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Dynamical disease: Identification, temporal aspects and treatment strategies of human illness

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Dynamical diseases are characterized by sudden changes in the qualitative dynamics of physiological processes, leading to abnormal dynamics and disease. Thus, there is a natural matching between the mathematical field of nonlinear dynamics and medicine. This paper summarizes advances in the study of dynamical disease with emphasis on a NATO Advanced Research Worshop held in Mont Tremblant, Québec, Canada in February 1994. We describe the international effort currently underway to identify dynamical diseases and to study these diseases from a perspective of nonlinear dynamics. Linear and nonlinear time series analysis combined with analysis of bifurcations in dynamics are being used to help understand mechanisms of pathological rhythms and offer the promise for better diagnostic and therapeutic techniques. © *1995 American Institute of Physics.*

I. INTRODUCTION

Physicians have long recognized the importance of considering the temporal dimension of illness for arriving at a diagnosis and deriving treatment strategies. Diseases can be distinguished by their onset (acute versus sub-acute) and by their subsequent clinical course (self-limiting, relapsing-remitting, cyclic, chronic progressive). Recognition of the temporal rhythms, combined with the knowledge that certain temporal rhythms respond best to certain treatment strategies, often provides a basis for therapy.

The recent and dramatic advances in molecular medicine have shifted the attention of the medical community away from considerations of temporal phenomena. At the current time, a strong impetus for studying disease dynamics is coming from the mathematics and physics communities. Advances in our understanding about the nature of oscillatory phenomena in the discipline of nonlinear dynamics offer the possibility of applying this new knowledge to gain insights into the etiology and treatment of diseases. The mathematical methods for understanding the origin, stability, and bifurcations of dynamical behavior in nonlinear equations appear to be ideally suited for the analysis of complex rhythms confronted by the physician on a daily basis.

Although the origins for the application of nonlinear dynamics to the study of human disease can be traced back to the analyses of certain cardiac arrhythmias in the 1920s,[1,2] the concept of a *dynamical disease* was first proposed by Mackey and Glass.[3,4] Dynamical diseases arise because of abnormalities in the underlying physiological control mechanisms. The hallmark of a dynamical disease is a sudden, qualitative change in the temporal pattern of physiological variables. Such changes are often associated with changes in physiological parameters or anatomical structures. The significance of identifying a dynamical disease is that it should be possible to develop therapeutic strategies based on our understanding of dynamics combined with manipulation of the physiological parameters back into normal ranges. Progress in this direction requires the careful documentation of the temporal aspects of disease combined with suitable theoretical analyses. Several books, conferences and reviews have focused on nonlinear dynamics and human disease.[5–10]

A workshop held in Mont Tremblant, Québec, Canada, February 1994 provided an opportunity to review recent advances in the study of dynamical disease. The meeting attracted a multidisciplinary audience of physicians, physiologists, mathematicians, and physicists. Topics included the identification of dynamical diseases, methods for analyzing the temporal aspects of diseases, onset and offset of rhythms, mechanisms of oscillatory phenomena, and the design of treatment strategies. In this article we provide an overview of our current understanding of dynamical disease. Although we emphasize material covered at the workshop, we also mention other work in order to provide a more balanced overview of the field.

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II. DYNAMICAL DISEASES

In a typical medical clinic, a significant proportion of patients present abnormalities in the dynamics of a physiological process. Easily identified arrhythmias are well known in cardiology, respirology, and neurology. Arrhythmias may be significant causes of patient mortality, as in cardiac arrest. Symptoms which recur frequently, such as obstructive sleep apnea or epileptic seizures, are important causes of patient morbidity.

One obstacle confronted by non-physicians studying dynamical disease is that they have little idea of the extraordinary range of dynamics that can be found in the human body. The papers in this volume provide a glimpse into what is going on. In an attempt to document dynamical disease in the nervous system, Milton and Black[11] carried out a literature survey that identified at least 32 diseases with interesting time courses in which symptoms and/or signs recur. Although many of these disorders are relatively common, for example, see the discussions in this volume of hiccups,[12] Parkinsonism,[13] tardive dyskinesia,[14] respiratory arrest,[15] there are also many obscure disorders. For example, Milton and Black[11] identify 8 different disorders associated with control of eye position and pupillary size. Even though the abnormal dynamics in these disorders are easy to observe and can be recorded noninvasively, there has been little analysis to date of the rhythms from the perspective of basic science and mathematics.

