The Analysis of Biological Signals

B. MC A. SAYERS

Sayers, B. McA.: The Analysis of Biological Signals. *Medinfo 1974*. pp. 13–20.

Biological signal analysis aims to characterize and enhance the features of dynamic biological variables, to indetify any separate contributions to the pattern of variation, or signal, and to establish what underlying mechanisms are responsible. Very many biological signals, although sometimes only incidental by-products of biological processes, carry some inherently useful information; in fact, various signals of clinical or physiological interest can be shown to be influenced by more than one underlying bodily mechanism, and careful analysis will allow there separate effects to be recognized, their contribution assessed, and the state of the responsible mechanisms evaluated. There are significant diagnostic and evaluative applications of this kind of analysis, and the techniques developed are also valuable in aiding analysis and interpretation of other signals – originating in physiological, biochemical, or psychophysical preparations, in biological images of various kinds, or even in environmental medicine or in epidemiological investigations.

Applications to signals from neurology, cardiology, epidemiology, and other specialities will be used to illustrate recent developments and current capability, and in particular, an account will be given of the way in which the unavoidable sampling variability (often illuminating in relation to its source) of many biological signals can be used in guiding analysis, again with applications to various kinds of signal.

B. McA. Sayers, Engineering in Medicine Laboratory, Imperial College, London, U.K.

The aim of this paper is to describe and illustrate some of the purposes and techniques of signal analysis and processing as applied to biological or medical signals originating in physiological preparations, in the patient, or in the context of public health and environmental medicine or epidemiology. This review is selectively concerned with techniques of general applicability, and with concepts that are generally valid, and it is hoped to clarify that a coherent assembly of methods is now available, together with a well-defined framework to guide their use, for a wide range of biological signals; it is argued that in the light of recent developments, a fresh reconsideration of many clinical and other signals is now appropriate.

1. The concept and content of the biological signal

A biological signal is the pattern traced out by any variable of biological origin that might warrant investigation. Individual clinical varibles like the electrocardiogram, the electromyogram, blood pressure waveforms, respiratory patterns, and fluctuations of blood-gas content, all represent typical biological signals. Both continuous signals (like those above), and point event signals (like neural spike sequences) are met in biology and the matters to be discussed here must be recognized to apply not only to those and similar individual signals of clinical or physiological origin, but also to the pattern of occurrences of cases in space and time (and other signals originating in public health medicine and epidemiology) as well as to the position-dependent variations of intensity met in biological images of various kinds (such as radiological images, scans of microscopic slides, or the results of remote-sensing of biologically-important regions of terrain by aircraft or satellite).

The first significant statement to be made about the biological signal is that it does sometimes contain much more usable information than may be superficially evident. This is such an important issue that it must be illustrated in one or two examples here–and supplemented by demonstrating the way in which analysis can separate any individual contributions to the signal that may come from different biological mechanisms.

The simplest example of a well-known signal with clinical interest is heart rate, or as discussed here, the related signal, made up of the sequence of intervals between successive heart beats, a signal which has been extensively investigated recently with interesting results [1]. There are three major contributions to the cardiac interval signal, together with other effects that warrant attention. The first and most well-known contribution to the signal is the respiratory sinus arrythmia which is readily seen in most cardiac-interval recordings, and is mediated through two mechanisms. It enters the blood pressure system (with heart rate consequences) first because changes in intrapleural pressure associated with breathing alter aortic transmural pressure and stimulate the aortic arch baro-receptors (which assess stretch of the aortic wall, normally due largely to changes in the intra-aortic pressure), and second through other thoracic stretch receptors. The result is that both heart rate and blood pressure are influenced, presumably through brain-stem pathways.

