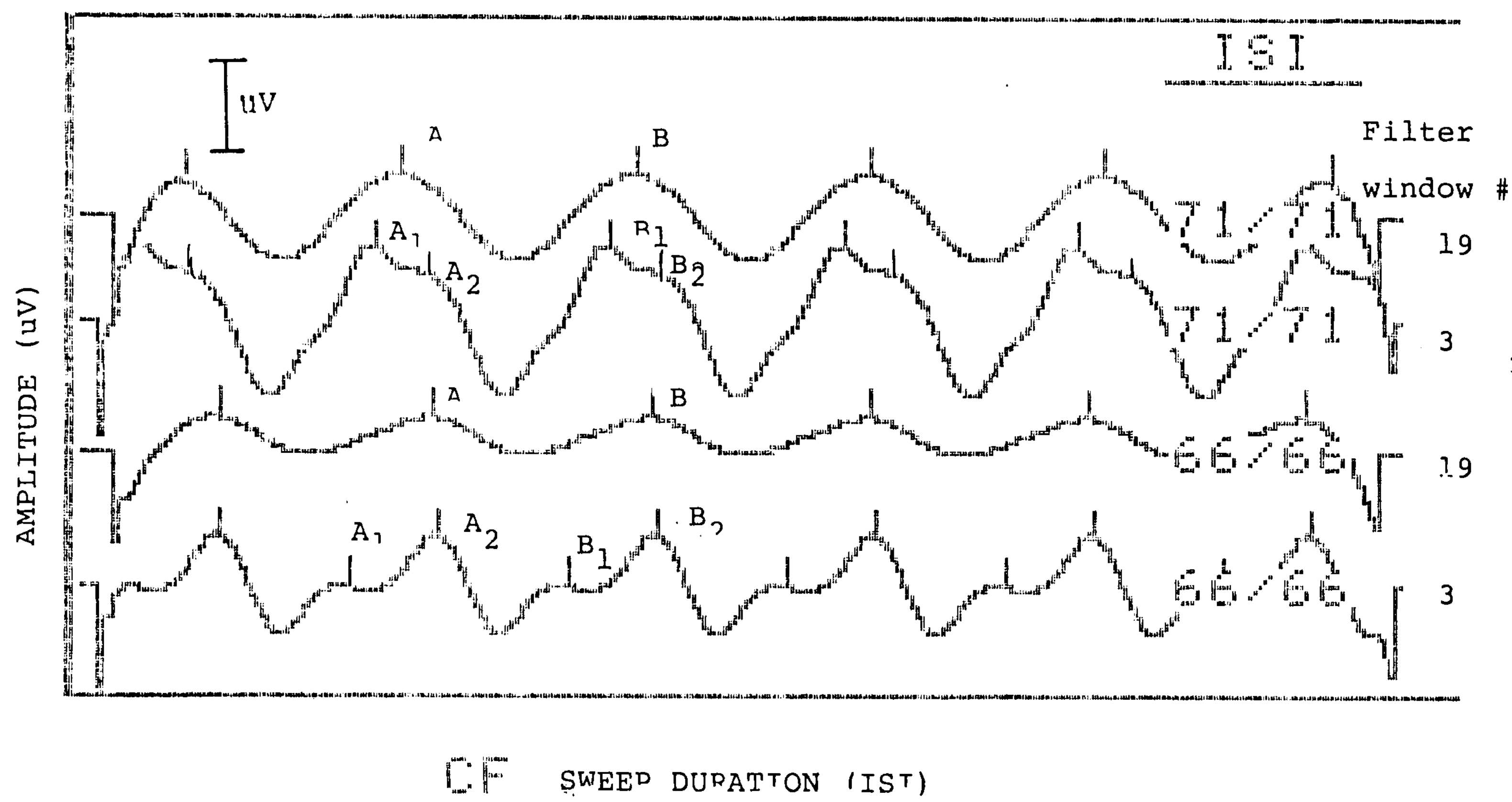


Figure 11.

Filter effects upon steady state response curves to red flicker for subject LD. Positive is up. Response is reduced to a single component EP. Filter window is either 3 or 19.

FILTER EFFECTS

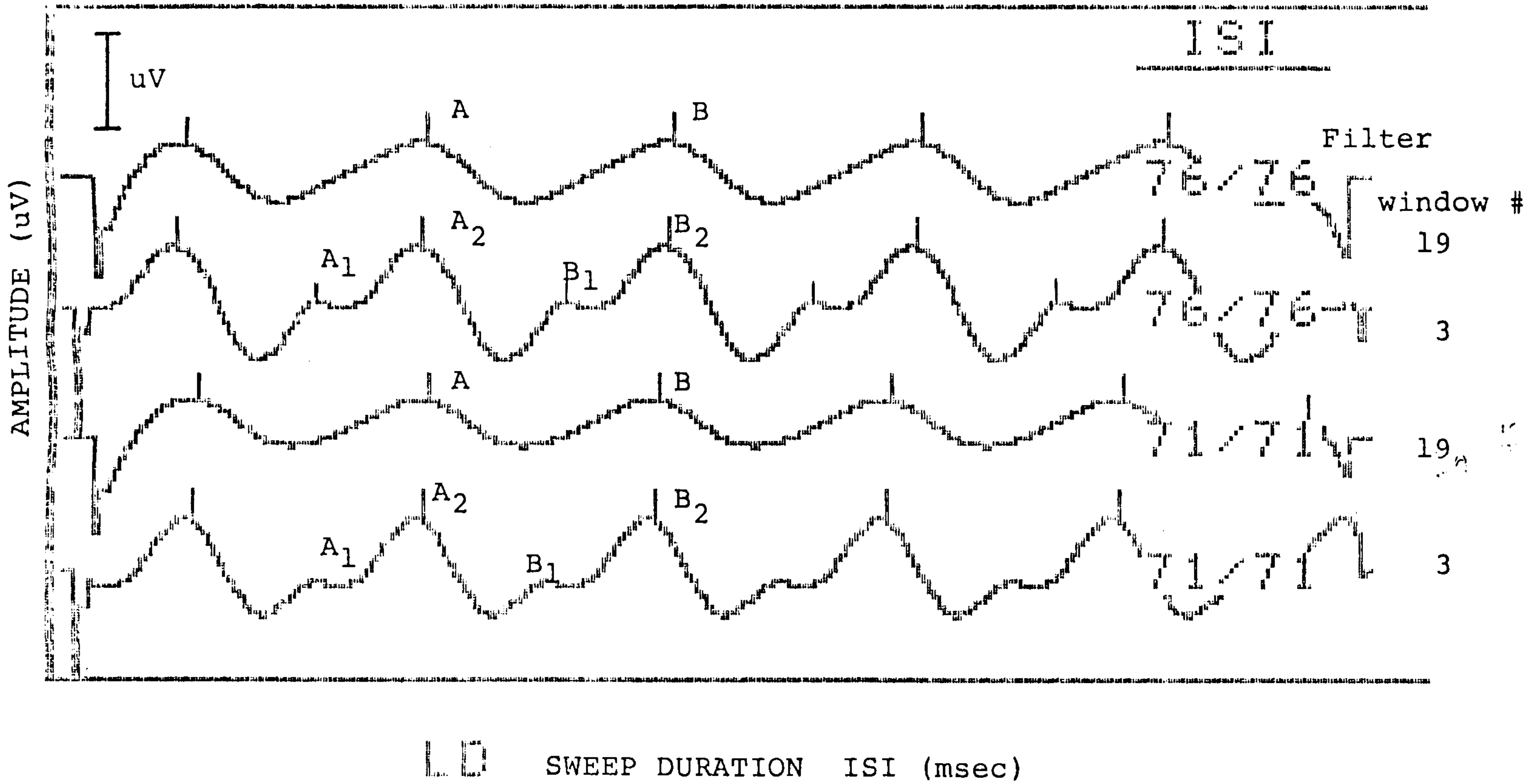


Figure 12.

The effects of a high filter (window 19) on positive peaks of the synchronous steady state EP. The EP peak plotted was selected as peak A, and its latency determined by the asynchronous procedure outlined on pages 31-34. For C.F., major peak shifts are evident from 61 to 66 msec and in the 81 to 121 msec range along the ISI axis.

