Use of Random Excitation and Spectral Analysis in the Study of Frequency-Dependent Parameters of the Cardiovascular System

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The use of Fourier series for the study of pulsatile events in the circulatory system is now well established, and a recent collection of papers in the field\(^1\) contains many references to the method. On the other hand the generalization of the process, power spectrum analysis, has hardly been applied to these problems, and the paper by Randall\(^2\) (1958) has remained for several years the only example of its use.

A good deal of attention is now being directed to the study of frequency-dependent properties of the arterial system, e.g., the input impedance of the aorta\(^3\) and pulmonary artery,\(^4\) and also to the examination of the servo-control mechanisms regulating the circulation.\(^5\) It is therefore opportune to re-examine the use of spectral analysis, since it can be made to provide a continuous set of values over a wide range of frequencies, rather than the discontinuous and restricted set of values obtainable by the use of Fourier series analysis. An objection to using it in the cardiovascular system is, as was found by Randall, that the pulsatile events are usually so regular in timing that their frequency spectrum is restricted to a few lines corresponding to the harmonics of the regular waveforms. The broadening of these lines by irregularities such as sinus arrhythmia is still insufficient to provide significant results except at frequencies at or near these lines. This paper describes a method whereby this limitation can be overcome, and which enables the full power of the technique to be exploited.

The use of random signals is a standard method in the study of input-output relationships in servo-mechanisms design and communications engineering; it is discussed in many books, e.g., Tsien (1954).\(^6\) The experiments to be described here demonstrate that it can be applied successfully to the cardiovascular system. Briefly, all that is required is to induce the appropriate irregularity or noise in the signals to be analysed. If these are made random instead of regular, then the line spectrum is replaced by a continuous one, so that determinations can be made of a particular parameter, for example, the arterial impedance, over a wide range of frequencies. By the previous method, using Fourier series analysis of single pulses, or pairs of pulses, the lowest frequency component available was that of the repetition frequency of the pulses; by slowing the heart by vagal stimulation or by surgical heart block, this lowest frequency could be brought down to between 0.5 and 1 cycle/sec. With random excitation, on the other hand, depending upon the length of recording available, the lowest frequency component can easily be 0.01 cycle/sec or even, as in some of the examples here, as low as 0.00125 cycle/sec.

The experiments to be described will illustrate the application of the method to the determination of the transmission function for pressure oscillations between the arch of the aorta and the femoral artery; and of arterial impedance of the ascending aorta and of the femoral artery; and, as an illustration of the special advantages of the method, an ultra low frequency analysis of the performance of the reflex system controlling blood pressure.

Methods

Eleven mongrel and greyhound dogs (weighing 20 to 35 kg) were anaesthetised with pentobarbitone (20 to 40 mg/kg intravenously), or...
chloralose urethane (5 ml/kg intravenously of a solution containing 1% chloralose and 10% urethane), after premedication with morphine sulphate (1 to 1.5 mg/kg) one hour before operation. In the three experiments dealing particularly with the baroreceptor responses, after application of the electrodes to the atrium and placing of the flowmeter probe on the ascending aorta, the chest was closed and the animal allowed to return to spontaneous respiration. When it was desired to study the impedance in the absence of baroreceptor control, ganglionic blockade was induced by the intravenous injection of hexamethonium bromide (10 mg/kg) the blood pressure being maintained at control levels by a slow intravenous infusion of noradrenalin (20 µg/ml).

Pressures were recorded through fine nylon catheters filled with heparinised boiled saline, using Sanborn capacitance manometers. The frequency responses of the catheter-manometer systems were determined by the pressure-step or pop method, and allowance made for these in the subsequent calculations. The damped natural frequencies normally lay between 60 to 100 cycles/sec. The catheters were inserted into the femoral artery via a small muscular branch, and into the arch of the aorta either by direct puncture of the wall, or via the superior thyroid branch of the common carotid artery. Flow was recorded in the ascending aorta or the femoral artery by means of coreless sine wave electromagnetic flowmeters. These had been calibrated hydraulically, with oscillating flow, and allowance for their frequency characteristics was made in the calculations. Pressure and flow signals were recorded on magnetic tape, and transferred to punched paper tape for computer analysis.