Next, a quasi-oscillatory component can be identified, with a period of about 10 seconds in man (0.08–0.12 Hz). It has been shown that this particular oscillation originates in the dynamic control systems that regulates mean arterial blood pressure in the short term, and is an incidental by-product of the control system structure[2]. It is probable that this oscillation is not important to the effectiveness of control, but it is certainly valuable in allowing characterization of the structure of the control system (which is strongly non-linear), and for other reasons to be discussed later. The fluctuation is quasi-oscillatory for three possible reasons: first, respiratory entrainment of the spontaneous frequency can occur if respiration is regular, with sufficient depth and appropriate rate (a frequency-selective entrainment is definitive for the non-linear control system structure concerned); second, there is a postural effect and third, it appears that there is a potentially-variable time-delay in the transmission pathway for feed-back signals in the control system (perhaps sited in the brain-stem). The last of these factors is probably the most important and it can be checked precisely, because the time-delay concerned can be discerned as between the same oscillatory components appearing simultaneously in blood pressure and heart rate. Control theory demonstrates that the oscillatory frequency should increase if the delay decreases, and this is related to the total loop phase-shift needed to sustain oscillation in a feed-back system of this kind. If the time delay becomes too small it is not possible for the oscillation to be sustained; it therefore ceases, and this is thought to be the most important reason why the oscillation is sometimes present and sometimes not.

The third component of this signal comprises an oscillation originating in the control system that regulates body temperature. The oscillation varies in amplitude and frequency but is undoubtedly actively generated in the process of thermal stabilization against small environment-linked changes in heat loss which can be compensated by adjustments of superficial blood flow; again entrainment by a periodic stimulus is possible. In general, the oscillation has a period in the order of 25 secs in man, and the oscillation can be observed not only in the cardiac signal but also in the blood flow signal.

There is a further fact of interest concerning the cardiac interbeat interval signal. The system is non-linear (at least for part of the time) and since all of the components mentioned above can occur simultaneously it is possible for them to interact. The existence of such interaction means that slow fluctuations (originating in the thermal system, say) can affect the way respiration affects heart rate; broadly speaking, the envelope of the fast component due to respiration, therefore closely parallels the very slow fluctuations associated with the thermal control system, and, to a lesser extent, the presence of pressure-vasomotor components may also be discerned in the envelope signal. (Under conditions of ergonomic interest, such as the application of a mental workload to the subject, this envelope effect is inhibited, and perhaps by hypothalamic mediation.) Taking all of these various contributions and effects into account, it appears that some 85 per cent of the total variability of the cardiac interval signal can be accounted for in this way.

This example using a quite rudimentary signal very well illustrates the possibilities of signal analysis, but very many other signals could be chosen; for reasons related to the subsequent matters, another example concerning the content of the electromyogram can usefully be introduced. The purpose in analysing this signal is to separate out for independent study, the two components that have been found to exist in this record, because it may be suspected, and indeed confirmed, that the two components behave quite differently. To be specific, the fatigue response of a muscle to load (a potentially valuable clinical measure) as shown in the EMG, is quite different for the two components; resolving the signal into the separate components, that can be independently assessed, leads to much clearer indications. This example could be replicated with many signal and it is therefore an important role of biological analysis to separate out contributory effects having different properties, so that these can be independently studied.

Indeed it is clear that a number of earlier attempts to use various clinical measurements for diagnostic and evaluative purposes that have been abandoned because of equivocal or insensitive indications, have foundered on precisely this or a similar difficulty because contributory components behave very differently; much the same would appear to go also for numerous physiological and psychophysical analyses.

2. Special effects in biological signals

A range of special effects occurs in biological signals due to the nature of the biological mechanisms by which they are influenced. First, as illustrated above, in signals that originate in physiology, it is often true that several separate physiological mechanisms affect the signal and these may change with the passage of time or with the influence of other factors, in a way that is sometimes apparantly sporadic or other times consistent and coherent. The existence of different components behaving differently in various physiological circumstances, requires identification, separation, and separate analysis of the components as previously stated.

The second effect of some general importance has also already been illustrated—the existence of quasi-oscillatory signals and short-bursts of recurrent events that behave in a broadly similar way. The former characteristically occur whenever potentially-oscillatory non-linear feedback systems that influence the signal exist in the body and the cardiovascular system is a source of several of these. The latter have the same effect as far as signal processing is concerned and are often seen when muscle behaviour is being investigated.

A third effect is also important. Biological signals are subject to considerable sampling variability and special patterns of signal variability are met. In certain circumstances special signal effects have characteristic variability "signatures" and can be so identified. In the situation in which quasi-oscillatory components exist, for example, the pattern of signal variability is dominated by such a component, and it is possible to make use of this fact to detect the existence of such special contributions to the signal waveform.