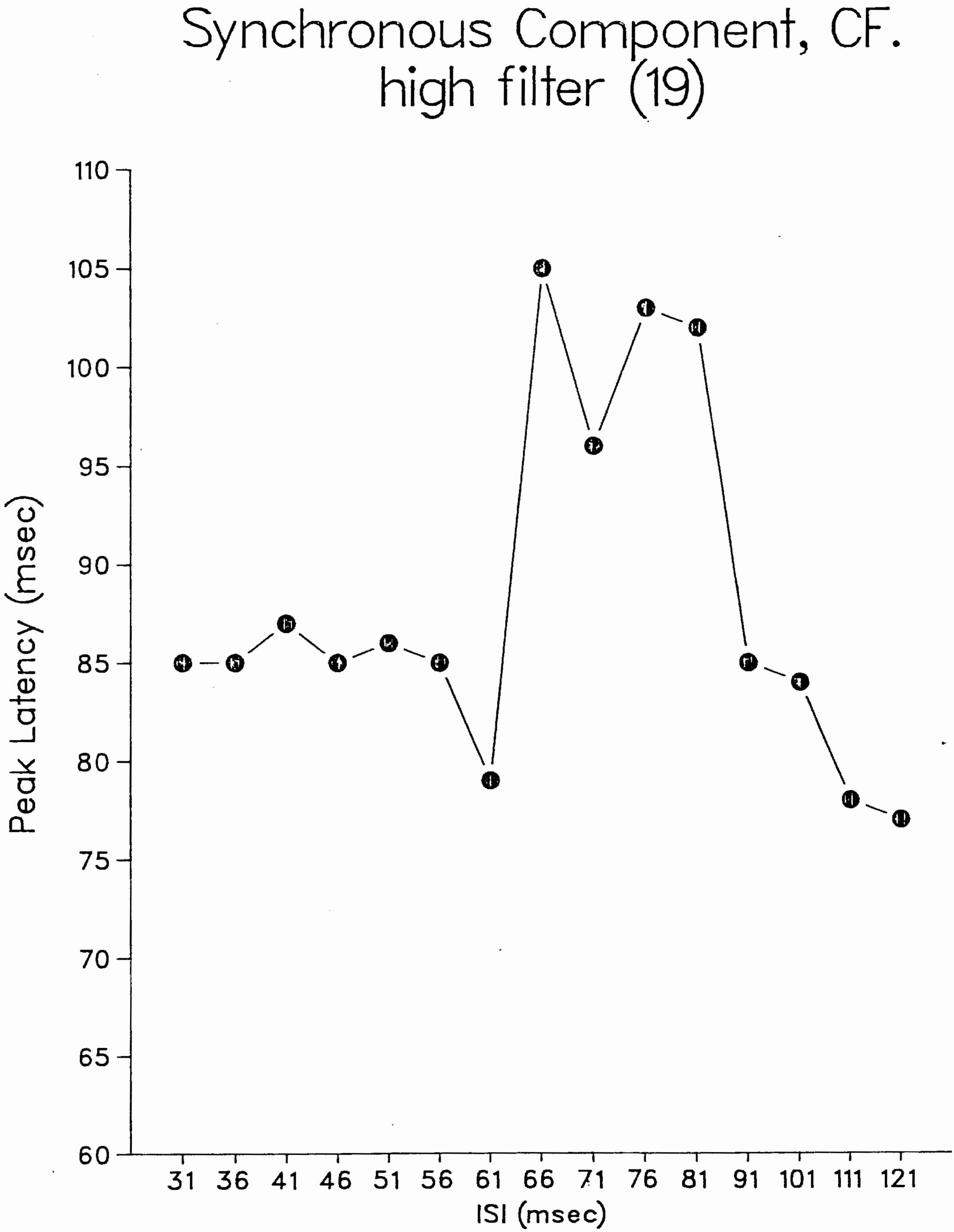

Synchronous Component, CF.
high filter (19)
Peak Latency (msec)
110
105
100
95
90
85
80
75
70
65
60
31 36 41 46 51 56 61 66 71 76 81 91 101 111 121
ISI (msec)

Figure 13.

The effect of a high filter (window 19) on the positive peaks of the synchronous steady state EP. The EP peak plotted was selected as peak A, and its latency was determined by the asynchronous procedure outlined on pages 31-34. For L.D., major peak shifts are evident from 41 to 46 msec and in the 81 to 121 msec range along the ISI axis.

Synchronous Component, LD.
high filter (19)

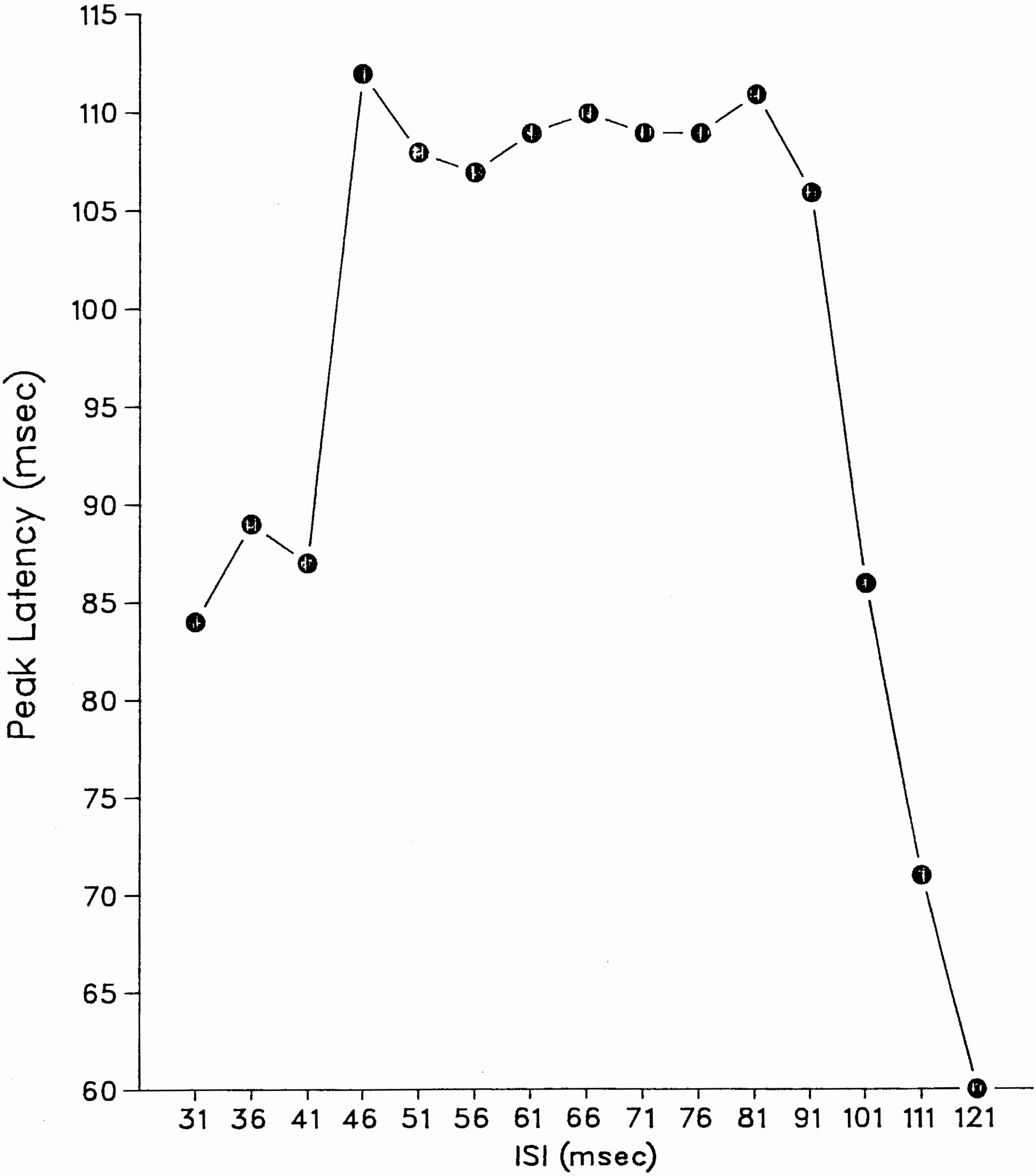


Figure 14.

The effects of a low filter (window 3) on the positive peaks of the synchronous steady EP for subject C.F. The plot of peak latency versus ISI is of the two components illustrated in Figure 10. The two component peaks were selected as A1 and A2 as determined by the asynchronous procedure outline on pages 31-34.

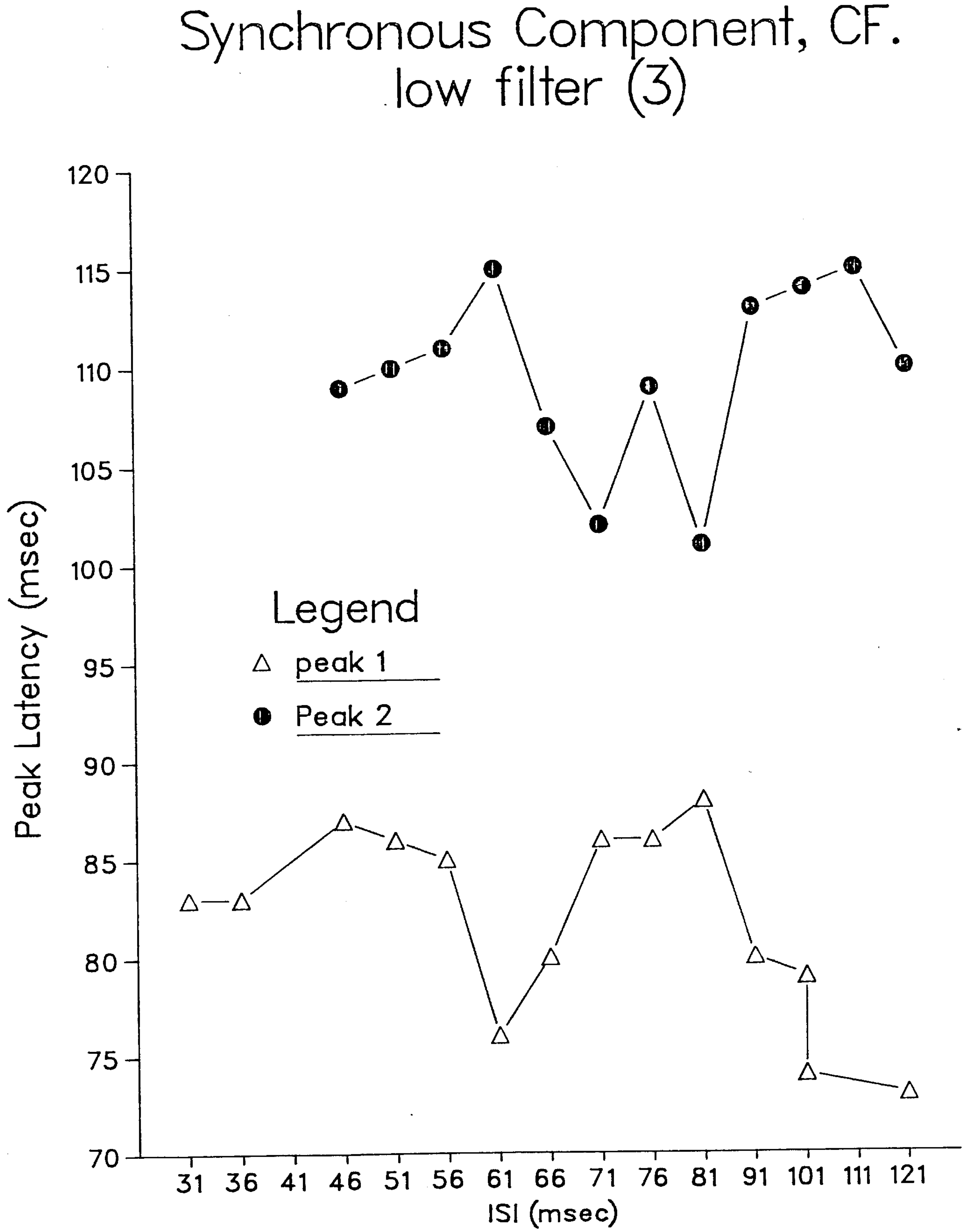
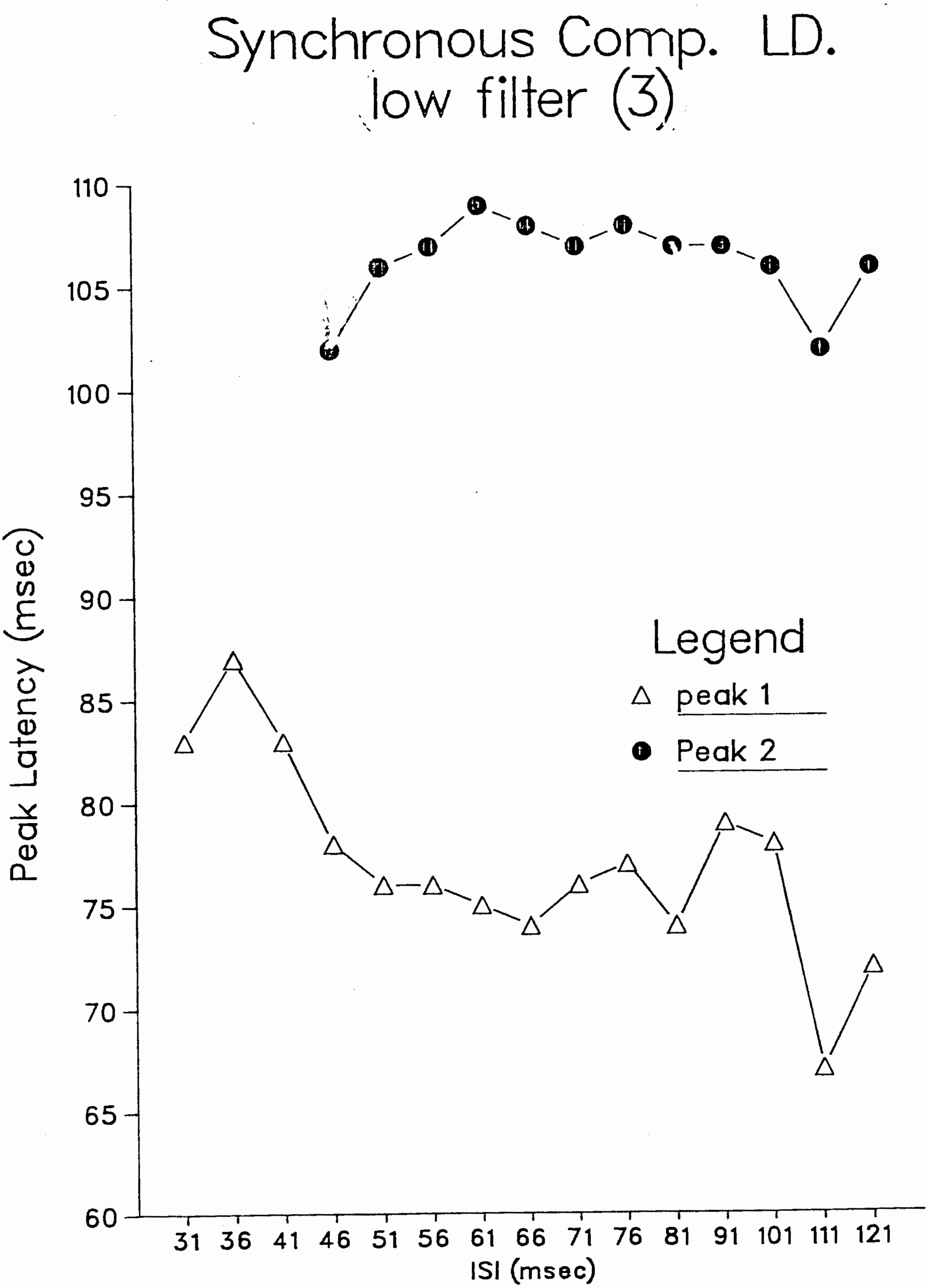

