SPECTRAL ANALYSIS OF THE HUMAN HEARTBEAT

Development of the analysis technique

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july, 1988

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Deze uitgave is te bestellen door het overmaken van *f* 15,90 (incl. BTW) op postrekening 20.22.77 van het NIPG/TNO onder vermelding van bestelnummer 88037.

CONTENT

PREFACE

There is ever-increasing evidence that psychosocial environment is a major factor in the etiology of essential hypertension. As Levi has pointed out (1971), man's phylogenetically old adaptation patterns, preparing the organism for defence, have likely become inadequate, and even harmful, in response to the predominately psychological and socioeconomic stressors prevalent in modern society. The physiological intricacies of the discoordination of the defence response in these circumstances has been admirably reviewed by Gilmore (1974).

In spite of the realization that a preventive emphasis in medicine demands taking such factors into account, there have been relatively few quantitative studies on the effect of psychological stress on cardiovascular regulatory processes in man. This may be due to the lack of - to date - an instrument for the accurate noninvasive monitoring of instantaneous arterial blood pressure and the fact that invasive measurements, particularly intra-arterial blood pressure, are precluded by the psychosomatic effects of catheterization.

Of the relatively few noninvasive cardiovascular measurements, the electrocardiogram is by far the most accessible and reliable. It is for these rather practical reasons that for the last few years we have been developing methods to extract information about the activity of cardiovascular regulatory processes from this signal. These studies have been confined to the R wave spike train of the ECG because such waves conveniently define the occurrence of a cardiac event, i.e., a heart beat, and the timing of these events is strongly influenced by the cyclic activity of various autonomic regulatory processes via the autonomic nervous system.

1. INTRODUCTION

Prior to the work of Hyndman and Mohn (1975) there had been many attempts to describe mathematically the effects of autonomic stimulation on cardiac RR-intervals (Rosenblueth & Simeone, 1934; Stade & Weiss, 1956; Warner & Cox, 1962; Katona, 1965; Chandra, 1967; Katona et al., 1967; Warner & Russell, 1969; Katona et al., 1970; Scher & Young, 1970; Chess & Calaresu, 1971). However, none had considered the nature of the information transmitted to the pacemaker and its encoding into the cardiac event sequence. Given the hypothesis that the cardiac event sequence is a modulated signal, the problem is to determine how accurately the modulating signal can be estimated.

2. REVIEW OF CARDIAC PACEMAKING

Cardiac excitation is normally initiated at the sino-atrial (SA) node. In the absence of external disturbances, the membrane potential of a SA nodal fibre depolarizes at approximately constant rate due to either a progressive increase in the membrane permeability to sodium ions or a progressive decrease in the permeability to potassium ions, or both (West, 1972). When the membrane potential of a given fibre reaches a certain value (the threshold potential), an action potential is generated which, in turn, activates other SA nodal fibres and initiates the spread of excitation through the heart.

Figure 1a is a recorded pacemaker potential in an excised rabbit sinus, and figure 1b shows schematically how pacemaker frequency can be altered (from Hecht, 1965). Deceleration will occur by increasing the threshold at which an action potential is initiated as in A, by decreasing the slope of diastolic depolarization as in B, or by increasing the maximal diastolic potential

as in C. Acceleration will occur if these parameter changes are reversed.

Stimulation of the sympathetic fibres that innervate the heart increases pacemaker frequency by increasing the slope of diastolic depolarization (Hutter & Trautwein, 1956), while weak to moderate stimulation of the parasympathetic fibres decrease pacemaker frequency by decreasing the slope (Anderson & Del Castillo, 1972). Thus, physiological variations in pacemaker frequency are likely due to changes in the slope of diastolic depolarization. These changes in slope are probably due to alterations in the rate of change of cell-membrane ion permeability by the release of transmitter substances in the SA node with autonomic stimulation.

3. THE MODEL

Figure 2a is a model of pacemaker frequency control by autonomic nervous control of the slope of diastolic depolarization (Hyndman & Mohn, 1975). Because of the relatively higher impulse rates compared to the pacemaker frequency, and the extensive nervous innervation of the pacemaker region, the neural activity has been represented as a continuous function. The problem is therefore one of relating the cardiac events to a continuous controlling signal which represents the effective autonomic activity. It has been assumed that rapid changes in autonomic activity can change the diastolic slope even within a single diastolic phase. The cell cluster constituting the pacemaker region is modelled as a single effective cell, because the individual cells are electrically synchronized (Wolf, 1969). The model simulates only the diastolic phase of pacemaker potential, as shown in figure 2b, since the only aspect of action potential of interest here is its time of onset. The diastolic depolarization

is simulated by integrating a constant term with one that represents the effect of autonomic activity on the diastolic slope. When this integral exceeds a fixed threshold (corresponding to the value of membrane potential which, when reached, results in the generation of the action potential), an impulse is generated that denotes the onset of an action potential, and the integrator is reset to the value of the membrane resting potential for the duration of the refractory period. With no modulation, the integration of the constant term simulates a diastolic depolarization which is linear with time. Although many reported recordings do show such a time course (such as the one depicted here), more complex functions could be fitted by replacing the pure integrator with other dynamics (e.g., a leaky integrator). Moreover, as Bayly (1968) has pointed out, modulation fidelity is not dependent on integration dynamics. The pure integrator will be assumed in this paper only to simplify the discussion.

The detailed relationship between diastolic slope and autonomic activity has not yet been reported. The results of some investigators (Rosenblueth & Simeone, 1934; Stade & Weiss, 1956; Warner & Cox, 1962; Chandra, 1967; Levy, 1971) would suggest that this relationship is highly nonlinear. The results of Katona et al. (1970) and those of Scher and Young (1970) suggest that the relationship is fairly linear. In either case, there may be some filtering action due to the dynamics associated with transmitter release in the SA node environment. However, the effect of (linear) dynamics can be compensated for by suitable processing of the output signal, whereas this is not generally possible if nonlinearities are present. Nonetheless, it is not necessary at this stage of the presentation to make any assumptions regarding this relationship. The experimental results described later in this paper will provide such information. The important feature of the model is that it suggests the way that autonomic informa-

tion is encoded into the cardiac event sequence and thus how this information can be retrieved from cardiac interval data.

When the refractory period is zero, the behaviour of the model is identical to that of an integral pulse frequency modulator (IPFM). Figure 3 illustrates the operation of such a modulator (Bayly, 1968). The input modulating signal $X_1(t)$, and a constant term X_0 which determines the free-running or carrier frequency f_o, are integrated with all initial conditions zero. When this integral, Z(t), reaches a fixed threshold value, an impulse occurs. The larger the X_1 value, the sooner the threshold is reached and the impulse generated. The integrator is then reset to zero but not held there. This process is repeated, thereby encoding the input signal into an impulsive train, Y(t).