Biological signals often exhibit average spectra that are broadly similar to that of a filtered random noise signal, any given length of which is subject to statistical sampling variability in whatever property is investigated. However, in the case of the biological signal, quite different patterns of variability are encountered from time to time, and certainly need to be understood in order to establish the significance of any observation originating in an individual record. In fact it emerges that the nature of the variability itself is sometimes a significant variable worth scrutiny in its own right, and likely to provide useful information about the source of the signal. Indeed it could be emphasized at this point that variability analysis is an important component of the variety of analytical methods for signals originating in public health medicine and is certainly not restricted only to signals of a physiological or clinical kind.

It is convenient to consider again the case of the heart rate signal to illustrate the potentialities of this approach, and we consider the variations from one to another sequential length of record obtained in a single individual. Averaging the power spectra of the various lengths of record available (assume for example that 20 such lengths are available, each comprising say, 256 sequential intervals) leads to a mean spectral density profile that can be treated as representative and used as the basis of a useful model of the underlying signal-generating process: specifically a random noise source, filtered to the same spectral profile as the average power spectrum obtained from the signal under study. The sampling variability of such a filtered source can be estimated accurately from the spectral profile according to a method due to Blackman and Tukey, in terms of the equivalent degrees of freedom (DF_e) of the individual length of record. Given the DF_e the expected variability of such lengths of signal record can be predicted as Chi-^{2} and expressed as the coefficient of variation of signal power, $CV_e = [2/DF_e]^{1/2}$.

In the case of records of resting heart rate, the observed coefficient of variability CV, calculated from the power in successive lengths of record, is found to be significantly less than the figure CV_e predicted in this way, and a similar analysis applied to several spectral bands of the signal shows that the consistency from one length of record to another is contributed mainly from the band centred on components having approximately a 10-second period. This can be traced to the recurrent bursts of pressure-vasomotor oscillation previously mentioned, thus making its presence obvious without *a priori* assumptions. It is also interesting that under ergonomically-relevant conditions of mental work-load, CV approaches CV_e for this band, and the closer study which is thus suggested indicates that the 10-second quasi-oscillatory component is inhibited under these circumstances: an effect which is perhaps the most obvious, even if not the primary, influence of a mental work-load task on the heart-rate signal, and which offers a basis for objective assessment.

Another example comes from the surface potential electromyography study mentioned above, in which the evaluation of EMG responses to muscle-loading is carried out as a clinical guide to the existence and severity of myoneural disease. It happens also in this case that CV_e estimated on the basis of the average power spectrum of lengths of EMG signal using the filtered-noise model, is under resting conditions approximately the same as the observed CV; as the load increases however, CV is observed to diminish appreciably. The effect occurs over most of the full spectral band and so must be due to wide-band signal components. Incidentally, the effect can be traced to the appearance of short-duration transient waveforms that are Poisson-distributed; at increasing muscle-loads these transient waveforms occur with sufficient rate that the distribution of inter-event intervals becomes approximately Gaussian and a broadly similar number of transients then occur in each length of record – thus contributing a substantial measure of consistent repeatability to successive record lengths. When these are removed from the new signal, the residual signal produces CV values that are statistically indistinguishable from the CV_e estimated from the random noise reference signal. Thus the variability analysis again draws attention to the existence of a significant effect.

It will be recognized that the efficiency of this approach with any given type of signal upon the reasonable validity of the model chosen to provide a basis for comparison. Since the purpose of the procedure is to guide further analysis, only a very broad similarity of character is required and once a type of structure has been justified for the reference waveform, repeated application in other circumstances is then valid. In the case of the EMG, the character of the signal (as expressed through its autocorrelation function, for example) evidently matches well the random noise description and no other choice would be rational; also, in the case of the cardiac interval signal, much the same is true. Variability analysis indicates however that in the latter case, during periods when the pressure-vasomotor oscillation is present in the record for a significant fraction of time, the signal power (variance) in the corresponding band is not distributed more-or-less uniformly as with random noise, but is restricted more to a narrow group of components within that band (the spectral-width depending generally on the duration of each burst of oscillation).