Synchronous Component, CF.
low filter (3)
Peak Latency (msec)
120
115
110
105
100
95
90
85
80
75
70
Legend
peak 1
Peak 2
31
36
41
46
51
56
61
66
71
76
81
91
101
111
121
ISI (msec)

Figure 15.

The effects of a low filter (window 3) on the positive peaks of the synchronous steady state EP for subject L.D. The plot of peak latency versus ISI is of the two components illustrated in Figure 10. The two component peaks were selected as A1 and A2 as determined by the asynchronous procedure outlined on pages 31-34.


Synchronous Comp. LD.
low filter (3)
Peak Latency (msec)
110
105
100
95
90
85
80
75
70
65
60
31 36 41 46 51 56 61 66 71 76 81 91 101 111 121
ISI (msec)
Legend
peak 1
Peak 2

selected as peak A as determined by the asynchronous procedure outlined on pages 63-64. The higher filter (window 19) produced a single component across all of the different ISIs. This is plotted in Figures 12 and 13. For the higher filter (single component) plot there seems to be a sharp break between the low and medium ISI values.

In contrast, the lower filter (window 3) yielded two component peaks per flash, (see Figures 14 and 15). Of the two, the early component, ranged in latency from 70 to 100 msec, among all subjects. The latency of the late component ranged between 105 and 115 msec. At the longer ISIs (from 111 to 121 msec) a third component peak appeared with a latency that ranged between 54 and 70 msec (preceding the other two components).

Traditional latency procedure and filter effects

Figures 16 to 19, illustrate the significant effects that filters can have upon the earlier traditional latency procedures (Regan, 1972; Diamond, 1977 a). These procedures have been based upon selecting corresponding peaks in the EP that are assumed to have constant latency values, and then calculating (by a regression technique, see p. 27) latency across consecutive ISIs. As shown in Figures 16 and 17, latency so determined for the higher filtered peaks, are extremely variable.

The lower filtered EP yielded two latency curves, one for

Figure 16

Synchronous latency procedure and filter effects for subject C.F. Each point represents a latency that was obtained by selecting corresponding peaks in the EP of three consecutive ISIs and determining latency by linear regression through data from these three ISIs (see Diamond, 1977 a). The higher filtered EPs produced anomalous latency values as indicated by the major latency shifts across ISIs.

Synchronous Latency. CF.
(high filter)

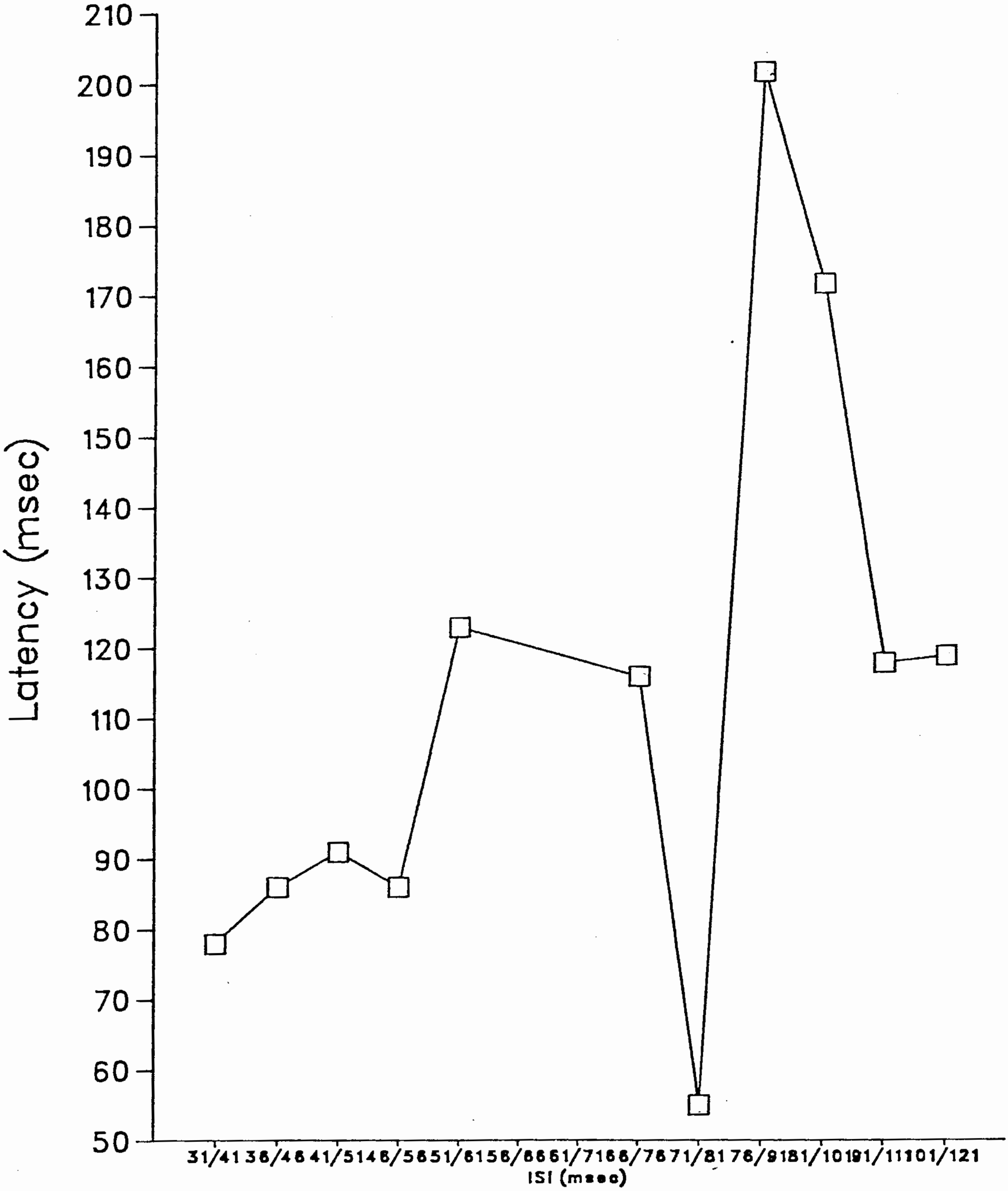


Figure 17.

Synchronous latency procedure and filter effects for subject L.D. Each point represents a latency that was obtained by selecting corresponding peaks in the EP of three consecutive ISIs and determining latency by linear regression through data from these three ISIs (see Diamond, 1977 a). The higher filtered EPs produced anomalous latency values as indicated by the major latency shifts across ISIs.