The way in which the randomness or noise is generated must be a matter of choice, dictated by the particular problem. It could be, for example, the superimposition of random pressure fluctuations in the arteries by some mechanical device; or the random stimulation of a nerve, or some part of the central nervous system; or the random changing of the concentrations of an injected drug, or the concentration of a gas in the inspired air.

For the present purposes, the irregularity in pressure and flow signals was induced by applying random stimulation to the right atrium, using bipolar electrodes. The irregularity in the signals provided noise which was limited in frequency content by the nature of the experiment, but had adequate energy (fig. 3B) in the range of frequencies of physiological interest. The electrodes were supplied through an isolating transformer to avoid interference with the electromagnetic flowmeter. The arrangement is shown in figure 1. The source of noise was a high gain a-c coupled transistor amplifier, with a 1-megohm input load. The output passed to a trigger circuit, which in turn operated a relay via a scale of two. The mean rate of the random switching of the relay could be adjusted by varying the threshold of the trigger, to give mean switching intervals down to 30 seconds. To provide pressure and flow signals with good coverage of the frequency range 0.25 to 25 cycles/sec, the mean rate of stimulation was made high, 7 to 10 cycles/sec, so that the pattern of ventricular activity resembled that accompanying atrial fibrillation. For the study of the ultra low frequency part of the spectrum, in the range 0.00125 to 0.125 cycle/sec, the mean rate of switching was adjusted to be about 1 in 30 seconds, and the stimulus frequency to the range 3 to 5/sec, so that the heart rate was made to step irregularly from its normal rate of about 2/sec to a tachycardia of 3 to 5/sec. Some trial and error was needed to find the appropriate rates and stimulus strength for individual animals, depending upon their resting heart rates. In some early experiments the pulse generator was triggered directly by the noise generator, but the bistable relay system was found to be more flexible.

**Computation**

With the data recorded on magnetic tape, a sampling track was also recorded, with signals at 100/sec, 0.5/sec, or other suitable frequency, depending upon the range required in the analysis. One channel of data at a time was then transferred to punched paper tape, via a sample-
and hold circuit and a digital voltmeter, as described previously.  

The replay speed of the magnetic tape was chosen either faster or slower according to the sampling rate involved; the maximum punching speed of the system was about 12/sec.

In order to avoid the influence of "aliasing," the signals were filtered electrically at the time of transfer, using a variable, low-pass active filter, which attenuated frequencies above the upper limit of 0.5 (sampling frequency). Since the same filter setting was used for each channel of data, no corrections were necessary for this. Depending upon the length of record available, the number of samples varied between 1000 and 2500, which was the maximum acceptable by the computer programme.

The programme was designed according to the method of Blackman and Tukey. The mean and any trends present were removed by subtracting from each data point the mean of itself and the 200 points on either side, with appropriate treatment of the first and last 200 points. The auto- and cross-correlations were then found for 200 lags. The Fourier transforms of the signals were filtered electrically at the time of recording, using 2,200 pairs of samples, 200 lags and 100 frequency steps, was approximately 90 seconds; a further two and one-half minutes were needed for input of the data tape and printing of the results.

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COHERENCE, ALIASING AND FILTERING

A quantity of much interest in the treatment of bivariate time-series is the coherence; this is analogous to a correlation coefficient and measures the stability of the relationship, at a particular frequency, between the two time-series; it varies between unity (perfect association) and zero (complete independence). The variables which are being dealt with in this paper can be regarded as the inputs and outputs of an unknown system, the properties of which are to be determined. If the system is ideal, linear, and time invariant, the coherence should be unity, but the presence of added noise or random variation in the output signal, bearing no relation to the input signal, will reduce this value. As will be discussed in more detail below, nonlinearities in the system will have the same effect.