Figure 4 depicts the amplitude spectrum of an IPFM impulse train with a small sinusoidal input signal (Bayly, 1968). The zero frequency component, '1', is accompanied by a single component, '2', at the modulation frequency. The spectrum also contains components '3' at all harmonics of the carrier frequency, each accompanied by an infinite set of sidebands that are removed from these harmonics by multiples of the modulation frequency. When the modulating signal's amplitude and frequency are small enough, the spread of each set of sidebands will be so limited that the input component will be isolated. This can be retrieved by low-pass filtering the impulse train as shown. The cut-off frequency of the filter must be greater than the modulation frequency but lower than any sideband component of significant amplitude.

The possibility of integral pulse frequency modulation as the encoding mechanism in the nervous system has been suggested by many investigators (Jones et al., 1961; Bayly, 1968; Lee, 1969; French & Holden, 1971; Gestri, 1971; Lee & Milsum, 1971; French et al., 1972; Gestri, 1972; Inbar, 1972; Stein et al., 1972; Michaelis & Chaplain, 1973). Prior to the work of Hyndman and Mohn

(1975), however, such studies had been confined to neuronal spike trains.

Cardiac intervals have been analyzed in the context of sampling statistics or, to a lesser degree, tiime series analysis. Spectral analysis has been carried out via the sampling statistics route to calculate the spectral density of cardiac intervals (Sayers, 1971; 1973) or via the time series analysis route to calculate the spectral density of an interpolated - but arbitrary - version of the cardiac event sequence (Womack, 1971; Luczak & Laurig, 1973). The latter approach has the advantage over the former in that it characterizes the signal as a function of time rather than interval number; the former thus precludes correlation with other real time phenomena; i.e., other physiological signals.

It is interesting to note that in 1968 Dick proposed a model for baroreceptor control of the cardiac interval (which was modified in 1969 by Snyder & Rideout) that embodies all the characteristics of an IPFM. However, this model was never justified on a physiological basis, nor were its implications used to develop a method for decoding the information in cardiac intervals.

4. SIGNAL PROCESSING OF EVENT SEQUENCES

To achieve a low-pass filtering without spectral biasing, the spectral window for the filter was chosen as in figure 5a, the corresponding weighting function of which is shown in figure 5b. The value of a particular sample of the resultant low-pass filtered signal is determined digitally by centering the weighting function at that sample point on the event sequence, and summing the weighting coefficients (the values of the weighting function at points where events occur) for previous and future events.

Mathematically, if the sequence of cardiac events, g(t), is represented by a series of delta functions occurring at times t_i, the occurrence times of cardiac events, then

$$g(t) = \sum_i \delta(t-t_i) \tag{1}$$

g(t) is then convoluted with the impulse response of an ideal filter. The sampled filter output, f*(t), is defined by

$$f^*(t) = \int_{-\infty}^{\infty} \frac{\sin(2\pi f_c \sigma)}{2\pi f_c \sigma} \sum_i \delta(t-t_i-\sigma)d\sigma \tag{2}$$

$$= \sum_{i=-\infty}^{i=\infty} \frac{\sin 2\pi f_c(nT-t_i)}{2\pi f_c(nT-t_i)} \tag{3}$$

where f_c is the filter cut-off frequency, n is the sample number, and T is the period between samples.

To achieve a fairly rectangular spectral window, as shown in figure 5c (for which f_c is 1.0 Hz), it is necessary to consider only the impulses that are less than ten cycles of the weighting function distant from the sample point. The truncated integral of the weighting function is within 2% of the integral evaluated between infinite limits. To avoid aliasing, the adjacent sample of the low-passed signal is determined by moving the centre of the weighting function at most $1/2f_c$ seconds (less than this value produces an interpolated signal), and summing the coefficients as before. This filter has a start-up time and a shut-down time equal to ten cycles of the weighting function (i.e., $10/f_c$ seconds of data). Thus there is a trade-off between the "idealness" of the filter and the amount of record lost in start-up or shut-down. This limitation is only of importance when short data records are used. This trade-off between idealness and amount of record lost can be improved by multiplying the sin x/x function by a Hanning lag window (Blackman & Tukey, 1959). Figure 6 is a logarithmic plot of the spectral window corresponding to a five-cycle weighting function. Figure 7 shows

the effect of the addition of the Hanning window. Here, the weighting function was only five cycles long but, as can be seen, the spectral window more closely approaches the ideal (Smitt, 1985).

This procedure produces the low-pass filtered cardiac event sequence (LPFCES), a regularly sampled signal that can be Fourier analyzed.

A more efficient approach (in terms of computing time) of calculating the value of a particular sample of the filter output is to centre the weighting function on the events (no more than ten cycles of the weighting function distant from the sample point), calculate for each event the value of the weighting function at the sample point, and sum these values. French and Holden (1971) have used this technique for filtering neuronal event sequences. Using this approach, the sine function needs only be evaluated once for each event, compared to the other method where it must be calculated on average 40 times for each event. The disadvantage of the faster version is that, since the period between output samples must be precisely $1/2f_c$, interpolation cannot be carried out simultaneously with the filtering operation. However, the interpolation (which is required only for the digital simulation of the model, and not for analysis of the LPFCES) can be achieved with the FFT operation by inserting zeros into the spectrum (Gold & Rader, 1969). Nonetheless, even for a moderate number of sample points (1,000 or more), this procedure requires as much computing time as the other.

5. DIGITAL SIMULATION OF THE MODEL

To determinate the analytically intractable effect of refractory period on modulation fidelity, the model of pacemaker frequency control was simulated digitally, assuming an average heart beat

frequency of 1.0 Hz. Providing that the input signal is sufficiently interpolated (by choosing T small enough), simple summation of the input signal samples accurately carries out the numerical integration. Samples of band-limited noise were synthesized digitally to produce the input signal, and the output signal (the modulated impulse train) was low-pass filtered to 0.5 Hz, the same frequency as the noise. Modulation fidelity was calculated by determining the coherence between the filtered output train (the LPFCES) and the input, since the coherence specifies the degree of linearity of the input-output relationship.