One area in which dynamical aspects are significant, but still are not well understood is endocrinology. The mammalian ovulation cycle is perhaps the most carefully studied, but there is still scant theoretical analysis.[16] Moreover, it is becoming clear that, in general, hormone secretion displays complex pulsatile secretion patterns. Since hormones are active in such small quantities, and assays are expensive, systematic studies are extremely difficult to carry out. Notable exceptions are provided by analyses of blood concentrations of parathyroid hormone,[17] insulin,[18] and growth hormone.[19] The gaps in our understanding of the control of hormone secretion are still huge. For example, although it is known that menopausal hot flashes are associated with changes in hormone secretion occurring at menopause,[20] the exact control mechanisms regulating the hot flashes are unknown. Similarly, there are many blood disorders characterized by striking dynamics, but the control circuits regulating these disorders are difficult to isolate and study.[3,6,7,21]

III. COLLECTION OF DATA

The first step towards obtaining a dynamical perspective of disease is the careful measurement of the phenomena as a function of time. Such measurements take the form of a time series, i.e. the tabulation of the phenomena as a function of time. The analysis of such time series may provide important insights into the etiology of the phenomena.

In medicine, collection and interpretation of time series always involves difficulties. Since physicians interact with patients, collection of data almost always requires the active collaboration of a physician. The physician's main interest is in identifying disorders that are associated with significant mortality and/or morbidity for which there is an adequate therapy. Collection of long time series often involves inconvenience and extra cost, and may be of little immediate benefit to the patient based on current knowledge. Studies of dynamical disease are notable for the variety of time series assembled, for the ingenuity of methodology used to collect them, and the wide range of different methods that are being developed to analyze them.

The techniques used to collect data include a variety of noninvasive and invasive techniques. Information about dynamical disease is derived from the following sources:

(1) Noninvasive methods
  - patient diaries;[11]
  - mechanical displacements of respiratory structures;[12]
  - air flow velocities and concentrations of oxygen and carbon dioxide in expired gases;[15]
  - motion of extremities using lasers and accelerometers;[13,14,22,23]
  - electromyographic (EMG) activity associated with muscle;[12,15,23]
  - sound waves generated by the voice;[24]
  - changes in pressure on a pressure plate associated with changes in posture;[25]
  - magnetic fields from the brain;[26]
  - blood pressure and electrical activity associated with the heart beat.[27–30]

(2) Invasive measurements
  - concentration of hormones in the blood;[17–19]
  - core body temperature;[20]
  - concentration of blood cells in the blood;[21]
  - intracardiac electrical activity, blood pressure and wall motion.[31]

The time scales of measurements range from seconds to days. Noninvasive measurements are capable of collecting vast amounts of data but limitations arise because of the necessity of appropriate methods of data storage, retrieval and analysis.

IV. TIME SERIES ANALYSIS

Typically times series of physiological data display significant irregularities. Various issues arise. Are the irregularities associated with noise or a deterministic process or some combination of the two? Independent of any understanding of underlying dynamic mechanism, is there any way to analyze the data to distinguish between subgroups of subjects (e.g. healthy versus diseased)? To what extent can an analysis of the time series give hints about mechanisms?

The simplest way to analyze a time series is to graph it and examine the time series by eye. For example, Whitelaw *et al.*[12] illustrated this approach in their discussion of hiccups. They were able to conclude that the timing of hiccups is controlled by a central neural oscillator which is influenced by both the cardiac and respiratory cycles.

A slightly more sophisticated method of data analysis is to form a histogram from the time series, i.e. a graph of the frequency at which the variable attains a certain value. These histograms can be described mathematically in terms of a density function. A clinically familiar density function is the "bell-shaped" normal distribution. Density functions are very useful shorthand descriptions of a time series since they can be used to calculate measurable quantities such as the mean value, the probability that the next value will be greater than a certain value, and so on. Demongeot *et al.*[32] suggest that it may be easier to analyze mathematical models describing neurophysiological networks from the point of view of density functions and their associated invariant measures. Thus the measurement of a density function provides one method to directly compare the predictions of a mathematical model to clinical observations.