Blackman and Tukey have discussed the effects exerted upon the estimation of the power spectrum over a given range of frequencies, by components outside this range. They refer to this as "aliasing," since, with discrete sampling of the data, a given set of data values may represent samples of either a low frequency oscillation or of the "alias" of a high frequency oscillation. From the practical point of view, this complication can be avoided by excluding the data, before sampling, all components of frequency higher than the "folding frequency," i.e., one-half (sampling frequency).

The importance of filtering in these analyses is illustrated in figure 2. The data are the same as those presented in figure 10, and reference forward should be made for its interpretation; we are concerned here only with the technical problem of filtering. Arterial impedance, in the ultralow frequency range was determined from a recording of aortic pressure and flow, using 2,200 points at a sampling rate of 0.5/sec. Two analyses were made of these data; the first treated the data without filtering, and the second after passage through the low-pass filter, set to attenuate all frequencies above 0.25/sec. It can be seen that the unfiltered data yielded results of small coherence, with estimates of the phase angle so erratic as to be useless. With proper filtering, however, the coherence was high, and the behaviour of the phase angle could be easily followed. The spectra of the unfiltered data showed a large amount of spurious low-frequency power, particularly for the flow. It is easy to see why this should be so, and that samples taken every two seconds from an unfiltered recording of aortic flow could give an extremely poor estimate of the low frequency variations. Most of the samples would fall on the zero-flow value, but every now and then would coincide with the large values of the peaks of systolic flow; severe
The same record of pressure and flow analysed with and without filtering. From above: the coherences, the impedance moduli (smoothed) and the phase angles (unsmoothed). For the unfiltered case, note the loss of the decline in impedance modulus below 0.03 cycle/sec, and the extremely erratic values of the phase angle.

"aliasing" by the high frequency components thus introduced is therefore not surprising.

Filtering to remove high frequency components can also be performed numerically, by digital filtering, whereby the series is replaced by the sums or means of successive groups of the original data. The disadvantage of this in the present application would be the enormous number of samples needed.

Results

(1) DISTINCTION BETWEEN REGULAR AND RANDOM SPECTRA

Figure 3a illustrates the spectrum of oscillatory components (expressed as amplitude, not power) in a train of regular pressure pulses recorded in the femoral artery, and it will be seen that it consists of a number of discrete spikes or "lines," at integral multiples of fundamental frequency, i.e., of the repetition frequency of the pulse. It is possible to distinguish these components out to the tenth harmonic, but there is almost no energy at the intermediate frequencies, and no valid information can be obtained except at or in the immediate neighbourhood of the lines.

By contrast, figure 3b illustrates the distribution of amplitudes of the components of a train of irregular pressure pulses, generated, as described above, by applying random stimuli to

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the atrium. Because of the irregularity of the pressure pulsations, the discrete spectrum has now been replaced by a more or less continuous one with considerable coverage of the low frequency end of the range (0.25 to 10 cycles/sec). Reference forward to figure 7 will illustrate the power spectra of pressure and flow in the ultra low frequency range (0.00125 to 0.125 cycle/sec). These examples illustrate how, by suitably choosing the time scale of the random excitation, low frequency components can be generated, having sufficient magnitude to allow the study of system parameters in almost any range. There is no reason why, with suitable experimental, recording and filtering arrangements, the frequency characteristics of the cardiovascular or other systems of the body could not be followed down to oscillations with periods of hours. We see, also, that spectral analysis is an inappropriate method for dealing with systems in steady state oscillation; for these the Fourier series approach is the correct one, and will provide all that is possible in the way of harmonic analysis, granted the limited number of frequency components available. Spectral analysis is appropriate, however, when the data are normally irregular, or have been made so, as in the present examples. Under these conditions advantage can be taken of the existence of a continuous distribution of frequency components, which extends far outside the range of frequencies covered by the components of the regular or steady state oscillatory data.

