Much more of this kind of thing can and should be done.

Along these lines we expect to begin an extensive program of job engineering for the physically handicapped. Simple devices would be of the type that enables a blind person to read a gage. There are, for instance, many jobs that could be performed by a blind worker except for the fact that a dial must be read. Optical, inductive, or capacitative sensing units could be developed, which the blind worker would apply to the dial face to convert the dial reading to an auditory or tactile signal. In other jobs it is necessary that some mark be made on a record slip, and a simple reading machine might enable the blind worker to locate the proper place to be marked with his number.

Effort Measurement

Studies of the motion and energy expenditures of lower animals and of man may be of considerable interest in designing more efficient techniques of work, in studying disease, and in developing equipment. We have been interested in studies of sleep in human subjects and found it necessary to devise equipment to measure the energy the subject expends during slumber. This may be related to the individual's physical and emotional condition and to the characteristics of the surface upon which he rests as well as to external physical and environmental factors such as temperature and humidity. Since existing equipment could not make these measurements, we have developed special sensing and recording techniques which not only record the frequency of these motions but also integrate energy. In addition, we measure the pressures exerted.

The development of instruments for biomechanical analysis involves many challenging problems. Here we must measure motion and determine velocity and acceleration and a variety of forces and momentums. Such studies are of interest, not only in evaluating prosthetic devices, but also in designing equipment and procedures for use by normal people.

Summary

A tremendous range of physical science problems and techniques, from all branches of engineering, are involved in bioengineering instrumentation. The examples I have cited typify the problems that arise, but the techniques we have used represent only an infinitesimal fraction of the resources that we must exploit. The main challenge to the bioengineer is that of defining the problem in terms of what is useful and economically justified. One must understand the possibilities of engineering development and the probability that an effort will reach any assignable goal within a given time. Only then is it possible to work out a practical solution to the instrumentation problem. It is very easy to become so absorbed in the engineering development that we lose sight of the final goal and the purpose of the development. It is also easy, in working out an experiment, to become obsessed with the need for a particular bit of data, or of too great a degree of precision, without considering that the cost of obtaining these data might not be justified by their value to the full development. Thus, the only principles that can be generally applied to a bioengineering problem are those which would apply to making any decision that leans heavily on judgment.

Biological Clock in the Unicorn

LaMont C. Cole

A physiologist colleague has urged me to examine some of the rapidly accumulating mass of evidence for the existence of rhythms of activity and of various physiological functions. This subject, it seems, is attracting increasing interest among physiologists, and new "cycles" are rapidly being discovered in such remotely related material as intact mammals and slices of living vegetables.

It is postulated that there are two fundamental types of cycles. On the one hand, organisms may exhibit exogenous rhythms and have their periods of activity adjusted to correspond to changes of light intensity, temperature, humidity, phase of the moon, height of tide, or, allegedly, to fluctuations in the intensity of cosmic radiation and of the earth's magnetic field. Presumably, the organisms may respond to several such factors simultaneously so that the raw data from experiments present an appearance of complexity. On the other hand, organisms may possess endogenous rhythms that persist for long periods, if not indefinitely, in the apparent absence of external stimuli. These rhythms may originally have been synchronized with environmental rhythms, but, possibly, some of the endogenous cycles are innate properties of the organisms.

It is not very difficult in theory to conceive of mechanisms for generating persistent rhythms in the absence of external stimuli. For example, a hormone might accumulate until it reaches some threshold value that initiates the activity in question and simultaneously begins to exhaust the store of hormone. It is, however, very difficult to insulate organisms from cosmic radiation and from the earth's magnetic field. Hence, innate rhythms and exogenous rhythms of different periods may be intermingled and lend a further appearance of complexity to the raw data.

Time Series

It would appear that the physiologist faces a major problem of recognizing the cycles in his data and of disentangling the components when several cycles are present simultaneously. Considerable ingenuity has been exercised in the analysis of such data, and the justification for some of the procedures used must lie in some particularly obscure statistical theory. Since this subject seems to be of such current interest, it may be worth while to warn the uninitiated that there is a possibility of being misled in the analysis of complicated time series. This is the purpose of the experiment to be described in the next section.

One approach that could be used for simplifying the experimental data would be to seek correlations between the series of observations and some environmental rhythm. The principal difficulty here is that time series sometimes exhibit the

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perverse behavior of yielding what Yule (*1*) called "nonsense correlations" because no causal connections are apparent. For example, I found a "statistically significant" coefficient of correlation between the growth of Douglas fir trees in Utah and a table of "random sampling numbers" (*2*). Biologists commonly award that certificate of accuracy known as "statistical significance" to any experimental result that has odds of 19 to 1 against its occurrence as a result of chance alone. Consequently, it appears that anyone who has experimental data and sufficient patience to compute different indices and to match these with several independent environmental fluctuations should have a reasonable expectation, in 20 or so trials, of obtaining at least one "statistically significant" result. In computing correlations between independent time series, the odds appear to be a little greater than this in the investigator's "favor." There is, however, a slight problem which is most conveniently ignored; most of the conventional tests of statistical significance involve assumptions that cannot strictly be assumed to hold when one is working with time series (*3*).