Synchronous Latency. LD.
(high filter)

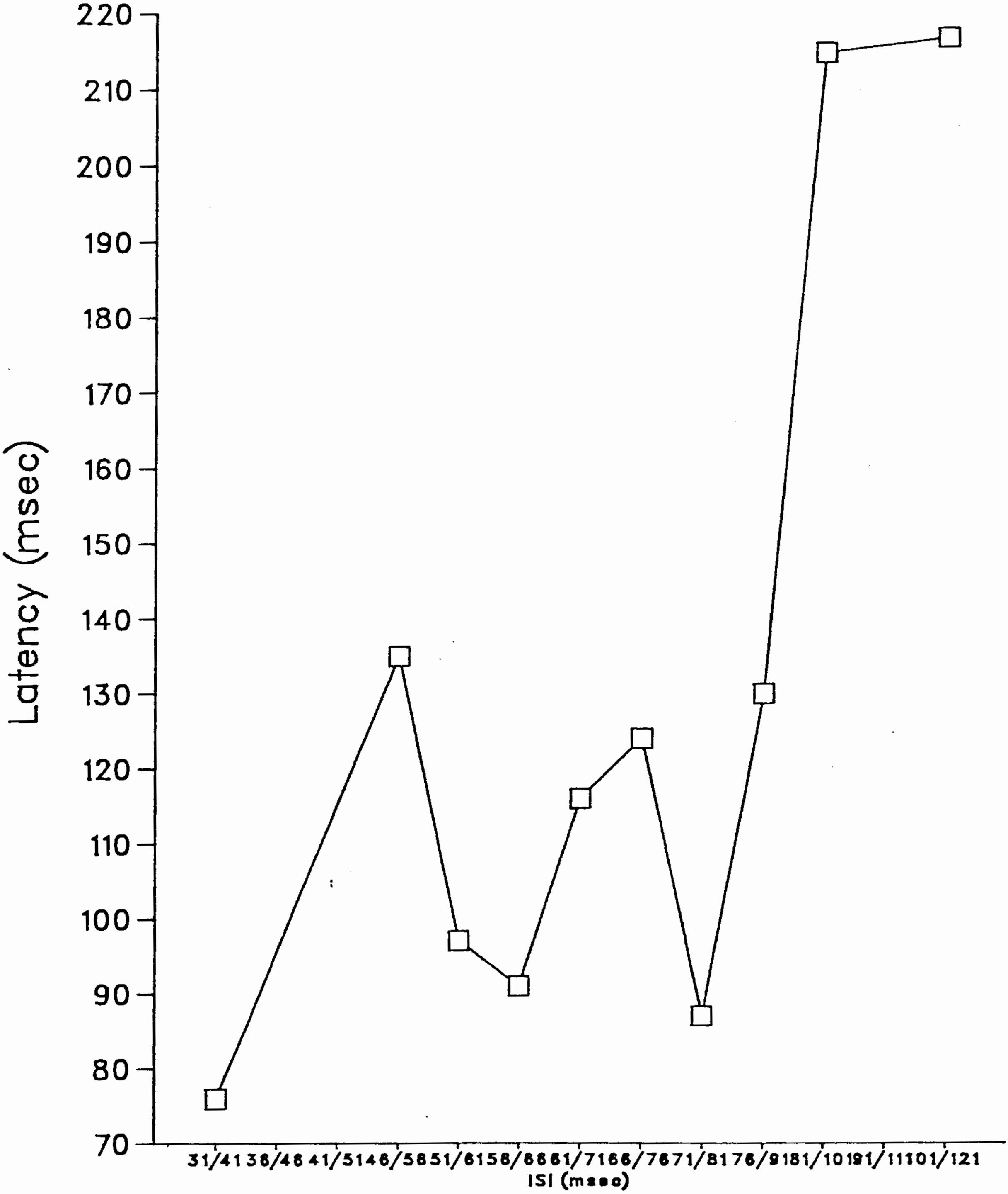


Figure 18.

Low filter effects and synchronous latency procedure for Subject C.F. The lower filtered EPs revealed two latency vs ISI curves. Latencies for both peaks varied significantly especially across the medium frequency range, between 51 and 76 msec ISI.

Synchronous Latency. Low filter. CF

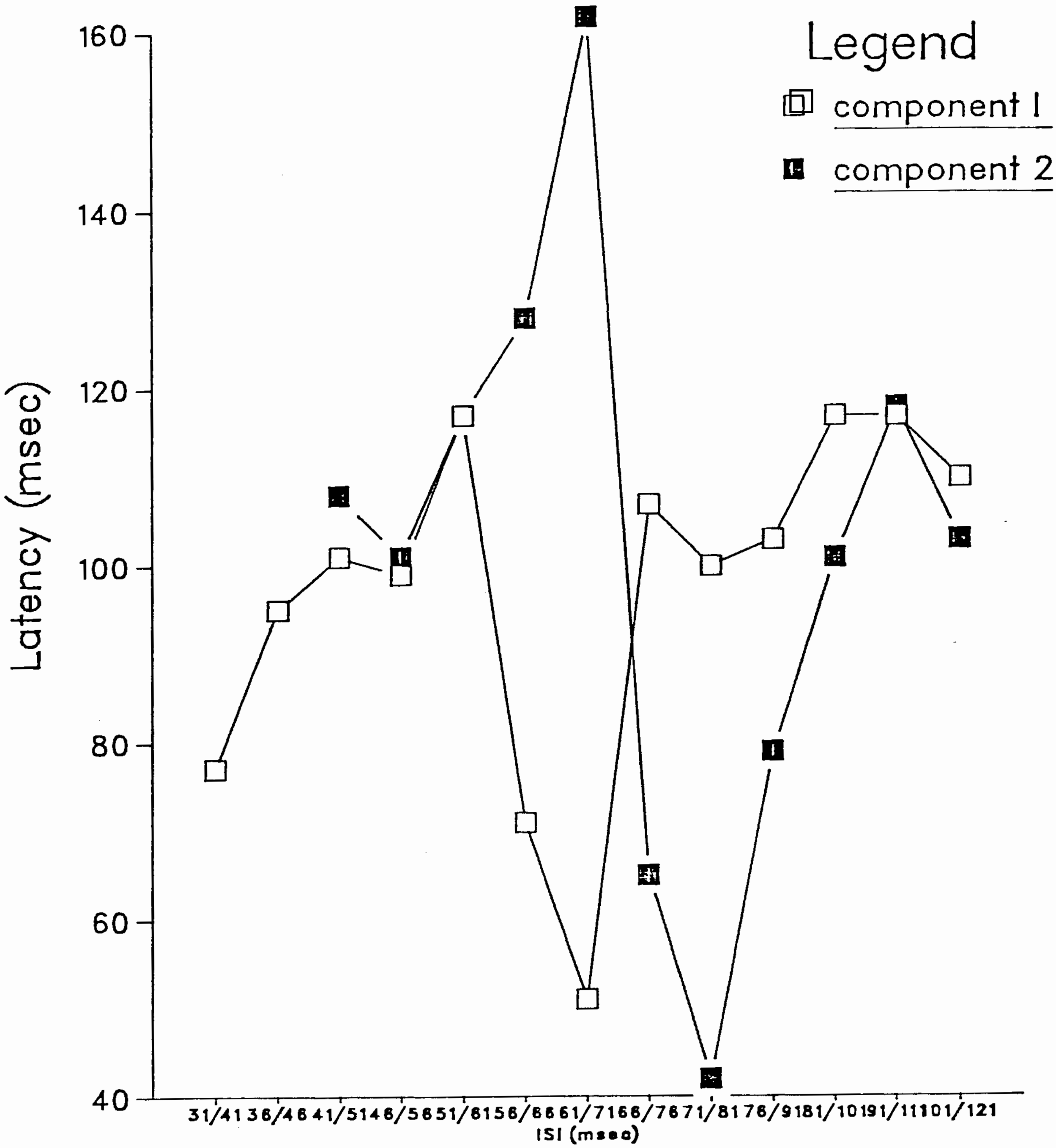
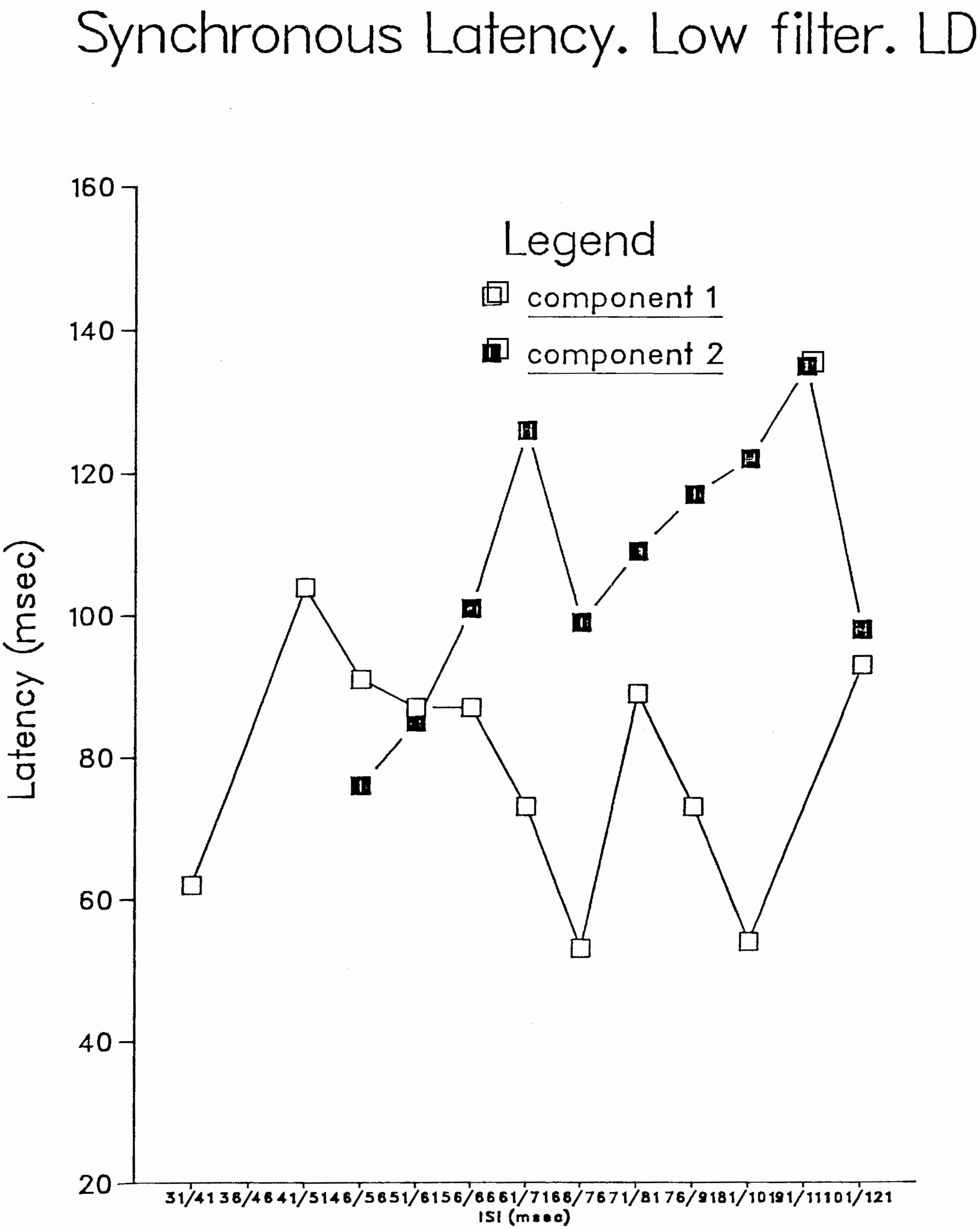


Figure 19.