2. PRESSURE PROPAGATION ALONG THE AORTA

The amplitude and phase relationships between pressure oscillations in a peripheral artery and in the aorta are of considerable interest in the study of the organization of the arterial system. It has been necessary in the past to determine this relationship from pairs of pulses recorded in the two sites, but the spectral analysis of random pulsations can most conveniently be applied to the problem. Figure 4 shows the results of such a determination. The reader is referred to previous publications for the interpretation of this result, but it should be noted that while the low frequency ratios (up to 12 cycles/sec) are consistent with the behaviour of oscillations travelling in a nonuniform elastic system, the values thereafter appear to be considerably influenced by viscous losses and attenuation. These factors were not included in the theoretical discussions cited above. In the higher range 12 to 25 cycles/sec it is possible to use the phase behaviour to determine the true phase velocity of oscillations over this section of the arterial system. From these data, with a distance of 40 cm between the recording sites, the velocity is found to be 6 m/sec. It can be seen also that the phase velocity in the low frequency range (being inversely proportional to the slope of the
phase-frequency plot) shows the fluctuations which would be expected to result from the presence of reflected components. Determinations in this range would therefore give not the true but the apparent phase velocity. It is not proposed to explore this in detail in this paper, where the experiment is included mainly as an illustration of the use of the method. It is clear, however, that this approach may prove very useful in obtaining that elusive quantity the true phase velocity of oscillations in the arteries, since it enables one to average over a sufficient range of frequencies to exclude the effects of reflection.

(3) FEMORAL ARTERY IMPEDANCE

Figure 5 illustrates the determination of impedance from the pressure and flow in the femoral artery; as in the previous section, the pulsations were made irregular by random stimulation of the atrium. The analyses were based on samples at 100/sec, 2,200 for the control determination and 1,500 for the remainder. To show the use of this method in following fairly rapid changes in a system, the impedances were examined over successive 15-second intervals after the intra-arterial injection of 100 µg acetylcholine. There are objections to employing spectral analysis in the study of nonstationary processes, but provided that the system is only changing slowly during the period of sampling, it appears that it can still be applied with caution.

The impedance values found in this experiment agree well with those previously determined by analysis of single pulses, showing a minimum at 9.5 cycles/sec, where there was also an abrupt change of phase angle. With vasodilation the minimum value became less marked, and the phase angle was decreased, indicating a decrease in the reflection coefficient of the terminations of the bed. As the effect of the acetylcholine diminished, the impedance modulus rose again, and the minimum value decreased; the phase angle also returned to the control values.

(4) AORTIC IMPEDANCE

From the spectral analysis of simultaneously recorded aortic pressure and flow, with irregular stimuli to the atrium, the input impedance of the arterial system was measured from the ascending aorta. In five experiments the same general behaviour of the impedance was found, as a function of frequency; the impedance modulus decreased steeply to a minimum value at about 6 cycles/sec; the phase angle was initially large and negative and passed through zero at or near the frequency at which the modulus reached its minimum. Figure 6 shows an example of such an experiment. This type of frequency dependence has been determined previously by the analysis of single pulse waves, but it has not otherwise been possible to examine in detail the behaviour at low frequencies nor to obtain such a set of results so conveniently from 15 to 20 seconds of recorded data. The form of the frequency dependence is consistent with that for the model of a branching, nonuniformly elastic system.

A feature of interest is the subsidiary
minimum at 2.5 cycles/sec, together with the associated variations in phase angle; this has been noted also in analyses based on single waves, and will be discussed in more detail in a subsequent publication. The most likely explanation is that it results from the asymmetry of the arterial distributions to the head and upper limbs in one direction and the trunk and lower limbs in the other. Resonance in the longer of these two divisions, that is the lower half of the body, is probably responsible for this early minimum.

The extension of the analysis to the ultra low frequency range, which has disclosed some most interesting features, will be discussed below.