Averaged estimates of the input, output and cross-spectral power densities, obtained by the Cooley-Tukey (1965) Fast Fourier Transform Alogorithm (FFT), were used to determine the coherence function γ_{XY}, (Bendat & Piersol, 1966) as follows:

$$\gamma^2_{XY} = \frac{|\overline{S_{XY}}|^2}{S_{XX}S_{YY}} \qquad (4)$$

where the numerator is the ensemble averaged cross-power spectral density and the denominator is the product of the ensemble averaged input and output power spectral densities. The model's threshold potential was adjusted to keep the average impulse frequency constant when refractory period was altered. In this way, the free period (the average impulse period minus the refractory period) is modulated to the same extent by a given input signal, regardless of the refractory period, although the overall gain is proportional to the ratio of the free period to total period. The slope of simulated diastolic depolarization is thereby unaffected by refractory period. Referring to figure 3, "modulation fraction" is defined as the ratio of the (peak) magnitude of X_1, to the value of X_0.

6. SIMULATION RESULTS

Using a substantial modulation fraction - 0.25 - the effect of refractory period on coherence was determined. As shown in figure 8a, coherence for zero refractory period exceeds 90 percent up to 0.35 Hz. Figure 8b illustrates that, even a refractory period 50 percent of the average interbeat interval only slightly degrades the modulation fidelity, and coherence still exceeds 90 percent in the frequency range where the majority of autonomic signal activity occurs. [Hoffman & Cranfield (1960) report that refractory period is typically 30% of interbeat interval in large mammals.] The effect of changing refractory period on coherence is, however, much more pronounced than the effect of changing modulation fraction.

From these results, it can be concluded that the presence of a refractory period in an IPFM does not significantly impair the input signal estimate obtained by low-pass filtering the impulse train.

7. EXPERIMENTAL RESULTS

Actual cardiac records are processed as shown in figure 9. The R wave of the human ECG is used to define a cardiac event, the latter being represented mathematically as a single impulse. A given record of events (defined by an array of inter-event interval times) is low-pass filtered to 0.5 Hz (the upper limit of autonomic activity) and the LPFCES multiplied by a Hanning window to prevent spectral 'leakage' between adjacent components, after mean and trend removal, is Fourier analyzed with the FFT. Spectral estimates were smoothed with a ten-point Hanning window (Blackman & Tukey, 1959).

Figure 10 shows a portion of the power spectrum of the LPFCES of a normal resting adult. A large, approximately sinusoidal, disturbance in blood pressure and thus in autonomic activity (Katona, 1965) was induced by forced sinusoidal respiration (see Dornhorst et al., 1952, for an explanation of this effect), and this produced the isolated component, 'A'. The amplitude distribution of the cluster of components distributed about the mean heartbeat frequency, f_o, is similar to those of an IPFM with a large sinusoidal input, the high frequency cluster of sidebands being larger in amplitude than the low frequncy sideband cluster. Since these components do not extend into the spectral domain of the disturbance signal, this signal can be retrieved by low-pass filtering the cardiac-event sequence. [The frequency distribution of the sidebands deviates somewhat from that of the IPFM. Closer inspection of the blood pressure spectrum revealed the presence of small, but significant, components, in addition to the disturbance, which could have produced the discrepancy.]

A pair of siinusoids, introduced into the blood pressure by forced respiration, was used to give an indication of whether the LPFCES is an undistorted representation of autonomic activity converging on the SA mode. Figure 11a is the resultant low-frequency power spectrum of the blood pressure, and figure 11b is that of the cardiac event sequence. The absence of cross-modulation components, or any significant components other than those at the modulation frequencies, suggests that the modulation process is fairly linear.

Figure 12a is a record of cardiac intervals of a normal resting adult. An interval is represented by a point whose ordinate is the value of the interval and whose abscissa is the time at which the cardiac event occurred. All the points are joined by straight lines to form the plot. Figure 12b is the corresponding record of the LPFCES. Dominant spectral components are evident in the (smoothed) power spectrum of the LPFCES (figure 12c), and

the three largest clusters coincide in frequency with three autonomic fucntions - themroregulation, blood pressure regulation, and respiration. [Other spectral peaks are associated with the nonlinear interaction of the last two functions.] Moreover, these clusters can be selectively eliminated by the appropriate form of periodic disturbance. The lowest frequency cluster can be eliminated by applying a higher frequency thermal disturbance to the extremities, and is therefore associated with the vascular regulation of body core temperature. The middle cluster can be eliminated by a higher frequency periodic disturbance in blood pressure, and is therefore associated with the vascular regulation of that quantity (Hyndman et al., 1971). If the mean respiratory rate is altered, the upper cluster will shift to the new respiratory frequency. This selective elimination substantiates the origin of these spectral components, all of which result from blood pressure oscillations, which are mediated via the autonomic nervous system to the pacemaker.

Figure 12d, plotted as in 12a, shows the output of an IPFM model whose input is the LPFCES. When the filter lag time is accounted for, the correlation between this signal and the first is 0.99. Thus, the signal obtained by low-pass filtering the cardiac event sequence can accurately reproduce that sequence when used as the input to an IPFM. This does not prove that the cardiac event sequence is generated by an IPFM-type process unless this signal corresponds to converging autonomic activity. [Indeed, a randomly synthesized sequence of intervals in which the interval variation is small compared to the mean can be regenerated in the same way.] However, figure 13 shows the similarity of the low frequency power spectra of the blood pressure (i.e., autonomic activity) and cardiac event sequence in a resting (spontaneously breathing) subject. The spectral peaks in the event spectrum correspond in frequency to those in the blood pressure spectrum (the origins of which have been discussed), thereby in-

dicating a fairly linear relationship. It is not possible to specify whether the slight degree of nonlinearity that is present is due to the way blood pressure affects autonomic nervous activity, or the way the latter quantity affects the slope of pacemaker depolarization. The relative magnitude of these spectral peaks somewhat differs from that of the blood pressure indicating the presence of some (linear) dynamics between the two signals. Thus, the LPFCES corresponds to autonomic activity converging on the pacemaker, notwithstanding the presence of some linear dynamics connecting the two.

8. DISCUSSION OF ANALYSIS TECHNIQUE

The IPFM model of the pacemaker first put forward by Hyndman and Mohn in 1975 has since been validated in numerous studies (Rompelman et al., 1977; Rompelman, 1980; Rompelman et al., 1982; De Boer et al., 1984; De Boer, 1985; De Boer et al., 1985 (a, b, c); Rompelman, 1986; Berger et al., 1986). To quote the Harvard-MIT group (Berger et al.), "The IPFM model is consistent with this description since it lumps autonomic control and all the other factors that affect heart rate into a single time-varying signal."