Most research involving data analysis requires computers. We briefly review several of the computer-based methods of data analysis.

Some of the methods involve traditional time series methods such as autocorrelation and power spectrum. For example, Deuschl *et al.*[22] used this approach to obtain a novel classification of tremor. They observed that in order to distinguish between the various types of tremors observed in clinical practice it was necessary to use methods based on waveform as well as frequency and amplitude of the tremor.

The role of noise in the generation of complex dynamics is being attacked at a variety of levels. At the most basic level, it is still not known whether the opening and closing of ion channels is associated with noise or a deterministic process. Guevara and Lewis[33] assume that there is a stochastic element in the opening and closing of ion channnels and investigate the effect this has on the timing of interbeat variability in a theoretical model of cardiac rhythm generation. They conclude that a significant degree of irregularity (about 3%) can arise solely as a consequence of the underlying variability in the ion channel dynamics. On a more phenomenological level, Boose *et al.*[23] modeled EMG behavior associated with tremor as sinusoidally modulated white noise. Collins and DeLuca[25] considered postural control during quiet standing from the point of view of a random walk. They concluded that both open and closed loop control is utilized by the nervous system in regulating postural sway. Finally, Paydarfar and Buerkel[15] include noise as a mechanism for switching between respiratory arrest and a normal respiratory rhythm. Analysis of experimental data in which there is a combination of both noise and deterministic chaos is a difficult issue that is treated by Schreiber and Kantz.[34]

"Nonlinear" methods for time series analysis developed in the last decade are being exercised against physiological time series. There are still significant methodological issues. Practical problems arise because of the shortness of the time series, lack of stationarity of time series, and the influence of noise on the measurements.

Probably the most commonly used nonlinear statistic for data analysis is the correlation dimension, originally used by Grassberger and Procaccia.[35] However, Kantz and Schreiber[36] describe the difficulties in applying the Grassberger–Procaccia correlation dimension algorithm to experimental data and present useful advice for novices. Newell *et al.*[14] use a measurement of the correlation dimension to demonstrate the finger tremor in patients with tardive dyskinesia is different from that measured in healthy controls. Bezerianos *et al.*[30] discuss the practical limitations during the application of the correlation dimension to heart rate time series. They find that heavy smoking and mild exercise do not alter the complexity of EKG rhythms.

Determination of the entropy or one of its variants provides an alternative method to characterize the "complexity" of a time series.[37] Using estimates of the dimension and entropy, Lipsitz[28] found that there is a decrease of complexity of heart dynamics associated with aging. Peng *et al.*[27] have examined long range fluctuations using the method of detrended fluctuation analysis. There appear to be significant differences between the fluctuations of heart rate in normal individuals and high risk cardiac patients.[27] Finally, Ding *et al.*[38] suggested that analysis of dwell times may be better than other measures of complexity for studying the dynamics of auditory perception.

If used only as a diagnostic tool, there is no need to have an interpretation of the dimension, approximate entropy, or other statistical measure of a time series. However, there is currently significant interest in using methods of nonlinear dynamics to control complex rhythms. In this enterprise, it may be useful (or essential) to understand more about the underlying dynamics. In particular, it may be important to know if the time series is generated by a deterministic or chaotic process. If a time series is generated by a deterministic process, then it should be possible to predict the dynamics (at least for short times into the future). Chang *et al.*[39] and Sauer[40] discuss prediction methods for time series analysis. If one can predict the future better for a given time series than for a suitable stochastic surrogate, then this provides good evidence that there is nonlinear determinism that can potentially be exploited in applications. For example, prediction of when clinically significant events will occur in the future would be of obvious benefit for the design of therapeutic strategies for the management of sudden cardiac death syndrome and epilepsy. Prank *et al.*[17] conclude from their computations of dimension of hormone levels that a nonlinear deterministic process is underlying the dynamics in this system. Based on theoretical modeling, Chang *et al.*[39] find that prediction is a better method to distinguish determinism from noise than other quantitative measures.