(5) ULTRA LOW FREQUENCY ANALYSIS OF AORTIC IMPEDANCE

The amplitude and phase relations between aortic pressure and flow were followed into

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the ultra low frequency range 0.00125 to 0.125 cycle/sec, using the flow irregularities produced by randomly intermittent tachycardia (fig. 9). As has been discussed above, analysis in this range requires careful filtering of data, and therefore the analysis was done not on samples from the finely detailed data shown in figure 9, but from a highly smoothed version, after passage through a low pass filter.

Figure 7 shows the power spectra of the pressure and flow resulting from such a procedure. It is based on 2,400 points each of pressure and flow from 80 minutes' recording sampled at 0.5/sec. It should be noted that the units here are power, not amplitude as in figure 2. It can be seen that there is a fairly good coverage of the lowest frequencies, and that below 0.03 cycle/sec the ratio of flow: pressure appears to be relatively greater than at the higher frequencies; above this frequency there is also a reversal in the sign of the quadrature power.

If these data are expressed as impedance (fig. 8) the modulus shows a generally declining relationship with increasing frequency, but below 0.03 cycle/sec the phase angle changes sign, and the modulus begins to decrease again. The behaviour at the three lowest frequencies is uncertain by reason of the reduced coherence there.

Theoretical considerations show that as the
frequency approaches zero, the impedance should steadily increase to approach a limiting d-c value; the phase angle should be negative, and approach zero with the frequency. These results show, however, that for the lowest frequencies the phase angle is positive, and that the modulus increases to a maximum at about 0.03 cycle/sec, after which frequency it declines in the expected fashion and the phase angle also becomes negative as expected. There is therefore a departure from the predicted behaviour of the passive system, for frequencies below about 0.03 cycle/sec, that is, for oscillations with periods longer than about 30 sec. This result was obtained only once in the first series of experiments, probably because of the combined depressant effects of pentobarbitone anaesthesia and possible hyperventilation of the open-chest animals. It was found in all three experiments using chloralose urethane anaesthesia, with the chest closed so that the animals were breathing spontaneously.

The explanation of this result is to be found in the baroreceptor responses. In essence, the behaviour of the impedance modulus indicates that at the very low frequencies a given flow oscillation produced smaller pressure oscillation than at the higher frequencies, and this can be attributed to the action of the baroreceptor reflexes in buffering low frequency pressure changes in the arterial system.

In order to test this view, two experiments were done in which, after a control determination, the baroreceptor reflexes were abolished by sympathetic ganglionic blockade with hexamethonium, the blood pressure being kept at control levels by a slow, steady infusion of noradrenaline. The variations in blood pressure which were found in response to intermittent tachycardia are shown in figure 9. It will be noted that in the control experiment there is clear evidence of compensatory control of the blood pressure, while in the same animal, after blockade, the pressure stepped from level to level with the changes in heart rate, and showed no evidence of compensation. This behaviour is reflected in the impedances determined from these data (fig. 10). The normal animal showed decreased impedance modulus below 0.04 cycle/sec, at which frequency there was also a reversal of phase. After blockade and abolition of the reflex compensatory mechanisms, the phase angle was consistently negative (as expected for a passive system) and the modulus was falling rather than rising over the range 0 to 0.04 cycle/sec.

Discussion

The results presented here illustrate the two main advantages of this method of analysis, namely, the wide range of frequencies which can be covered, and further, the relatively small amounts of data required. The analyses given in figure 5 were based on a control recording lasting 22 seconds, and three experimental recordings of 15 seconds each. Approximately one hour was required to prepare the data tapes, and the four analyses occupied 15 minutes of computer time. For the ultra low frequency analyses, somewhat over one hour of continuous recording was needed; but considering that this yielded information on the behaviour of the system for oscillations with periods ranging from 8 seconds to just over 13 minutes, the amount of data does not seem excessive.
Comparison of these results with those obtained by the use of Fourier series methods on single pulses, has shown that as far as the arterial impedance in the range 0 to 25 cycles/sec is concerned, the agreement is excellent. Single pulse Fourier analysis has not, of course, been applied to the study of baroreceptor behaviour; there have, however, been some experiments reported which have studied the frequency characteristics of these control mechanisms, by following the responses of the systemic blood pressure to slow sinusoidal variation of the pressure in the isolated carotid sinus or to electrical stimulation of the carotid sinus nerve. These results agree in demonstrating that the response falls off sharply for disturbances of period less than 10 to 20 seconds; the value of 25 seconds (0.04 cycle/sec) given by the present method is therefore not inconsistent with previous findings.