The usefulness of spectral analysis of the heartbeat has been demonstrated in such diverse fields as ergonomics/psychophysiology (Hyndman & Gregory, 1975; Rompelman et al., 1980; Luczak et al., 1980; Mulder, 1980; Mulder & Mulder, 1981; Egelund, 1982; Zwiener et al., 1982; Lindqvist, 1983a; Porges et al., 1985; Hatch, 1986), paediatrics (in the study of SIDS - suddent infant death syndrome) (Lindqvist et al., 1983b; Finley & Nugent, 1983; Kitney, 1984; Giddens & Kitney, 1985; Kitney & Ong, 1986), neurology (e.g., in the study of autonomic diabetic neuropathy) (Kitney et al., 1982; Brodie et al., 1983; Van den Akker et al.,

1983; Pomeranz et al., 1985) and internal medicine (in the study of essential hypertension) (Akselrod et al., 1981; Pagani et al., 1984; Akselrod et al., 1985). This last group has illustrated the importance of spectral analysis of the heartbeat in studying essential hypertension by showing how low-frequency spectral power increases with blockade of the renin-angiotensin system for regulating blood pressure. To quote them "We believe this approach could provide a versatile, noninvasive clinical method for assessing the integrity of the cardiovascular control system in a variety of disease states."

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Figure 1a. Recorded pacemaker potential in an excised rabbit sinus

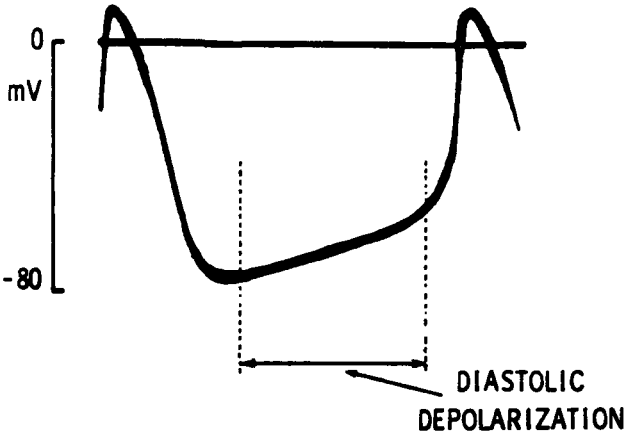


Figure 1b. Showing schematically how pacemaker frequency can be altered. Deceleration will occur by increasing the threshold at which an action potential is initiated (A), by decreasing the slope of diastolic depolarization (B), or by increasing the maximal diastolic potential (C). (From Hecht, 1965)

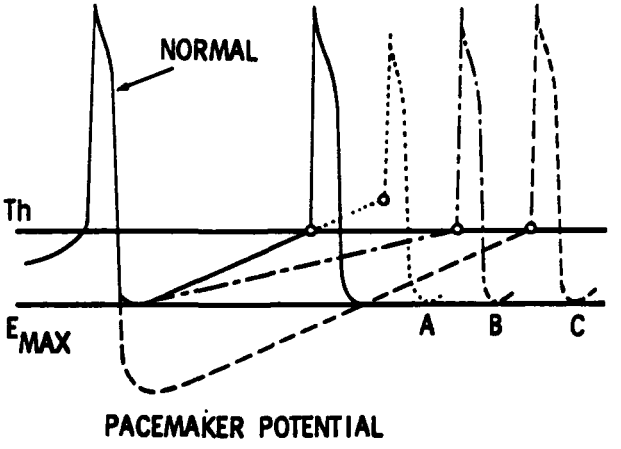


Figure 2a. Proposed model of autonomic control pacemaker frequency

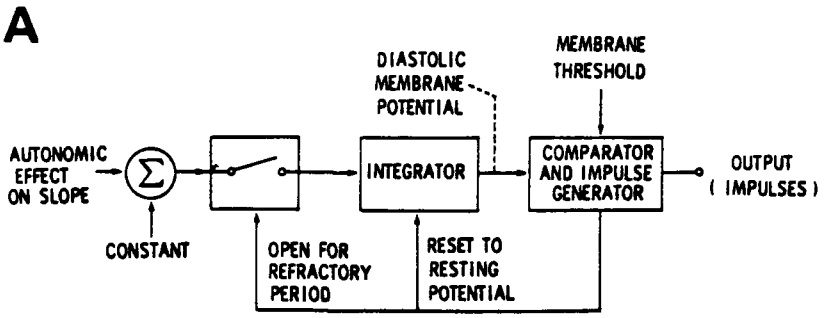


Figure 2b. Showing the aspect of actual pacemaker potential (from Hecht, 1965) which is simulated by the model

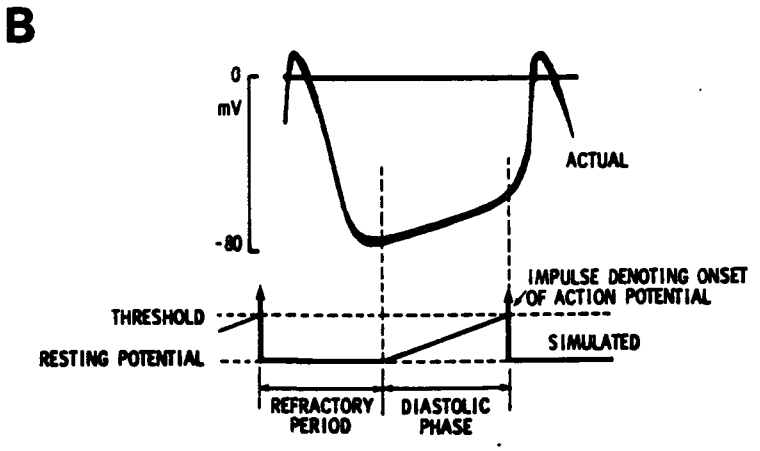


Figure 3. Schematic representation of an "integral pulse frequency modulator"