Overall, it is difficult at this time to conclude that one method or style of data analysis is better than another. There are heated debates between proponents of the various methods. Each method has its advantages and disadvantages. It is of pressing importance that the different groups make both their data and their algorithms available to facilitate convergence to common methodologies. At this stage, humility in the face of complexity is essential. Dynamics in physiological systems reflect random and deterministic processes at a variety of levels ranging from the molecular level, to the system level, to the environment. It is impossible to control all random influences and the problem of interpretation is formidable. Facile generalizations and easy answers should be viewed with skepticism.

V. BIFURCATIONS IN DYNAMICS AND ORIGINS OF DYNAMICAL DISEASE

A striking aspect of some dynamical diseases is the sudden change in qualitative dynamics. The most dramatic of these changes lead to imminent death as in respiratory or cardiac arrest or a seizure in a patient with epilepsy. From a mathematical perspective, the observations of qualitative changes in dynamics may provide a clue for the initiation of theoretical analyses. Indeed, mathematical analyses of bifurcations in nonlinear equations combined with experimental obsevations of dynamics in biological systems often provide an entry point for theoretical analyses.

A. Bifurcations in maps

One of the most extensively studied problems in nonlinear dynamics of biological systems is the periodic forcing of oscillatory and excitable biological systems.[7] Understanding of the dynamics in these systems has implications for a wide variety of phenomena ranging from generation of cardiac arrhythmias from the competition between competing pacemakers to the entrainment of the circadian rhythm by light. In the simplest cases, biological systems can be modeled by low dimensional maps. Kunysz *et al.*[41] described the effects of periodic stimulation on *in vitro* preparations of atrioventricular (AV) nodal tissue. This work is directly relevant to functioning of AV node in normal and pathological conditions. Periodic stimulation of the tissue generated rhythms similar to what is observed during AV heart block. Kunysz *et al.* found however that one dimensional maps are not adequate to interpret the entire range of phenomena observed.[41]

The effects of periodic forcing in hormonal and control systems is more difficult to analyze because of the experimental difficulties of measuring hormonal concentrations. However, Sturis *et al.*[18] analyzed the effects of periodic glucose infusion in humans and in mathematical models. They found evidence for phase locking between the glucose infusion rhythm and the insulin rhythm. The phenomena they observed are similar to bifurcations in low dimensional maps proposed for phase locking. Foweraker *et al.*[42] modeled the pulsatile release of luteinizing hormone releasing factor (LHRH) from the hypothalamus. LHRH regulates the release of two hormones from the pituitary gland which are essential for the maintenance of normal reproductive function. In their model, the external periodic forcing arises from adrenergic inputs to the hypothalamus and the oscillator is formed by a network composed of reciprocally connected LHRH neurons and gamma-aminobutyric acid containing neurons. To analyze this they carried out extensive simulations of periodically forced Fitzhugh–Nagumo equations. The bifurcations observed can be at least partially understood from bifurcations of low dimensional maps. Finally, Mayer *et al.*[21] show that periodic forcing of a simple model for the immune system can display chaotic dynamics.

These studies of different systems underscore the following observation: periodic forcing of nonlinear oscillations gives rise to a large number of different regular and irregular rhythms that can be understood based on fundamental mathematical principles related to bifurcations of low dimensional maps.[7] Because of the relevance of the dynamics in model systems to human health and disease, periodic forcing is an important technique to study physiological dynamics and control.

B. Hopf bifurcation

From a mathematical perspective, one of the best known and understood bifurcations is the Hopf bifurcation. In the Hopf bifurcation, as a parameter is changed, a stable steady state is destabilized and is supplanted by a stable oscillation. This occurs in two different ways. In the supercritical Hopf bifurcation, the amplitude of the oscillation grows gradually larger, and no parameter values lead to bistability between a steady state and an oscillation. In the subcritical Hopf bifurcation, there is a range of parameter values that gives either a stable steady state or stable oscillation, depending on the initial condition. A dynamical signature of a subcritical Hopf bifurcation is a sudden onset of a high amplitude oscillation as a parameter changes with hysteresis effects depending on whether the parameter is increased or decreased.