On the other hand, when a point-event epidemological signal like the occurrence of cases of a specific disease throughout the year say, is being investigated, the reference model could be linked to a point-event Poisson process, or the whole problem would with advantage be returned to the continuous signal domain by the expedient of low-pass filtering the point-event sequence, in which case the appropriate model might then be the low-pass filtered version of the sequence of events produced by the presumed Poisson process. (This kind of analysis is usable to indicate if special seasonal variations may be present, that warrant more detailed study.)

In short, the more realistic the modell the more useful a variability analysis is likely to be, but the important result would in any case lie in the factors to which attention is drawn, that warrant detailed study. Further illustrations of these matters will follow below in a different context.

3. Optimal processing of biological signals

In general terms there are two aims in biological signal analysis: to achieve some insight into the nature of the system generating the signal, or by comparative quantitative analysis, to establish the state of the system. In the context of clinical medicine, this means the diagnostic or clinical evaluation of the patient in specific respects, based on an identification of which body processes influence the relevant signal measurement, and how; in the context of public health medicine, it could mean for example, the quantitative confirmation of the fact and manner of geographical dependence of a disease and the seasonal dynamics of its occurrence, from which appropriate interventions can be devised. Three categories of processing are needed to provide for the two aims; they can be broadly described as follows:

(1) Improving Signal/Noise Ratio or, more explicitly, the enhancement of wanted components in the signal at the expense of unwanted components.
(2) The quantitative representation of a signal in compact and informative terms that can be used to identify separate contributions to the signal and allow its partitioning in valid and illuminating ways.
(3) Establishing the existence and form of relationships between signals.

Clarifying the signal

It is evident that, for example, an ECG recording is not improved by the presence of mains frequency interference, and filtering is often necessary to suppress noise. An elaborate range of efficient digital computer filters is now available, most with the vital zero-phase characteristic that is necessary in biological signal processing, to meet such requirements. However such linear filters operate effectively only when there is a substantial difference between the spectral distribution of the signal and that of the interfering noise or any other unwanted component. Other forms of such filtering techniques, like matched filtering or averaging, also suffer from this difficulty. In the past, it has naturally been the signals that are well-handled by such procedures for which they have been used; however all the large-scale gains due to such linear filtering methods have now been largely realized, and widely recognized. Further improvements of signal processing are now sought in many cases, and different techniques are being tried to effect the further improvement required. A representative case in which this situation now exists concerns the use of EEG measurements to determine sensory thresholds, as with the use of evoked-response audiometry for young or unco-operative patients. Averaging the EEG waveform following many repeated stimuli does effectively suppress that part of the background noise which occupies a different spectral band from the wanted response pattern, but even when this has been carried out, the resultant averaged waveform still often shows the presence of interfering activity in the same frequency range as that of the signal. This situation calls for quite different techniques in order to allow an unequivocal decision whether or not a legitimate response has been elicited by a given level of stimulus. Both non-linear and phase-dependent techniques have been applied successfully to this problem, and some mention is included below.

Sometimes however, the unwanted components that must be suppressed in a given signal are much more complicated. In the case of a two-dimensional signal, like a biological image (of say an ultrasonic B-scan) the spatial variations of energy transmission, and the existence of unwanted echoes from scattering sources, adds a considerable amount of background uncertainty to an image which in any case is often not well-resolved. The problem of improving the signal-noise ratio in this case is much more elaborate and cannot always be attacked by a linear filtering method. Homomorphic filtering has been used with some success in certain such images but much more investigation of the nature of this signal is clearly warranted, and now been carried out.

A different kind of uncertainty exists in the case of records which are strongly subject to statistical variation, and indeed the example of a one-dimensional (or perhaps spatial) point-event signal illustrates the difficulties very well. There is a measure of variability of occurrence times in for example, neural spike sequences, which is often totally independent of the underlying information being communicated. Similarly, the distribution of cases of disease in space and time is subject to an obvious statistical variability in occurence locations or times that greatly confuses the picture and valid underlying pattern of *a priori* unknown kind usually calls for very special measures, as discussed later.