Another way of overcoming the consternation one may feel while contemplating complex time series is to "smooth" the data. This is usually done by means of moving averages or comparable devices, and it is certain that this approach does increase the prospect of finding cycles. Slutzky (*4*) showed in 1927 that such smoothing would actually create cycles in random data. The more refined, and arithmetically more difficult, analyses by means of correlelograms and periodograms (*5*) are also known to create cycles in data where none existed before and to be unreliable as devices for finding actual cycles (*6*). One can, of course, resort to harmonic analysis and express any series, even a constant, in terms of cycles, but here the biologist is likely to find the results difficult to interpret.

My previous interest in time series has been confined to the study of the year-to-year fluctuations in the sizes of animal populations (*2, 7*). Here, the year is a natural unit of time, and it is legitimate to compare population sizes of each year with those of the preceding and following years—that is, time may be treated as a discontinuous variable. This approach, however, is not appropriate for studying hour-to-hour changes in, say, metabolic rate. The hour is an arbitrary unit of time, and an instrument that records amount of activity per hour might indicate differences between two precisely synchronized animals if one always began its activity on the half-hour and the other on the hour. Thus, in analyzing these physiological and behavioral rhythms, we must regard time as continuous in the mathematical sense.

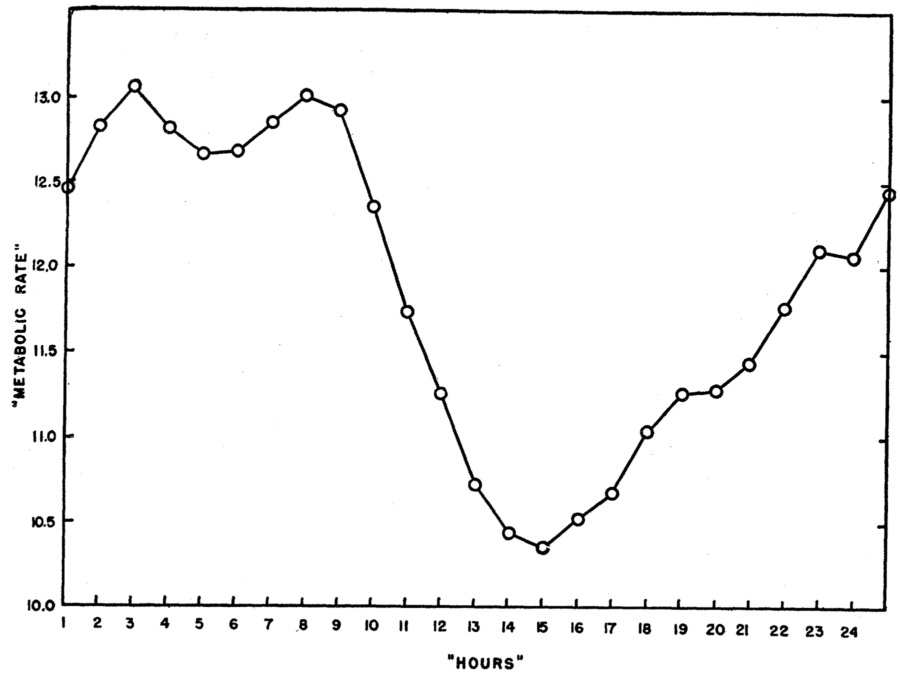

Fig. 1. Cycle of average hourly metabolic rate in a unicorn taken over five consecutive days, with succeeding days retarded 1 hour to allow for change in the time of moonrise.

An Experiment

Now, when we want to decide whether or not a phenomenon is real, a logical procedure is to deduce the results that we would expect to obtain if the phenomenon did not exist. Experimental results can then be compared with the hypothetical results and, conventionally, a result not in accord with the hypothesis of nonexistence of a phenomenon is regarded as evidence in favor of its existence. What we need then is some sort of a "null" hypothesis with which to compare our data on biological rhythms. It would doubtless be possible to attack this problem analytically, but the present study deals entirely with an experimental approach.

Because of the difficulty, already alluded to, of insulating experimental organisms from all environmental rhythms, the experimenter usually must face the possibility that exogenous and endogenous rhythms may be confounded in his results. This difficulty could be eliminated if one could employ an experimental organism that is totally insulated from all exogenous rhythms. The famous unicorn admirably fulfills this criterion and was, therefore, selected as the experimental animal in this study.

It is possible to treat time as a continuous variable by following the amounts of change of activity between hours. The Rand Corporation (*8*) has recently published 100,000 values that seem eminently appropriate for representing the metabolic activity of unicorns. These numbers were obtained by solving for x, the normal deviate, in the equation

$$D + \tfrac{1}{2} = \frac{10^5}{\sqrt{2\pi}} \int_{-\infty}^{x} e^{-\frac{t^2}{2}}\, dt$$

where D is a five-digit random number from a table that has passed extensive tests for randomness.

In our experimental approach we assume that the unicorn has some "standard" metabolic rate, measured in arbitrary units, and subject to change with time. The average amount of change from hour to hour, when measured over a long time span such as the life of the unicorn, is assumed to be normally distributed about a mean value of zero. In going from one hour to the next, however, the direction and amount of change is assumed to be a random normal deviate.