Low filter effects and synchronous latency procedure for subject L.D. The lower filtered EPs revealed two latency vs ISI curves. Latencies for both peaks varied significantly especially across the medium frequency range, between 51 and 76 msec ISI.



Synchronous Latency. Low filter. LD
Legend
component 1
component 2
Latency (msec)
160
140
120
100
80
60
40
20
31/41 36/46 41/51 46/56 51/61 56/66 61/71 66/76 71/81 76/91 81/101 91/111 101/121
ISI (msec)

each component, and as shown in Figures 18 and 19, these curves reveal somewhat less variability as a function of calculating across ISIs. However, latencies were still quite variable for most subjects in the 61 to 66 msec ISI range.

Revised latency procedure: Asynchronous method

Significant variability in latency is evident, when latency is calculated in the traditional manner (Regan, 1972; Diamond, 1977). This may be because the assumption that latency is constant across the ISIs, used when calculating, is an invalid assumption.

In asynchronous latency determination the only assumption is that the latency of the EP to flash A does not change across the four different asynchronous condition (see Figure 7a). This assumption is based on the fact that the ISI preceding flash A is always constant, i.e., (BA) is always 36 msec. Therefore, in the EP response in Figure 7b, there should be an EP peak which does not change in latency across the four different asynchronous conditions. This is peak A, in figure 7b. The "alternate" positive peak is labelled B. The EP peak A, is then identified in the synchronous condition (labelled 36/36, in Figure 7b). Next, the time lapse between flash A and EP peak A is measured as the latency of peak A. Peak A latency was then plotted for all synchronous ISI values from 31 to 121 msec. Where there is a two component response to peak A these components are plotted as peak 1 and peak 2 (see Figures 14 and 15).

Amplitude of the steady state EP as a function of ISI and its effects on latency.

The data in Figures 20 and 21, illustrate the differences between subjects in the maximum amplitude of the steady state EP, as a function of synchronous ISI. The maximum amplitude of the response was determined by measuring the voltage difference between the largest positive and largest negative peak in a complete EP cycle. Generally, EP amplitude was low at the shorter ISIs, however, C.F., was an exception (see Figure 22). As ISI increased the EP amplitude generally increased to a maximum, then fell off for the longest ISIs (101 msec or longer).

Figure 20.

Steady state EP amplitude - ISI curves for subject C.F. Amplitude generally increased as a function of ISI but the increase was not linear.

Amplitude as a function of ISI. CF. synchronous

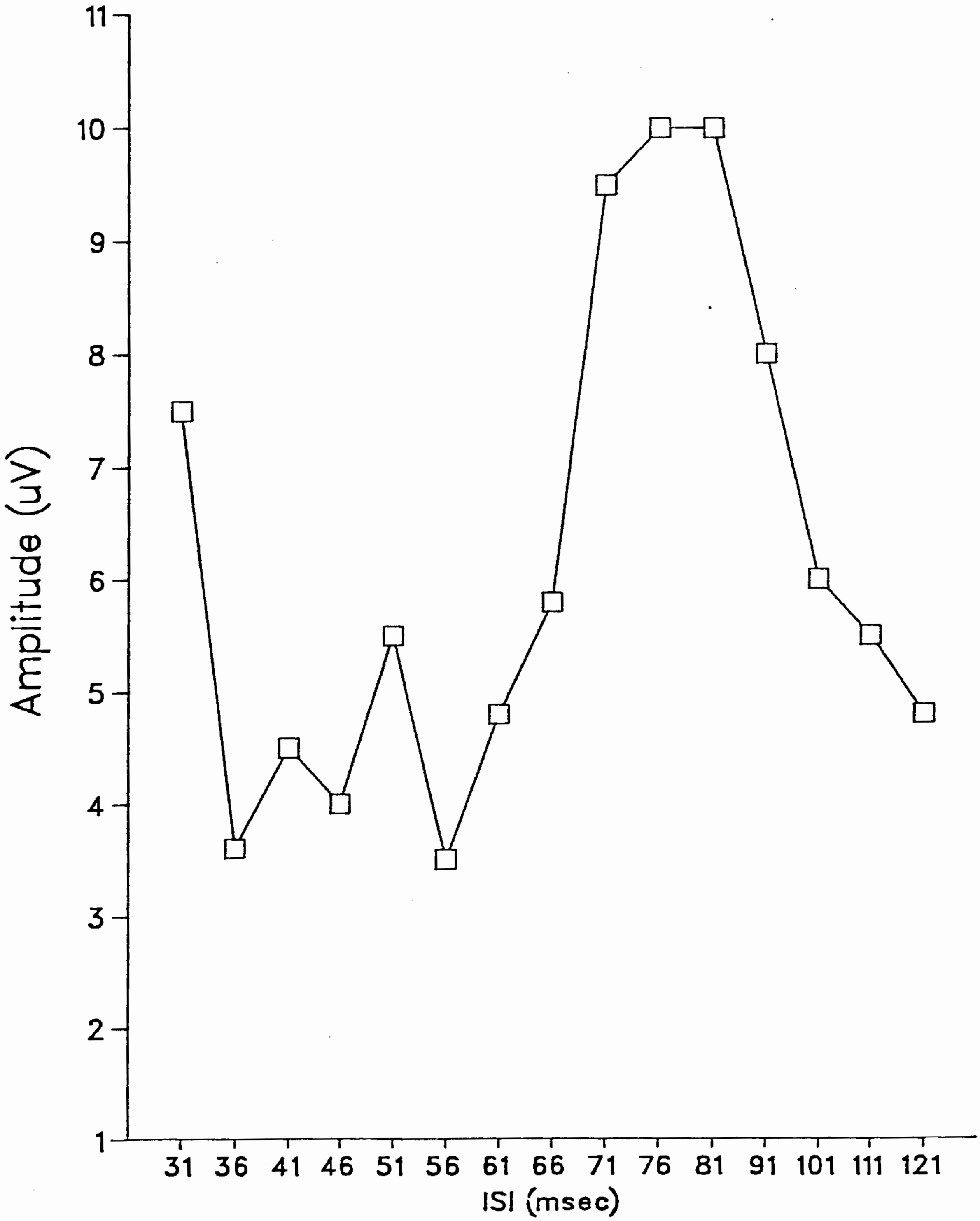
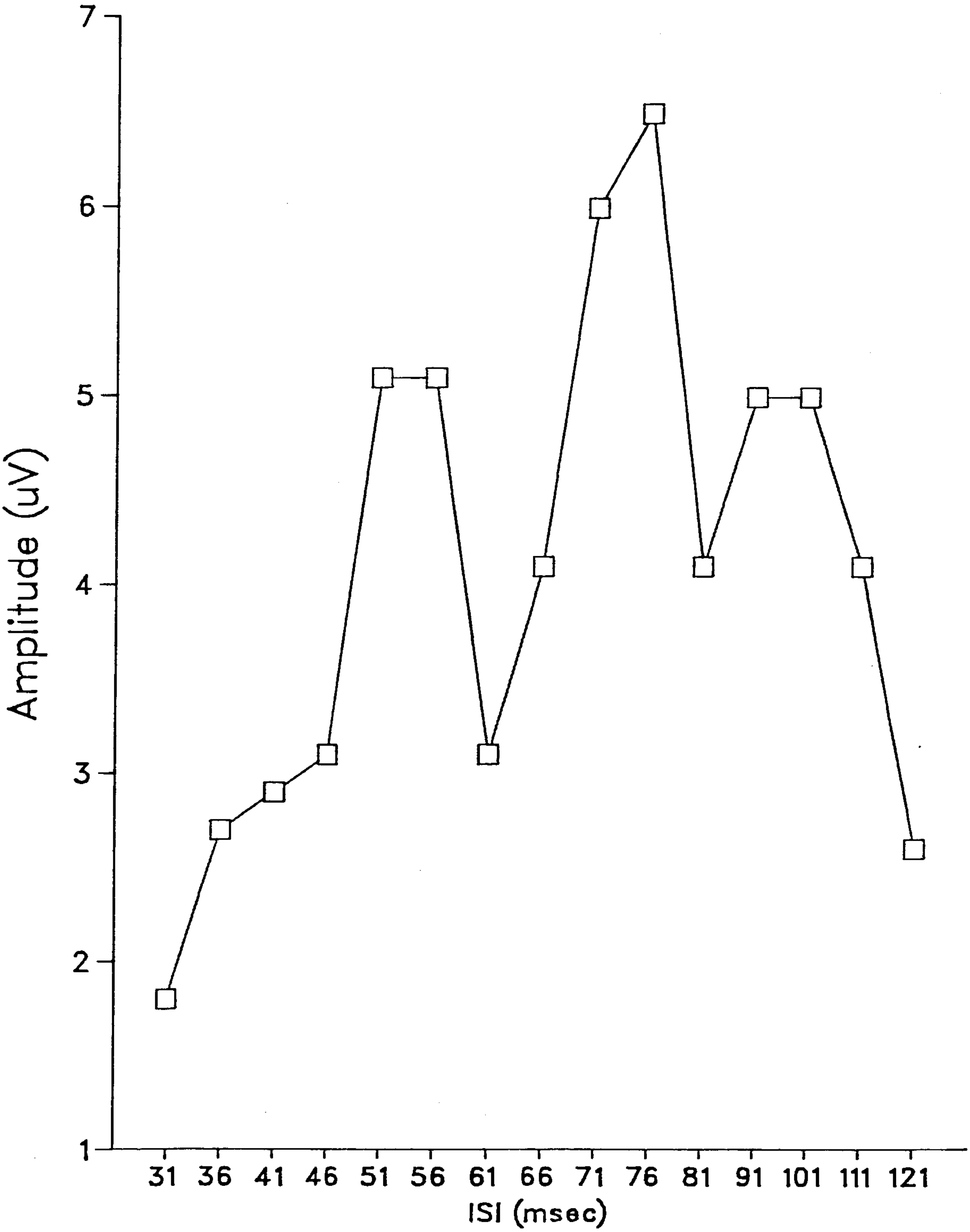


Figure 21.