Nevertheless, it will already be clear that the range of problems met in attempting to carry out a simple task like improving the ratio of wanted to unwanted components of a signal, may lead to very many as yet unsolved difficulties; however, this process is often mandatory in handling any biological signal, and as an essential pre-requisite to any further investigation of the signal, cannot be by-passed in any way. It will be explained later that many of the procedures which are now proving effective or at least promising, depend upon linear methods employing filter parameters that are adjusted in accordance with the features of the signal being handled. Many of the techniquest that are employed for the first stage of signal processing, to improve signal-noise ratio, are applicable in a different way to provide the second group of processing operations – intended to achieve a compact quantified representation of the signal that will guide and permit its partitioning into separate conbributing components, the identification of which will be informative. Indeed, it can be argued, since it is now evident that biological signals may certainly contain more readily usable information than is perhaps obvious, and because closer analysis and effective separation of contributing components is now feasible, that a reconsideration might well be given to the possible content and method of analysis of a variety of common biological signals, expecially those of clinical interest.

Two points should now be clear. The processing likely to be most effective in handling biological signals, must be chosen with regard to the details of the signal itself; even if the procedure then adopted is, as it usually must be, linear, the overall process introduces a signal-dependent component into its operation, and therefore constitutes a non-linear procedure in which judgment, rather than any automated process, controls the choice of linear parameter to be used. Non-linear filtering is now clearly mandatory for the effective analysis of many biological signals but the only generally practical way of effecting such non-linear operations is in the way outlined above, which must depend on *a priori* knowledge about special effects in the signal, and specifically, what (possibly interacting) contributions are likely to be present. Naturally once a procedure has been established, it can usually be more generally applied without further visual scrutiny of the individual signal.

The second point is that there is usually every advantage in separating a signal into its separate contributing components, but this process must take into account the fact that the contributions may not enter additively.

A classic example of the advantage to be gained by resolving a signal into its non-additive contributing components is provided by the problem of analysing lengths of blood pressure record. The pressure pulses are obviously generated at instants determined by the succession of QRS complexes, and the sequence of instants (as a point-event signal) is the first contributory component. This sequence can be envisaged as convoluted with the (time-dependent) individual pattern of the blood-pressure waveform, exactly as if one signal was applied to a time-varying system representing (in its impulse response) the other. The former (the time sequence) is not specifically or substantially relevant to the problem of evaluating haemodynamic aspects of interest here; but the latter, the individual pattern, is influenced greatly and dominantly by circulatory parameters subject to physiological and pathological effects, but relatively little influenced by heart-beat intervals. However the signal is dominated by the inevitably-irregular sequence of cardiac intervals and any attempt at a compact representation of the system by methods that depend on frequency descriptions or linear filtering in any way (as for example, virtually all methods of trend detection) will be rather unsatisfactory because such methods are thus very insensitive to the most significant part of the signal. However, the non-stationary set of individual patterns can be isolated, and studied by methods of ensemble analysis, and a substantial improvement in sensitivity to changes in the individual blood pressure pattern can then be achieved, with consequent advantages in patient surveillance say (of the cardiac post-surgical patient, for example. Thus a simple reconsideration of this particular signal leads to a quite minor modification of procedure that makes available for clinical use a greatly enhanced quantitative representation that is much more sensitive to relevant trends than the raw signal. Corresponding advances are already available for a number of such signals and there would appear to be every reason to explore a range of the signals in common use to determine how more, or more effective, information can be made available from the current methods of measurement.

A further example illustrates a signal in which it now appears that attention has long been focused on a secondary rather than the primarily-relevant component; variability analysis clarifies unequivocally the way the signal should be further investigated. The signal concerned originates in the spontaneous EEG of individuals under investigation for sensory threshold abnormalities and specifically in the effect of an auditory stimulus in evoking and EEG response. In the on-going level of spontaneous EEG, the effect of a single supra-threshold stimulus is usually difficult to see; the usual practice is to average the results of many repeated presentations to determine if the stimulus used has been sufficient to evoke a response and thus to establish the sensory threshold. The basis for this procedure is an assumption that the evoked response, if present, contributes additively to the on-going spontaneous activity.