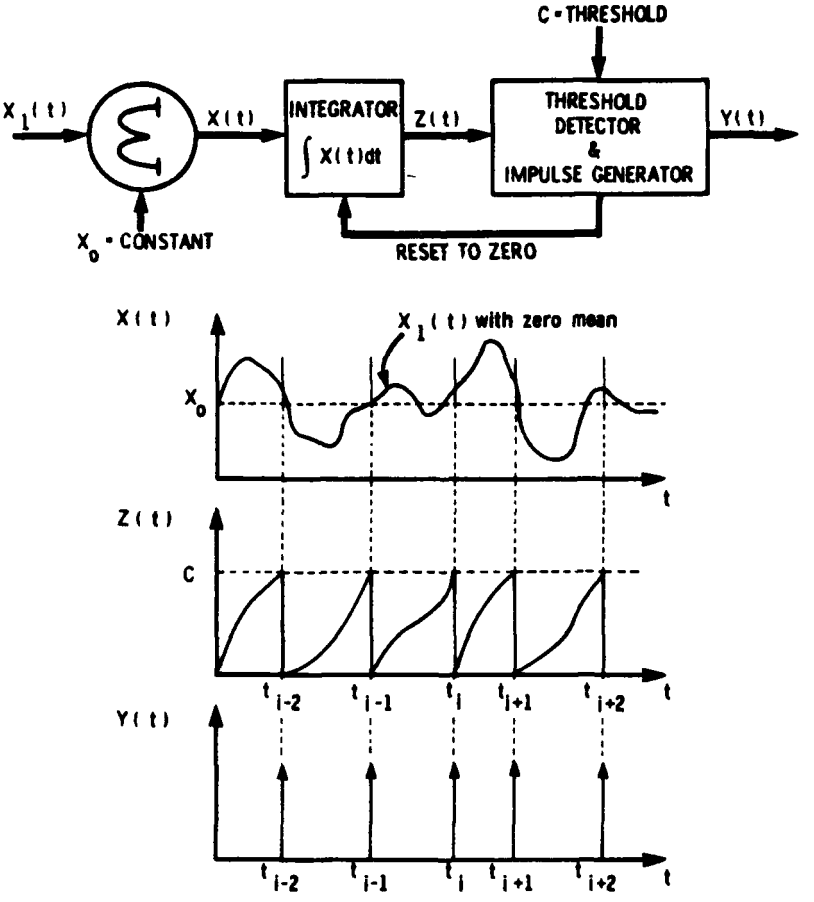


Figure 4. Spectral power density of the output signal from an "integral pulse frequency modulator", when the input is a small sinusoid. Demodulation is achieved by low-pass filtering, as shown

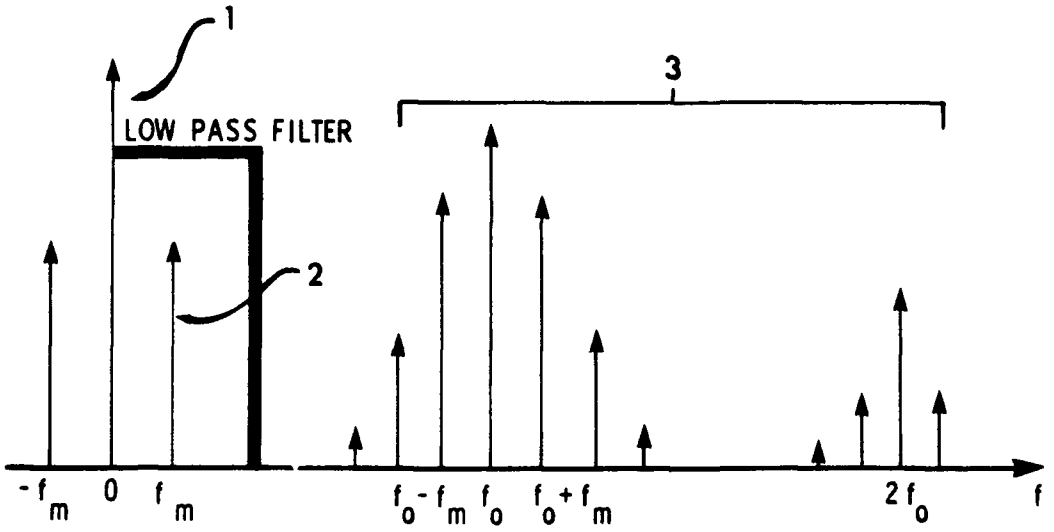
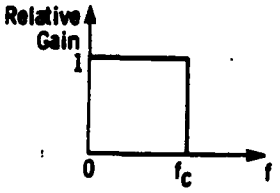


Figure 5a. The desired frequency profile of the digital filter

A SPECTRAL WINDOW (IDEAL)



$F(w) = 1 \quad 0 \leq f \leq f_c$

$= 0 \quad f > f_c$

Figure 5b. The corresponding weighting function (impulse response), however, exists for all time past and future

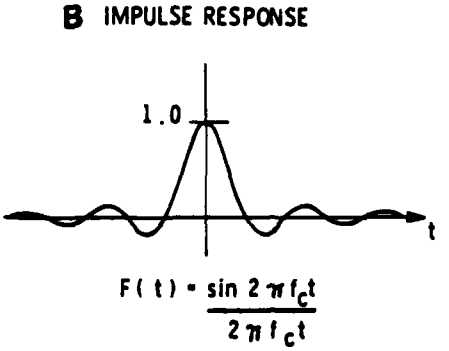


Figure 5c. The actual frequency profile of the digital filter (0.1 Hz cut-off) when the weighting function is truncated to ten cycles

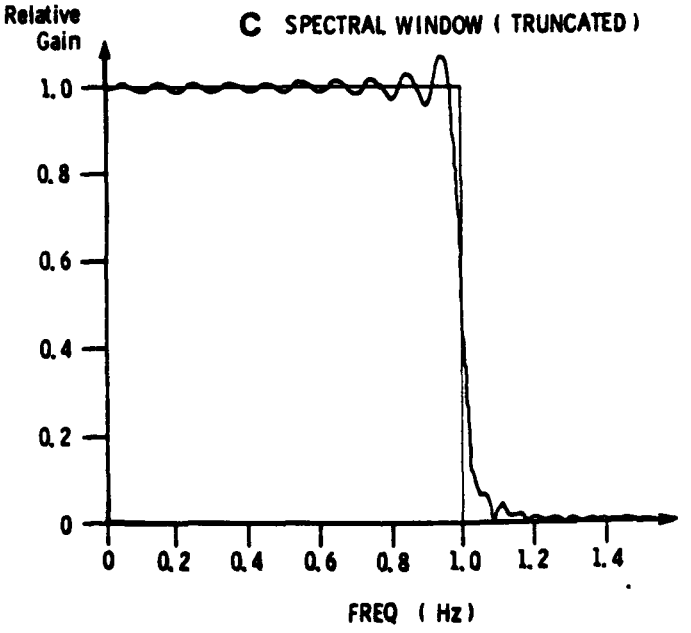


Figure 6. Logarithmic plot of the digital filter (0.5 Hz cut-off) when the weighting function is truncated to five cycles