In considering this result in relation to properties of the baroreceptor reflexes in the intact animal, it must be pointed out that the artificially induced tachycardia has interfered with the changes in heart rate which would normally accompany a change in carotid sinus pressure. The period of 10 to 20 seconds cited above was derived from experiments in which the vagus nerve had been cut and in which the normal changes in heart rate had thus also been suppressed. Although the frequency characteristics of the baroreceptor reflexes in the intact animal were not reported, Grodins

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**FIGURE 9**

*Pressure and flow patterns in the ascending aorta during random tachycardia. Above: control conditions; note the compensatory return of blood pressure after onset of tachycardia. Below: after ganglionic blockade; note that the blood pressure now steps from level to level without any evidence of reflex compensation.*
FIGURE 10

Aortic impedance (ultra low frequency) before and after ganglionic blockade (see fig. 9). Note that in the range 0 to 0.04 cycle/sec the modulus is increasing and the phase angle is positive under normal conditions, but not when the baroreceptor reflexes have been blocked.

has compared the responses of systemic blood pressure to changes in carotid sinus pressure, before and after atropinization, and observed that "the fast response in the intact animal is due to a prompt bradycardia"; Scher and Young have made a similar observation. It is proposed to make a more detailed study of this point.

In conclusion, it may be well to discuss the question of linearity, since it may be objected that the nonlinearities of the arterial system must make such a method as spectral analysis basically inapplicable. Goodman et al., in addition to giving a full and valuable discussion of the technique, have presented results of experimental determinations of the frequency characteristics of a linear and a highly nonlinear system. They found that "the agreement between the theoretical and experimental results was reasonably good for the linear process, but noticeably poorer for the nonlinear process, and, as might be expected, progressively poorer for the nonlinear process as the amplitude of the probing noise was increased."

It is clear, therefore, that caution will be required in the use of this method in the analysis of physiological systems, and it must be admitted that the presence of nonlinearities will set a limit to the amount of detailed interpretation which such analyses will bear. On the other hand, it has been shown elsewhere that there is excellent agreement between the values of arterial impedance found by harmonic analyses of single pulses, even though these pulses may be of quite different frequencies. From such determinations of impedance, it appeared that at least in the range 0 to 12 cycles/sec, the nonlinear interactions between the harmonics were so small that the pressure flow relations in the arterial system could reasonably be regarded as linear.

The results presented in this paper agree quite satisfactorily with those obtained by other methods which suggests that, at least in the instances dealt with here, the assumption of linearity is justifiable, provided that, in its application to other situations, due attention is given to questions of filtering and possible nonlinearities. It is hoped that this technique may prove to be a useful addition to current procedures.

**Summary**

If a randomly varying signal or noise is used as input, it is possible to study the input-output relations of a system, over a wide band of frequencies, by the use of power spectrum analysis. This technique has been applied to the cardiovascular system, by deliberately introducing irregularity in the pressure and flow pattern, by random electrical pacing of the heart. Examples are given of the deter-
mination, by spectral analysis in the range of 0.25 to 25 cycles/sec, of aortic and femoral arterial impedance in the dog, and also of the transmission ratio for pressure oscillations along the aorta. The results agreed satisfactorily with those obtained by the Fourier analysis of single pulses. When the time scale of the irregularities was made sufficiently great, it was possible to examine aortic impedance in the very low frequency range 0.00125 to 0.125 cycle/sec. In this range the operation of the baroreceptor reflexes became apparent.

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