Analysis shows however, by comparing post-stimulus and pre-stimulus lengths of EEG signal for repeated stimuli, in the light of the variability seen, that no additive contribution need be present at all even though a satisfactory response is certainly achieved. The unavoidable conclusion, argued elsewhere [2], is that effective stimuli act first by imposing a control on the phases of the different Fourier components existing in the spontaneous EEG, and no other mechanism is needed. This immediately establishes incidentally that a basis is thus available for achieving a quantitative, rather than subjective, judgment that a response has been achieved. Furthermore, it draws attention in more general terms to the importance of time-synchronization in the components contributing to the EEG, and indicates, contrary to most earlier opinion, that phase information may be of considerable importance in the analysis of the EEG. In particular it suggests that there is an important series of studies to be carried out along these lines, perhaps even before further investigation of non-linear methods is continued; naturally, the methods are inherently complicated but new techniques and representations in relation to phase spectral manipulation and interpretation are potentially most instructive.

Establishing relationships between signals

The important feature of a biological signal is very frequently the relationship it bears to another signal, perhaps recorded simultaneously at a different site, or at i different time form the same site. The questions that arise in this case often relate to the existence of possible correlations (linear or non-linear) between the signals, or to the existence of patterns in the data which can be compared with previously-selected refernce patterns.

When two signals occur simultaneously at different sites, it is frequently reasonable and instructive to determine the relationship between the two in terms of the system that can be envisaged as connecting them, i. eg. transforming one into the other; the problem is then recognized as one of system identification, a matter of very general significance for the elucidation of various biological mechanisms (both in the individual, and in community or public health medicine) or for the purpose of characterizing relationships between the signals in a compact fashion. If, for example, a general model can be devised for the relationships first between spatial distribution of vegetation on which insect disease-vectors breed, and the insect density distribution, and second with the subsequent outbreaks of the relevant disease, then the parameters of this general model can be identified in individual cases and employed for purposes of forecasting health hazard situations and seasons.

Another relational matter of some significance originates in the possible geographic dependence of spatial distributions of disease cases; in this case the purpose of identifying relationships is to establish factors that may be relevant to the genesis or incidence of the disease. Very many demanding technical problems arise in the context of studies of this kind because it is necessary to relate a spatio-temporal stochastic process to a grid of (usually regular) measurements of potentially-related variables. Several dimensions of sampling difficulty arise in this situation where a stochastic point process is being related to a sample continuous function, but even in the seemingly-simpler case of two point-event signals (as with simultaneous neural signals) the difficulties are considerable. We consider this case first. Random coincidences of events in two simultaneous observed neural pathways are inevitable, but a very small (and so statistically-difficult) increase in actual coincidences over those occurring randomly may be of totally disproportionate significance, and this fact cannot be disregarded in any point-event problem of this type. For example, consider the somewhat idealised situation in which a stream of presynaptic nerve spikes flows in parallel to two separate cells causing corresponding post-synaptic activation; if the two cells have different membrane states, subjected to individually small excitatory effects due to each presynaptic event, the output spike train will show nevertheless very few other than random coincidences. The analysis problem is then the difficult one of confirming the significance of a small change superimposed on a large background. It has been found that the usual method of cross correlating the two neural simultaneous sequences to be compared is not easy to interpret for statistical significance testing. However, it is possible to show that the cross-correlation function can be resolved into separate components known as recurrence-time distributions of increasing order (the forward recurrence-time in this context is the interval from an event in one channel forward to an event in the other channel; the selected event is the next occurring in the case of the first-order recurrence, or the second occurring in the case of the second-order recurrence and so on). Significance testing of the recurrence-times is, in principle, straightforward and sensitive but, the possible presence of non-stationarity and other effects in the records does complicate the problem; results often can only be realistically interpreted against the indication of a simulation, which is a powerful aid in this context.