Steady state EP amplitude - ISI curve for subject L.D. Amplitude generally increased as a function of ISI but the increase was not linear.

Amplitude as a function of ISI. LD. synchronous



DISCUSSION

This study has shown that at least two fundamental components in the EP appear over a wide range of frequencies. These results are not consistent with Regan's (1972) idea that separate EP fundamental components are evoked only within separate and distinct frequency ranges, and that each frequency range is associated with a different latency system. Therefore, this suggests, contrary to Regan's theory, that there are not three latency systems set off by three frequency ranges, or channels. Rather, there are a number of fundamental components in each steady state EP cycle at all flash frequencies, and each component has a different latency.

Regan's latency channels as produced by filtering the EP response

Theoretically, the Fourier analysis employed by Regan (1972) and the filtering procedure employed in the present experiment both involved reducing the multiple component EP to a single fundamental response for each light flash. This is seen in Figures 10 and 11. As shown in Figure 12, for subject C.F., there is a major shift in peak latency from about 85 msec at the shorter ISIs (31 to 56 msec) to about 103 msec at the longer ISIs (66-81 msec). For L.D., (Figure 13) there is a major shift in peak latency from about 87 msec, at 31 to 41 msec ISI, to about 108 msec at 51 to 91 msec ISI. This often produced abrupt and major shifts in the latency/ISI plots.

Regan's latency procedure in which only the fundamental response to each flash is measured, would result in the same abrupt latency shift with changes in stimulus frequency. Such an abrupt shift implies a possible shift, with stimulus frequency, from one latency/frequency system to another. This is in fact the conclusion to which Regan has come (Regan, 1972).

Moreover, it was found that the time difference between peaks in the multiple component EPs was approximately 30 msec. This is the time difference that separates the estimated latencies of Regan's three frequency channels, 60 msec (fast frequency), 90 msec (medium frequency) and, 120 msec (slow frequency).

Note that the peak shift between 41 and 46 msec ISI, in Figure 13, corresponds to where Regan has determined that a major shift in latency occurs between the fast and medium frequency systems. This is also where most subjects begin to show the double component response, if the EP is not forcibly reduced to one fundamental by a Fourier analysis or heavy filtering.

If it is true that as ISI increases, more than one component is included in the EP response, then one alternative hypothesis is that the steady state EP may be analogous to the transient EP as illustrated in Figure 1 (a). That is, it is possible that as the ISI is increased, more and more of the transient waveform becomes evident in the steady state EP. This hypothesis was tested by Kinney et al (1972) and partially supported by her results. Although, additional experimentation is required to fully explore such a hypothesis.

Diamond's time domain procedure.

In order to employ Diamond's latency procedure (1977 a), it is assumed that for the consecutive ISI values used in a latency calculation, the EP latency remains constant. However, if we measure latency with the asynchronous method, as in the present study, this assumption does not appear to be valid. The plot of latency versus ISI in Figures 14 and 15, shows that latency cannot assumed to be constant as ISI is varied. To the extent that latency varies with ISI, Diamond's (1977 a) procedure misrepresents the actual steady state latency as a function of ISI.

Asynchronous latency procedure.

With the asynchronous method it was possible to circumvent the problems encountered in the two previous procedures by determining latency at a single ISI. That is, the ISI preceding flash A was always held constant during an asynchronous procedure. The resulting latency for the EP to flash A was, therefore, not contaminated by a different possible effect at each ISI, as in the prior methods of Regan (1972) and Diamond (1977 a).

The asynchronous procedure, however, because it is a new procedure does require further comment. For example, the asynchronous analysis was a combination of (1) automatic computer selection of peak values, and (2) selection of peak A (see Figure 7b) on the basis of a low variability in peak duration for ISI to ISI. That is, the vertical line-up of peak A in Figure 7b, was determined by measurement of the variability in peaks between ISI conditions. For four peaks in Figure 7b to be considered to line up vertically, their standard deviation had to be 2 msec or less. In this way, positive peaks taken from the four ISI conditions were not combined to identify peak A unless the standard deviation of their four duration values was less than 2 msec.

The asynchronous procedure did not yield the three frequency channels, each with a different latency, that was found by Regan (1972). Instead the results have suggested that perhaps a single channel exists with one or more EP components. For example, in Figures 14 and 15, it is seen that each EP component is responsive over the same ISI ranges.

Red versus white flicker.

A direct comparison of these results with the studies of Regan (1972) and Diamond (1977 a) is encumbered by the fact that they recorded steady state EPs to a flickering white light whereas the present study utilized red light flicker. Therefore, the seemingly contradictory results found in this study may partially be a result of this difference. It is possible that steady state EPs to red light are reflecting different aspects of the underlying physiology of the visual system, namely the red receptors. Recording steady state EPs to flicker that varied in wavelength would be a major step in attempting to further clarify these apparent contradictions.

APPENDIX A

PEAK IDENTIFICATION ALGORITHM.

Peak determination on the EP waveform proceeded from left to right. Positive maximum voltage (amplitude) changes were identified as components (peaks). Component (latencies) were identified by a time-domain analysis and the duration time was determined in msec, and point values (from 1 to 256 points used along the baseline). Each msec and point value was displayed on the screen during peak detection and was followed by a computer print out, an example of which follows in Table 1.

FIGURE 22.

Flow chart illustrating sequence of events in the peak detection algorithm.

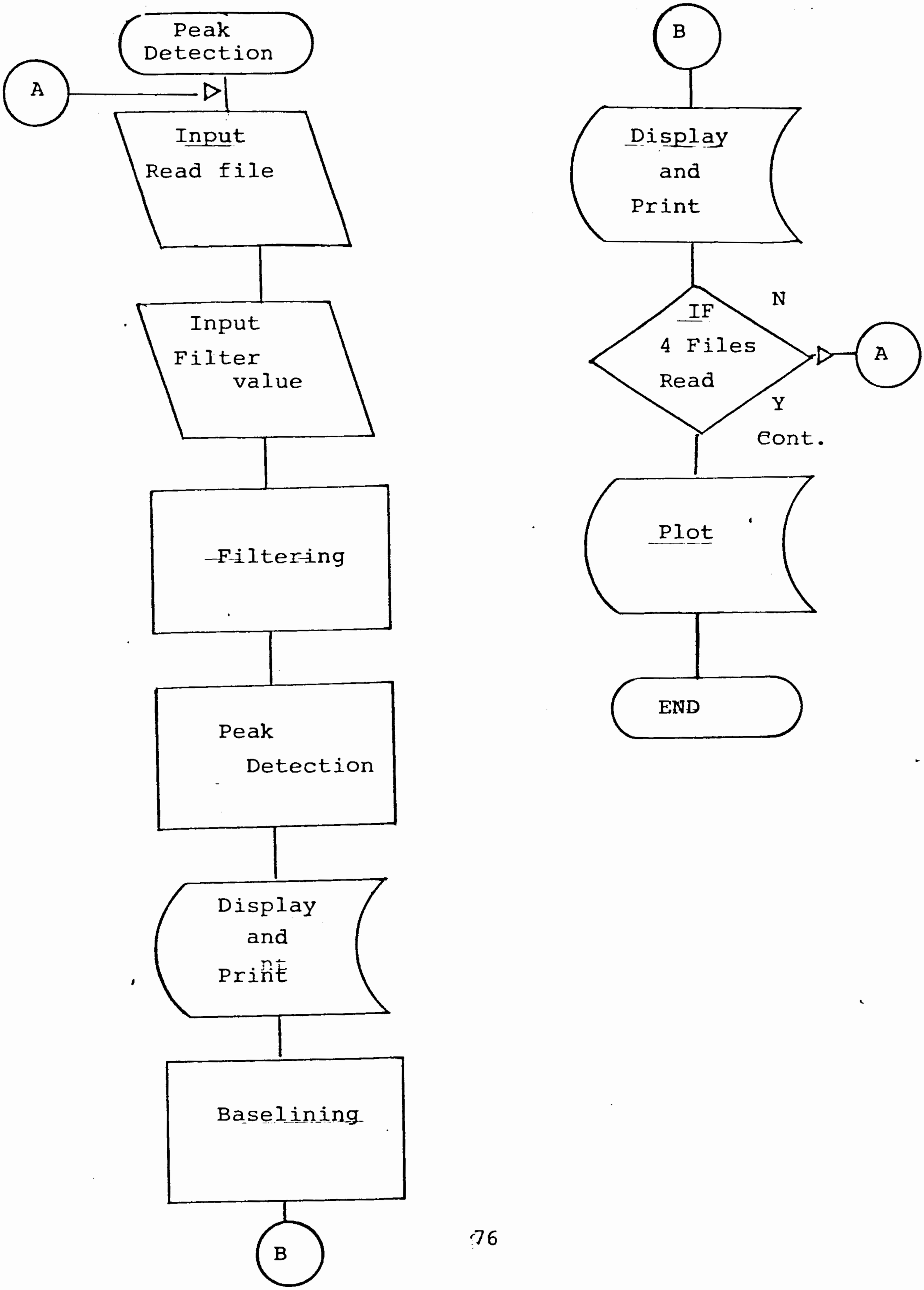

Peak Detection
A
Input
Read file
Input
Filter value
Filtering
Peak Detection
Display and Print
Baselining
B
B
Display and Print
IF 4 Files Read
N
A
Y
Cont.
Plot
END

TABLE 1

TABLE 1

Computer print out of msec and point latencies generated by the peak detection algorithm in response to a synchronous ISI of 31 msec.

PEAK MSEC AND POINT LATENCIES	
21.09375	24
52.2949219	59.5
82.6171875	94
113.818359	129.5
144.140625	164.
175.341797	199.5
205.664063	234.