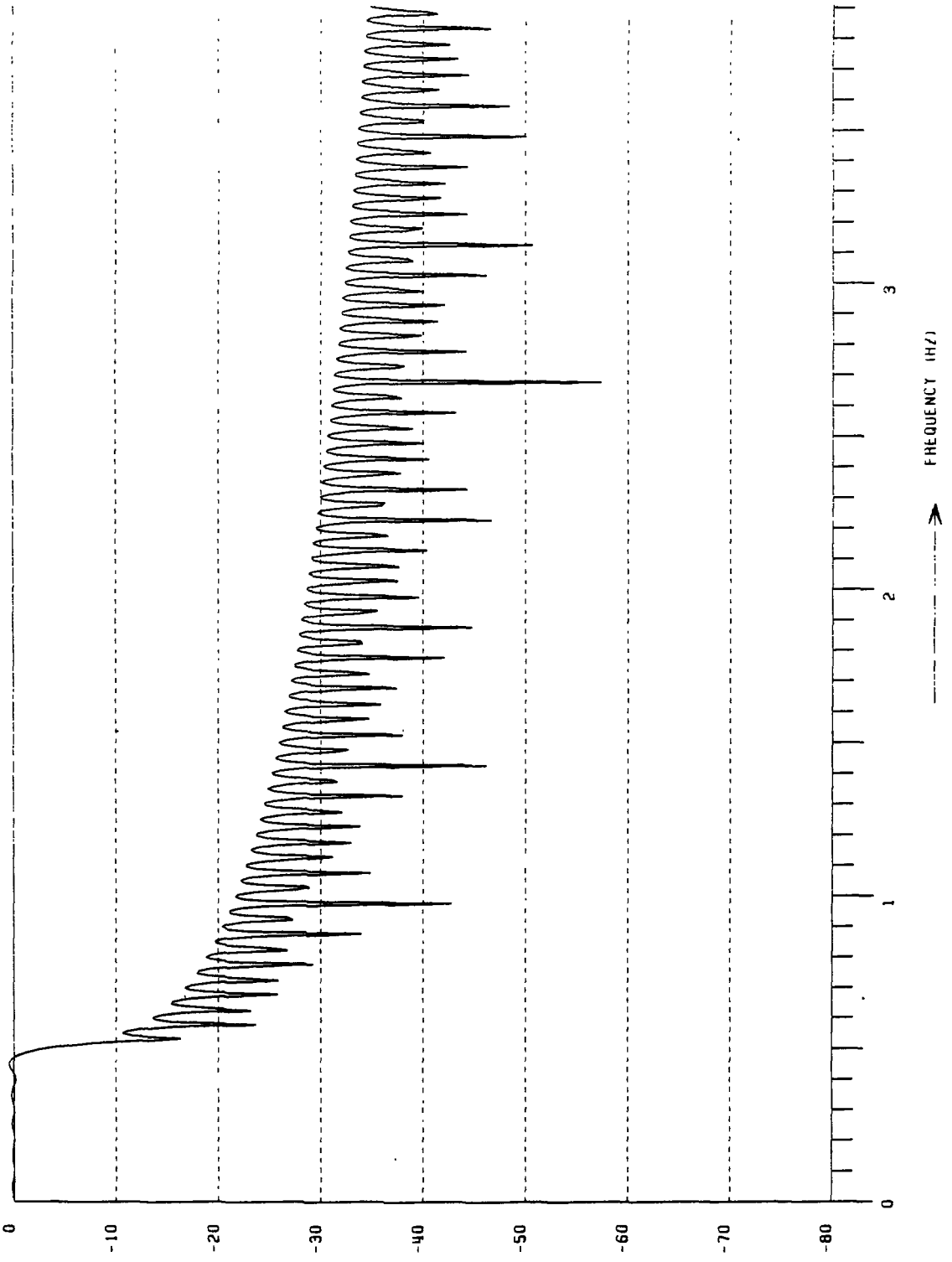


Figure 7. Logarithmic plot of the digital filter (0.5 Hz cut-off) when the weighting function is truncated to five cycles but multiplied by a Hanning lag window ('cosine hump')