The other problem previously mentioned applies most forcefully when it is necessary to investigate the possible existence of a coherent underlying pattern influencing the rate of the stochastic point-event process as, for example, in public health medicine where say, the possible seasonal-linkage of disease incidence is being tested, or perhaps when the possible geographical-linkage of incidence is in question. Indeed, a more realistically general problem enquires if the distribution of cases as a function of time throughout the year say, can be shown to vary in a coherent fashion from one geographical region to another. In each of these situations it is necessary to extract some underlying continuous function which can be thought to influence the rate of appearance fo cases either in space or time, or both. This underlying function can be treated as a variable parameter of a stochastic process, or it can be more directly abstracted by low-pass filtering the signal in space or time, much as if the rate modulation of a neural spike sequence were in question. Naturally, when this exercise is carried out on real data, a pattern invariably emerges, and the basic question must be whether this has arisen purely by chance or whether it assumes its specific shape because of a relationship with the underlying variable to which it is being compared. This is inevitably a two-stage process because it is first necessary to determine what relationship might exist, and then to enquire, on this assumption, with what probability the specific pattern observed could have arisen by chance.

In the case of the distribution of cases of disease throughout the year, it is possible to proceed in the following way. The hypothesized underlying control function is applied to the random simulation process as mentioned above, and a large number of samples of the simulated process on the hypothesis concerned is then obtained. A recurrence-time test can then be used to compare the real data with the simulated data, to test the probability that the real data could have come from the simulated process. Alternatively, the individual samples of the simulated occurrence of the disease may be low-pass filtered to extract the underlying pattern; again the question is posed: with what probability could the pattern observed have been produced from a process of the kind simulated? Whether the testing is based on a strictly point-event procedure, as in the former case, or depends on a continuous function abstracted from the point signal as in the latter, a control situation is available in that the simulation can be operated without any variation to the parameters, and this affords a reasonable test basis.

This kind of procedure has been successfully applied to the elucidation of factors underlying the incidence of cases of disease that occur with relative infrequency; very often this situation arises not because the incidence rates are very small but because the numbers of cases for which full reasonable relevant information is available may be a very small sub-set of the total data available.

Possibilities and Conclusions

Several aspects of biological signal analysis have been selected for special attention here. First, it was argued that many biological signals contain usable information quite beyond what may be superficially evident, and this will be illustrated by specific examples; without doubt simple physiological signals sometimes carry clear and positive information about the operation of body control systems and this source of spontaneous information cannot justifiably be neglected. There are applications not only to the surveillance of the acutely-ill patient, but also in occupational health and ergonomics in which the responses and reactions of the typical individual in a work-load situation are of concern. Evidently there is a case for the utilization of a much wider range of signals in these areas of application, and necessarily therefore for the re-consideration of many other signals.

Second, some discussion of technique for manipulating and investigating various continuous or point-process signals has been made. It is an important feature of biological signals that various special effects recur often enough to warrant special mention, and special methods or response to their appearance. Some such factors influence the variability of biological signals and it has been pointed out that the detailed scrutiny of this variability may be helpful in optimising subsequent analysis, especially when special effects obtrude in the signal. It is also argued that for various reasons there are major advantages in separating a signal for study or description into its component contributions; the contributions sometimes enter additively but often in a different way and this fact can be very usefully taken into account. Indeed, it suggests quite different ways of investigating clinical signals.

Third, some weight has been given to the significance of relationships between signals. Trend detection, system indentification, and pattern recognition all involve the notion of relationships and whether carried out for clinical surveillance of patients, identification of new anatomical pathways, or the automatic screening of biological images, related techniques can be employed. By no means all of these are linear, because the parameters of the processing are often very properly caused to depend upon signal structure, and this is one of the areas of signal processing in which our best experience with the power of non-linear operations is being obtained.

Finally, the significant assistance being afforded by simulation methods has been discussed. Without doubt, the use of the indications offered by a computer simulation that incorporates the biological effects thought to result from the analysis of a real signal, can be extremely helpful in justifying or guiding interpretation of the results of processing. This is particularly true in the case of point-event signals such as originate with neural records or with outbreaks or occurrences of disease in space and time, and further development is certainly on the horizon with signal analysis applied to epidemiology and various aspects of public health.

Perhaps the major feature of biological signal analysis as it now stands is that beneath all the variety of approaches and procedures applied to very many signals, there exists something of a coherent framework to guide the analysis and interpretation of biological signals, and without overemphasizing its importance, this is a remarkably helpful development.