It is known that gradual tuning of parameters in negative feedback loops can give rise to a supercritical Hopf bifurcation.[7] An intriguing but speculative possibility is that dynamical diseases with an insidious onset may be associated with supercritical Hopf bifurcations. For example, perhaps the gradual development of abnormal tremor in tardive dyskinesia is associated with gradual modification of feedback loops for movement control.[14] Similarly, some of the altered dynamics in aging may occur as a consequence of changes in the time delays and sensitivity of physiological feedback loops.[28]

Sudden onset or offset of large amplitude oscillations is observed in many circumstances. An important case is respiratory arrest, studied by Paydarfar and Buerkel.[15] They propose that this important clinical arrhythmia may be associated with a bistability between a steady state and an oscillation where there is a perturbation that can take you from one basin of attraction to another. This analysis emphasizes an important point of direct relevance for an understanding of human disease. In dynamical systems with multiple basins of attraction, changes in dynamics can arise as a consequence of: changes in control parameters that destabilize the basins of attraction; changes in the boundary basins as a consequence of parameter modification; and perturbations that take you from one basin to the other. However, much more analysis is needed of such phenomena as paroxysmal cardiac arrhythmias, hiccups, hot flashes, and respiratory apnea in order to identify the origin of the abnormal rhythms.

Another important class of phenomena are those in which there is a sudden switch between two qualitative rhythms. A striking example is provided in the study of Beuter and Vasilakos[13] who demonstrated a sudden switch to large amplitude Parkinsonian tremor from a tremor that appeared superficially to be normal. This is similar to the subcritical Hopf bifurcation, but there is a bistability between different rhythms. Switches between physiological tremor and pathological tremor are also described by Boose *et al.*[23]

C. Skipped beat rhythms

In some biological rhythms, there appears to be a clock setting the rhythm, but there is a haphazard appearance to expressed rhythms with a seemingly random dropping of beats. As Longtin[43] discusses, such rhythms can arise from a number of different mechanisms—the simplest might be a gradual increase of a variable controlling a rhythm to an oscillating threshold combined with noise. Experimental observations of this type of rhythm are common in neurophysiology and in some types of cardiac arrhythmias. To date, these rhythms have not been studied in great detail and it is not known the extent to which they are important in basic physiology or pathophysiology.

D. Spatio-temporal bifurcations

Data consisting of a time series collected from a single site directs attention to the sorts of comparatively simple theoretical explanations based on the bifurcations in low dimensional maps and equations. However, it is important to recognize that the body is three dimensional, and understanding bifurcations in space and time may be crucial. Progress in these areas is necessarily difficult due to the necessity for collecting data from a spatially distributed system. Probably the most important clinical and theoretical applications to date have been in the mapping of spatio-temporal patterns of excitation associated with cardiac arrhythmias.[31] In the conference, an elegant demonstration of a qualitative change in spatio-temporal dynamics in the spread of neural activity in the brain was provided by the work of Kelso and Fuchs.[26] In their experiment, a human subject is asked to syncopate with a periodic tone. When the rate of the periodic tone exceeds a certain critical value, the subject is unable to perform this task. With the use of an array of SQUIDs (Superconducting QUantum Interference Devices) placed over the scalp, they were able to demonstrate that at this critical frequency the spatiotemporal pattern of brain activity changes.

Herzel *et al.*[24] showed that irregularities in voiced speech relate to intrinsic nonlinearities in the vibration of the vocal folds and provided a convincing demonstration of bifurcations involved in the production of sound in normal and pathological situations.

VI. TREATMENT STRATEGIES

To date, most research into dynamical disease has focused on simplified models, data collection, and time series analysis as sketched out above. There has been a serious absence of practical applications of the theory.