NUMBER OF PEAKS/CYCLE

FILTER 3 = 3

FILENAME = C31/2

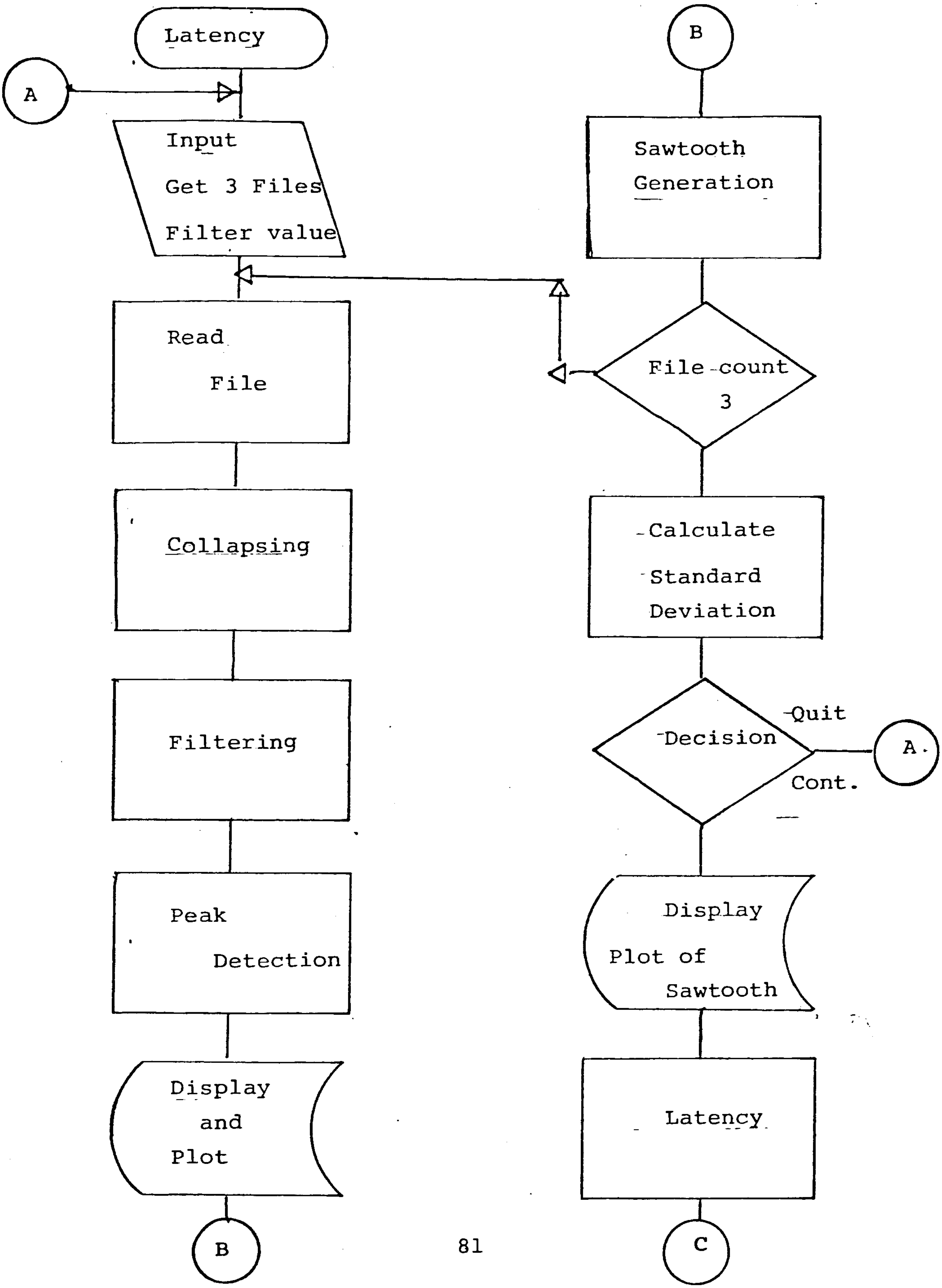
APPENDIX B

LATENCY ALGORITHM.

Components (peaks) were determined algorithmically (i.e., in the procedure previously discussed). Corresponding components (peaks) in the EP were selected and combined across three consecutive ISIs. Sawtooth waves were generated at each ISI, and represented where the component's (peak) latency occured. Next, the three sawtooth waves were combined (superimposed) and latency was determined where the least amount of variance between the three waves occurred. For an example of this procedure see the following illustrations in Figures 25a and 25b.

FIGURE 23.

Algorithm flow chart illustrating the sequence of events for determining latency.


Latency
A
Input
Get 3 Files
Filter value
Read
File
Collapsing
Filtering
Peak
Detection
Display
and
Plot
B
B
Sawtooth
Generation
File-count
3
Calculate
Standard
Deviation
Decision
Quit
Cont.
A.
Display
Plot of
Sawtooth
Latency
C

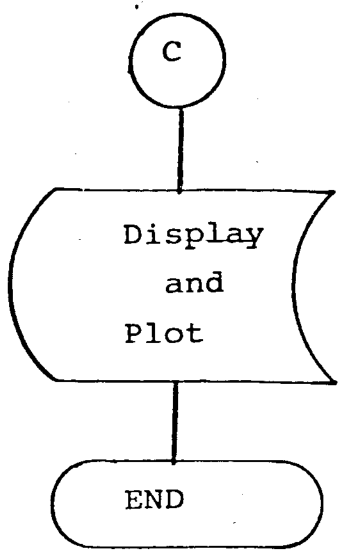
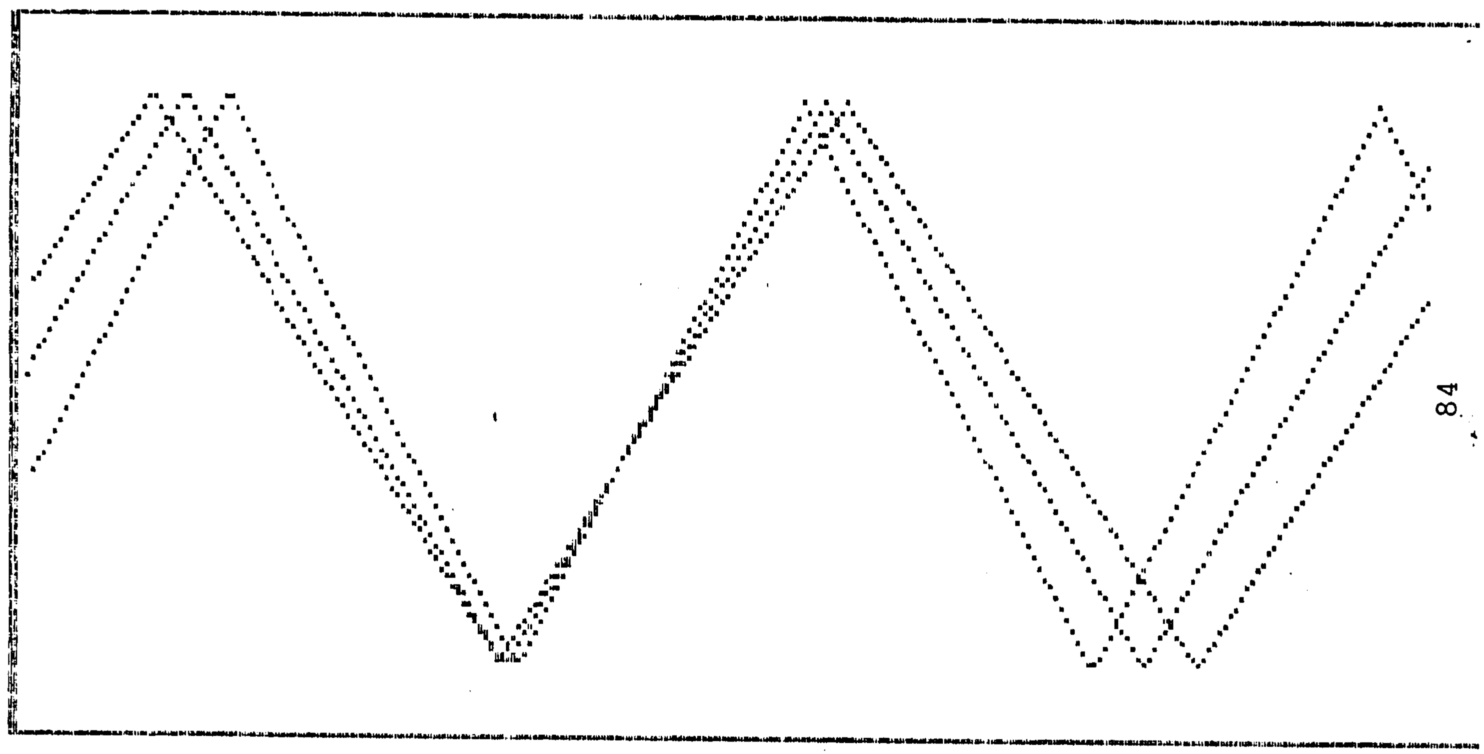

C
Display
and
Plot
END

FIGURE 24.

An example of sawtooth waves generated and combined across three ISIs. As shown in Figure 24a, when the three waves line up closely, latency is determined where the standard deviation between the curves is at a minimum. In this case the standard deviation is zero.