In our arbitrary units, we assigned the unicorn an initial metabolic rate of 20. Then we started through the table of normal deviates to find the metabolic rates in subsequent hours. In the first hour, for example, the rate was 20–1.276, or 18.724, in the second hour it was 18.724–1.218, or 17.505, and so on. One hundred and twenty consecutive observations of metabolic rate were made in this way. These were taken to correspond to hourly readings over 5 consecutive days.

It seems to be standard procedure in analyzing data on physiological rhythms to average the corresponding hourly data of several days. We did that in this case and the data seemed to suggest underlying rhythms, but no pattern was clearly apparent.

While contemplating the data, it occurred to me that in summer at 40° north latitude the hour of rise of the moon may be retarded by approximately 1 hour each night. Consequently, to eliminate any such lunar rhythm, we "slipped" the data one hour per day, aligning "hour 1" of the first day with "hour 2" of the second day, with "hour 3" of the third day, and so on. This seems to be a standard sort of procedure for analyzing such data. Now, when the hourly figures for the five days were averaged, a daily rhythm came clearly into focus. This rhythm must have been obscured by the simultaneous presence of the lunar rhythm.

Another standard procedure for analyzing such data consists of smoothing the activity cycles by means of a three-point moving average. Consequently, this was done before graphing the results to produce the representation of unicorn activity shown in Fig. 1.

Figure 1 seems to tell a clear story of an endogenous rhythm. Eliminating the effect of the lunar periodicity shows that the peak of endogenous activity occurs at "3 A.M." and that the minimum occurs exactly 12 hours later. The unicorn obviously tends to be active in the early morning and quiescent in midday. The "midmorning" dip in activity indicated in the figure remains unexplained but may possibly be a subject for future research. It seems almost superfluous to mention that, like other "biological clocks," this rhythm is independent of the temperature at which the observations were made.

This example illustrates some of the possibilities for detecting "cycles" by means of relatively simple arithmetic procedures. A rhythm as definite as that in Fig. 1 could easily be shown to be highly correlated with environmental fluctuations, but the nature of the material employed in this experiment seems to preclude any such causal relationships.

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News of Science

German Physicists Protest Nuclear Weapons

Eighteen leading nuclear physicists in West Germany, four of them Nobel prize winners, have announced formally that they would refuse to cooperate in any way in the production, testing, or use of atomic weapons. In a statement issued through the Max Planck Institute of Physics in Göttingen, the physicists said in part:

"We do not feel competent to make concrete proposals regarding the policy of the great powers [on atomic weapons]. But we believe that a small country like the Federal Republic can best protect itself and help world peace if it expressly and voluntarily renounces possession of atomic weapons of any kind."

On the other hand, the men commented that it is of the utmost importance to develop the peaceful use of atomic energy, and in this they are prepared to cooperate. The signers of the statement acknowledged that they were not politicians but maintained that their scientific work placed upon them the responsibility for the possible consequences of their labor. Therefore, they feel that they cannot remain silent on political questions. The statement concluded with a warning that no technical means have yet been developed to protect large concentrations of people from nuclear warfare.

The Nobel laureates who signed the statement were Otto Hahn, the first physicist to split the atom, Werner Heisenberg, Max von Laue, and Max Born. The other signers, all professors, were Carl Friedrich von Weizsaecker, Fritz Bopp, Rudolf Fleischmann, Walther Gerlach, Otto Haxel, Hans Hopfermann, Josef Mattauch, Freidrich-Adolf Paneth, Wolfgang Paul, Wolfgang Riezler, Fritz Strassman, Wilhelm Walcher, and Karl Wirtz.

The statement, which was released on 12 Apr., had a tremendous impact in West Germany and brought an immediate response from Chancellor Adenauer, whose remarks included the following:

"If these gentlemen intended to advocate a general ban on atomic weapons valid for all countries, it would coincide completely with the views of the Government. . . . If however, they meant to say that . . . the Federal Republic should renounce such weapons, then I must say that this has nothing to do with physical science. That is a purely foreign policy matter." Adenauer also commented that the scientists seemed ignorant of recent United States experiments for protecting against the effects of atomic weapons.

On 14 Apr. five of the 18 physicists, led by von Weizsaecker, categorically rejected the Chancellor's replies. They implied that the government's leaders had deceived the German people about the destructive power of tactical atomic weapons. They repudiated Adenauer's assertion that atomic armament was a political matter for which he, as head of the government, was primarily responsible and contended that they had a duty as citizens to take a stand and warn the people against the dangers of atomic weapons.

The five professors also implied that the Chancellor was guilty of concealing the truth when he indicated that their earlier warning had come as a surprise to him. They said that their views had been transmitted in writing last December to the defense and atomic affairs ministers and that there had been private discussions with these ministers in January.

Hahn, one of the group that made the second statement, explained to the press that the question of atomic armament was a matter of conscience for him. He said that the atomic bomb dropped on Hiroshima in 1945 had made a frightful impression on him and that, as one of the pioneers in atomic research, he felt a certain responsibility for what had happened.