This is not to say that there is not active intervention by physicians that lead to a modification of dynamical aspects of disease. Many types of drug, surgical, and device therapies are specifically directed towards eliminating abnormal and dangerous rhythms. For example, on a daily basis cardiologists, neurologists, and endocrinologists choose among a range of different treatment strategies that alter internal rhythms. However, to date the methods of nonlinear dynamics have not played a significant role in the development of therapies.

In this section we wish to summarize the directions that now seem the most promising.

(1) Diagnosis. There is active work trying to utilize time series analysis for practical applications. These include: identification of those at high risk for cardiac death,[27] early diagnosis and classification of abnormalities of tremor[13,14,22] and postural control.[25]

(2) Therapy—drug delivery and hormone replacement therapy. There is a pressing need for understanding better the dynamics of control systems to help improve administration of drugs and hormones. For example, it is not yet known how the temporal delivery of many drugs influences their effectiveness. This is likely to be most important for hormone replacement therapies. An intriguing possibility is that theoretical insight and modeling will enable one to alter parameters. For example, Claude[44] analyzes a control-theoretic approach to alter the parameters regulating a limit cycle in a pathological regime back to a normal condition. Although technological advances have made available a number of sophisticated drug delivery apparatus,[45] there is still need for a better understanding of the global regulatory mechanisms involved in the controlled physiological systems. Also, optimization of temporal administration of prescription medicine may be possible by incorporating the findings from chronopharmacology.[46]

(3) Device design. At the current time, there are extremely sophisticated devices to control cardiac rhythm.[31] Such devices can deliver electrical impulses to the atria and/or ventricles, and can be programmed in a number of different ways. Devices exist to convert rapid tachycardias to a normal rhythm either by rapid pacing, or by delivering a shock. These devices have been developed largely by engineers working with cardiac electrophysiologists. An intriguing possibility is that future devices might be able to exploit in a more direct manner understanding of the dynamics of arrhythmias. For example, pacing might be able to avert a dangerous arrhythmia before it started. Alternatively, there is considerable interest in identifying deterministic dynamics in complex settings. In this case it might be possible to design stimulation protocols based on nonlinear dynamics. There have been suggestions that this might be important for cardiac arrhythmias, such as atrial or ventricular fibrillation[47,48] and neural rhythms found in epilepsy.[49]

VII. CONCLUSIONS

One focus in dynamical disease is on the control parameter. In this sense the strategies in the study of dynamical disease bear similarities to those of molecular medicine. However, whereas molecular medicine concerns itself with the chemical composition of biomolecules and their synthesis, in dynamical disease the emphasis is on the interrelationship between the molecule's concentration and the resulting physiological dynamics. Moreover there is the recognition that certain molecules are of more crucial importance than others.

Many present-day physicians and medical researchers are searching for the "magic bullet." They hope that by replacing molecules that are altered or made deficient by disease, or by delivering the right drug, disease will be cured. Although one cannot dispute the profound successes of this strategy (in the discovery of many miracle drugs—antibiotics, hormones, cortisone), theoretical analyses of complex systems such as presented here shift attention to system interactions and dynamics. Dynamics can be extraordinarily sensitive to minute changes in drug concentration. The cardiac arrhythmia suppression trial offers a striking example of increased mortality associated with increased sudden cardiac death in patients receiving a drug that reduced certain types of cardiac arrhythmias.[50] Another graphic example is in Sacks' recounting of the difficulties encountered in titrating the concentration of dopamine in encephalitis patients.[51] Even small changes of delivered drug can change a potential beneficial effect to an effect that causes significant patient morbidity or even mortality.

The road from the development of ideas at the benchtop to their application at the bedside is fraught with false turns and hidden pitfalls. Scientific wisdom dictates that the crucially important experiments cannot be performed without a theoretical knowledge of the properties of the underlying control mechanisms and their response to perturbations. Nonetheless, the use of empirical methods, such as drug trials involving animals and patients, is the mainstay of present-day clinical research. This meeting drew attention to the fundamental importance of carefully documenting the temporal aspects of disease and emphasized that "pencil and paper" research may have important implications for managing patients at the bedside. It is anticipated that forming an effective partnership between theorists studying dynamical disease, basic biological scientists, and clinical investigators holds great promise for treating human disease.

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