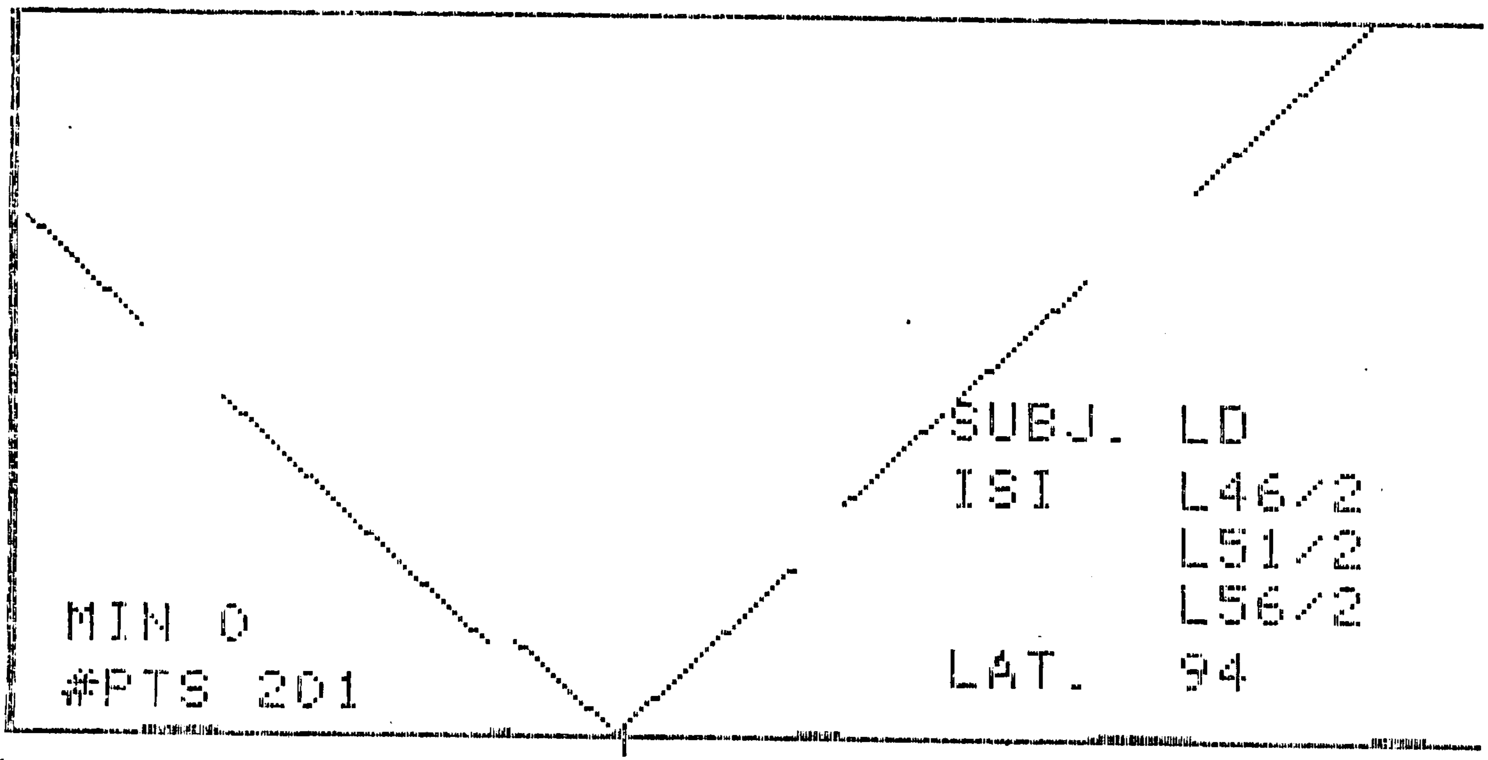
In figure 24b latency is determined at the zero standard deviation point value and changed to a msec latency value. Note, the two plots correspond; that is, the printed latency value in Figure 27b, corresponds to the point at which the three sawtooth curves come together (at a minimum variability point).



a.

(MSEC)

Three sawtooth waves generated by 46, 51, and 46 msec ISI.

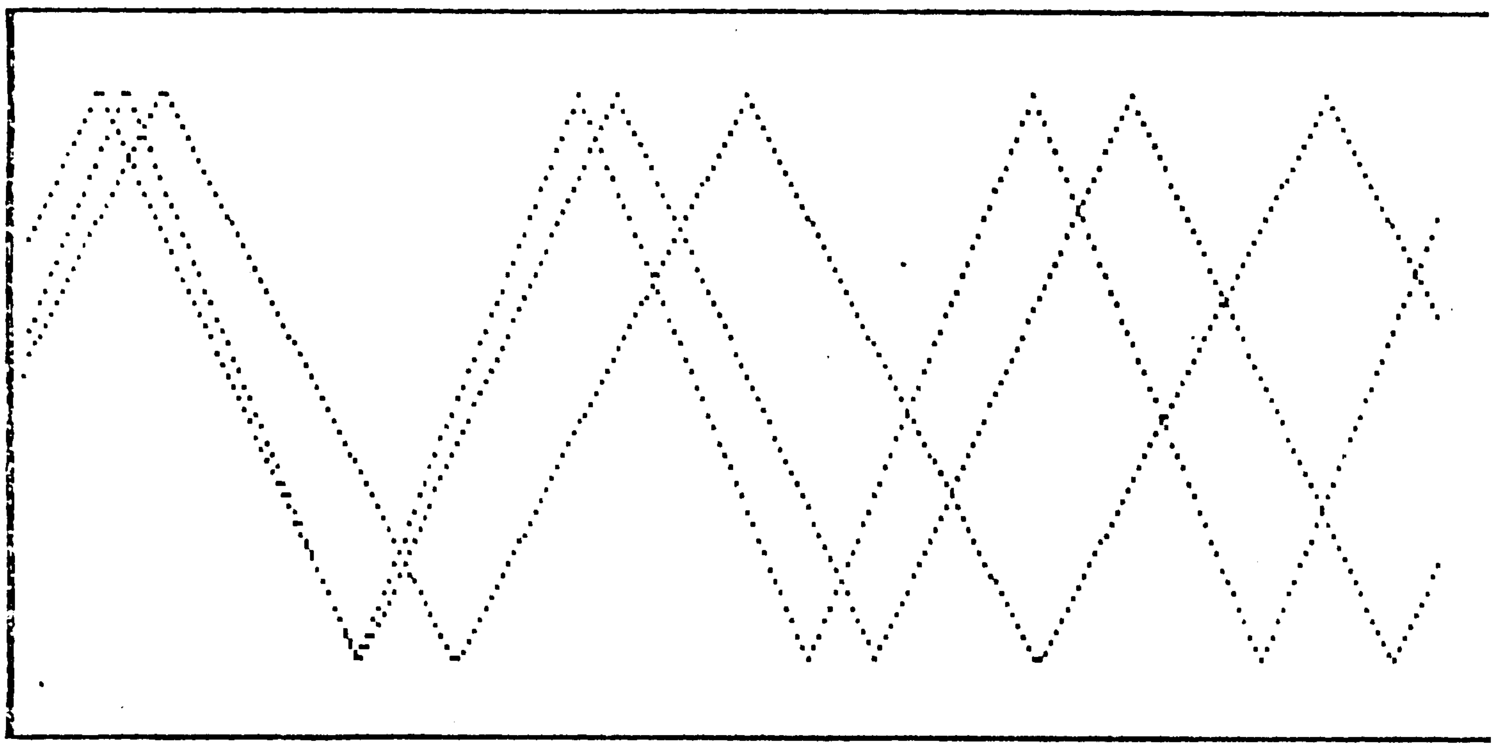


b.

Latency determined at 0 Standard deviation.

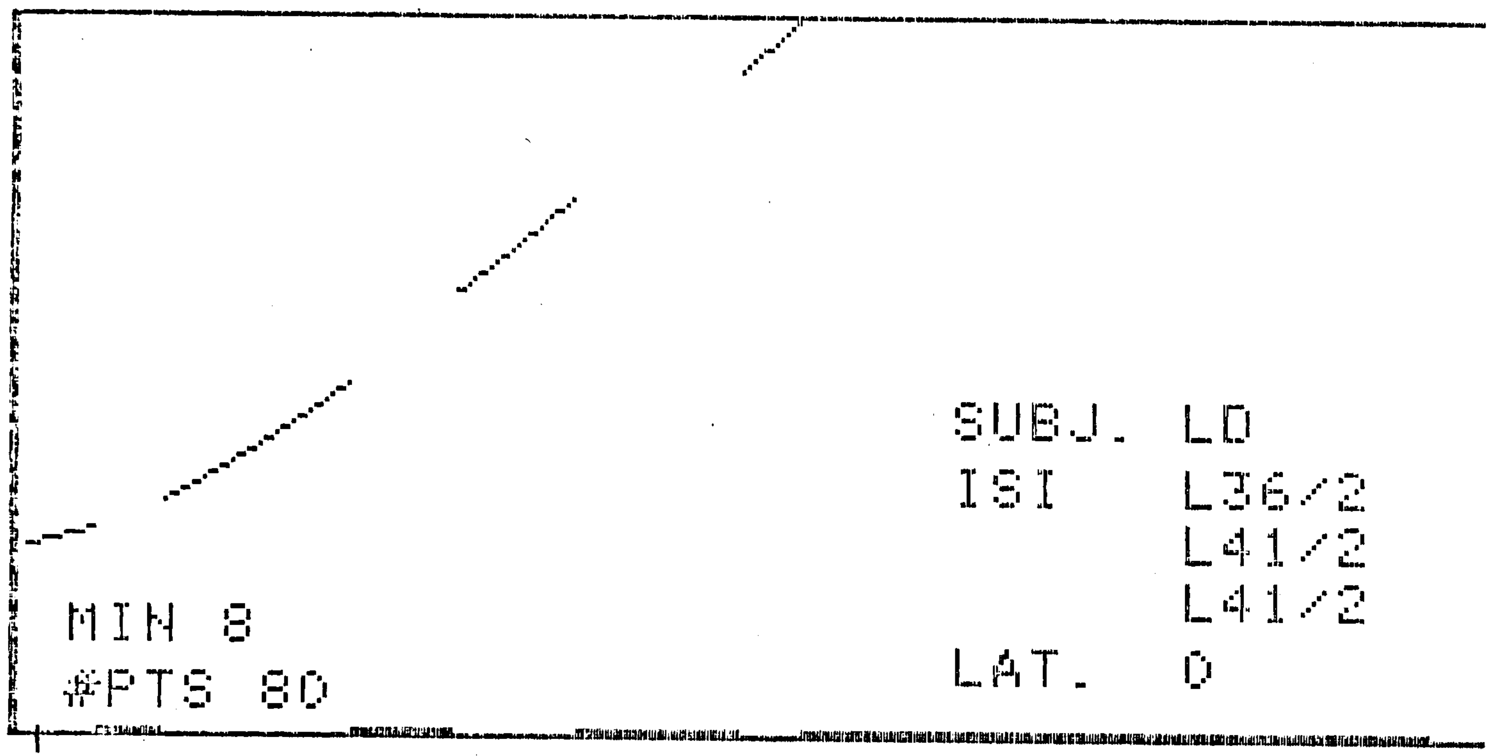
FIGURE 25.

a. An example of the generation of sawtooth waves for components that do not correspond. b. This produces an anomalous latency value.



a. (MSEC)

Three sawtooth waves generated by 36, 41 and 46 msec ISI.



b.

(MSEC)

Latency determination.

APPENDIX C

FILTERING PROCEDURES

The filter procedure employed a running average smoothing technique (also known as a Brick Wall filter technique). The running average was of a variable number of points defined as a "window" , from a minimum of 3 to a maximum of 19. This window was moved successively from point to point along the entire 256 points included along the duration axis.

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