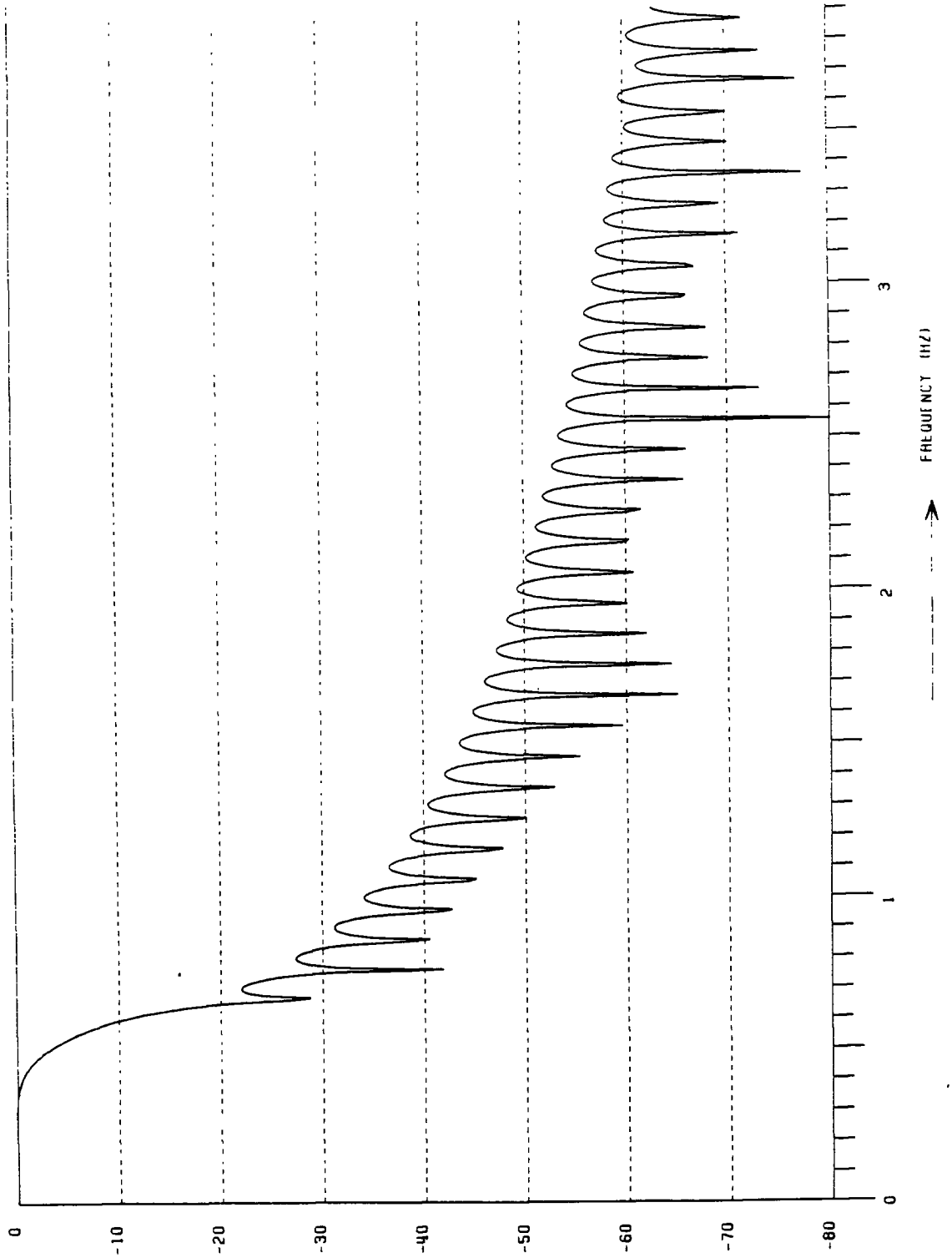


Figure 8a. Coherence (corresponding to modulation fidelity) as a function of refractory period of the model. Coherence for the pure IPFM; i.e., zero refractory period

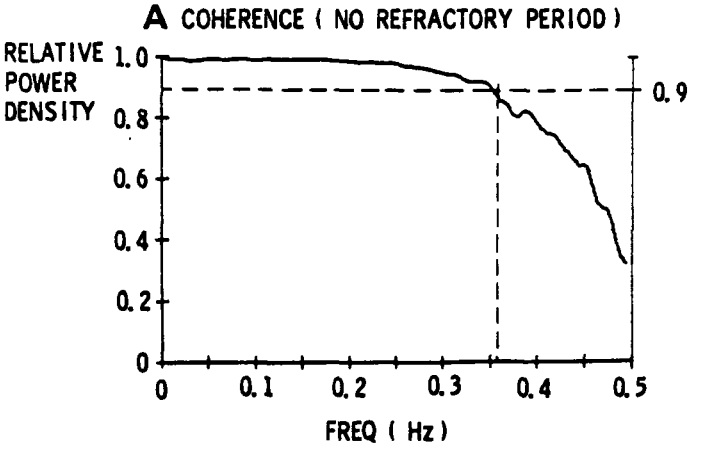


Figure 8b. Coherence (corresponding to modulation fidelity) as a function of refractory period of the model. Coherence when refractory period is 50% of the average inter-event interval

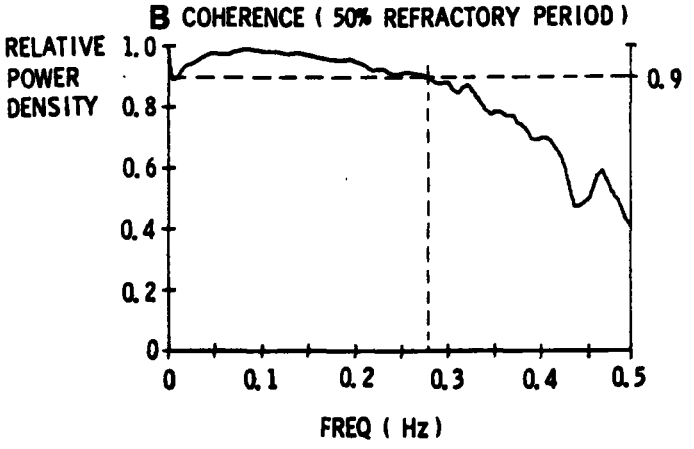


Figure 9. The sequence of operations required to transform an ECG signal into the "low-pass filtered cardiac event sequence" (LPFCES)

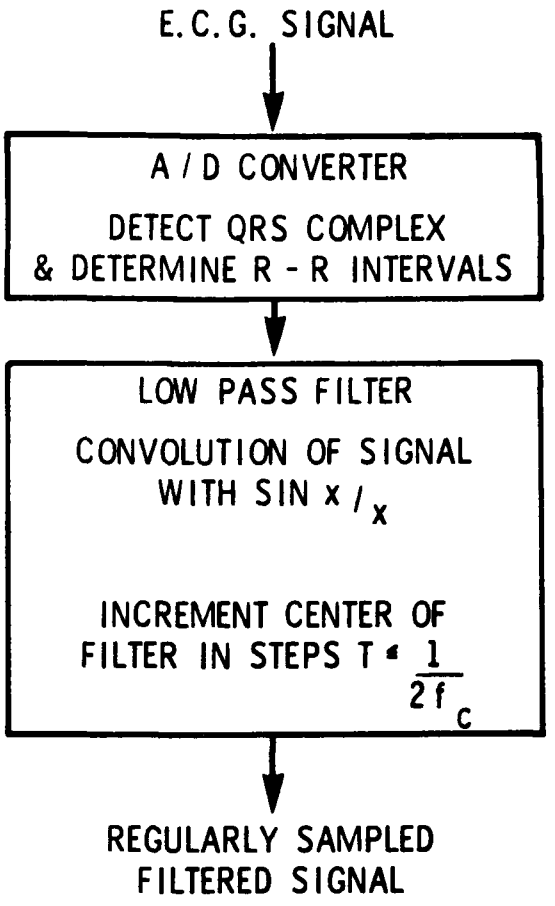


Figure IO. The spectral power density of a subject's LPFCES when the subject is breathing sinusoidally. The sideband components distrubuted about the mean heartbeat frequency, f_o, are similar to those of an IPFM, but are shown to be well clear of the "signal" component, A

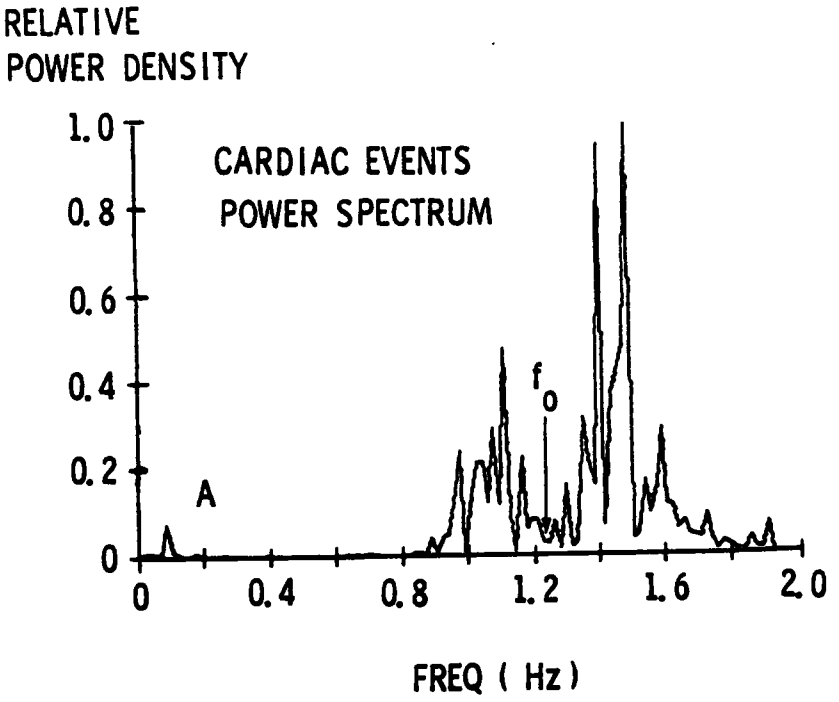


Figure 11. The effect of a double sinusoid disturbance in blood pressure (shown in A) on the LPFCES signal (shown in B). The similarity of the two spectra suggests that the modulation process is fairly linear

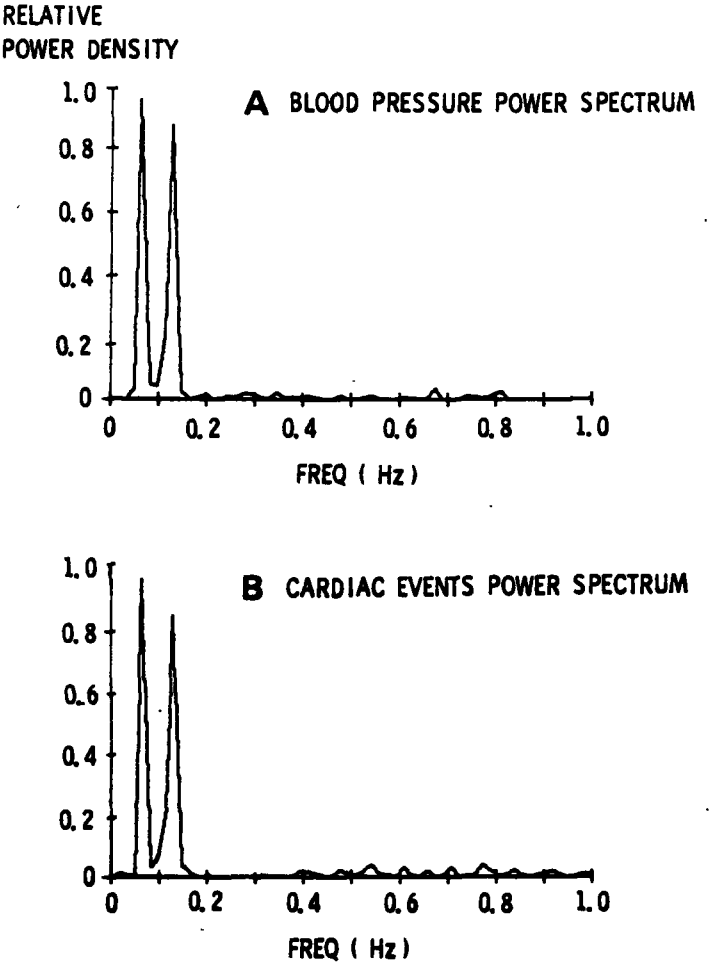


Figure 12. Showing that the information between d.c. and 0.5 Hz completely defines the cardiac event sequence. The cardiac interval sequence, A, defines an event sequence which is low-pass filtered to 0.5 Hz, thereby creating the regularly sampled signal, B, whose power spectrum is depicted in C. When this signal is uses as the input to an IPFM model, the interval sequence, D, results. When the filter lag time is accounted for, the correlation between D and A exceeds 0.99

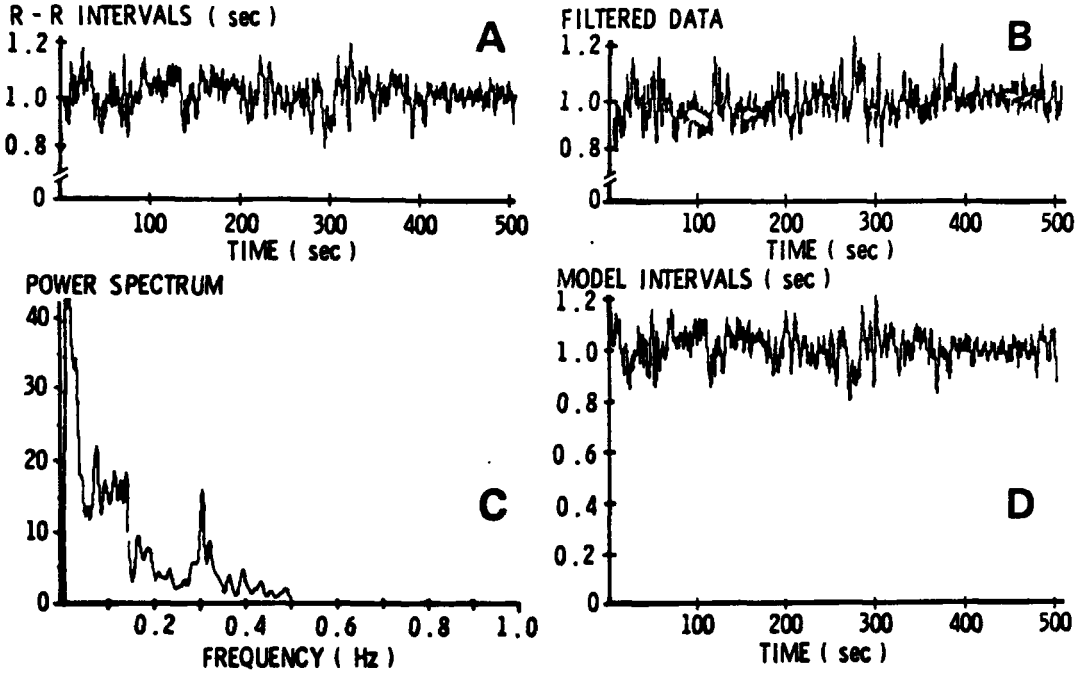


Figure F3. Showing that the low-passed filtered cardiac event sequence corresponds to the autonomic signal controlling the cardiac interval. The low-frequency spectrum of the blood pressure, A, is very similar to that of the cardiac event sequence, B