MODELING BLOOD GLUCOSE DYNAMICS

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For the past several years, various simulations of the blood glucose regulatory system have been performed. Mathematical models of such a system have enabled data reduction, diagnostic classification, hypothesis testing and design of critical experiments. These mathematical models, which simulate the behavior of the real physiological systems, are in turn simulated using various digital and analog computer techniques. A single basic model relating blood glucose and plasma insulin has been shown to adequately describe responses of the glucose regulatory system to various challenge stimuli. Specific examples discussed included responses to an oral glucose tolerance test and an intravenous insulin infusion test. The significance of the model conformations to such tests is discussed in view of the goals of modeling and the extension of knowledge of blood glucose dynamics. Although this model is a highly oversimplified representation of the physiological control system, it has been used successfully in a variety of applications.

INTRODUCTION

Physicists and engineers in studies of electrical circuits, control theory, and systems analysis have lumped together various aspects of the phenomona under consideration into a group of black boxes which are convenient for humans to use (Seifert and Steeg, 1960). The number and complexity of these boxes must be sufficient to describe the phenomona in the limited ranges of interest. Similar techniques can be used in studies of physiological systems. In this paper, we seek to illustrate such physical, deterministic modeling of a particular physiological control system, namely that concerned with the regulation of blood glucose levels.

Studies of blood glucose dynamics have attracted the interest of persons with a variety of backgrounds. Glucose plays an essential role in the intermediary metabolism of many tissues; both extremely high values and extremely low values of blood glucose are associated with severe pathological symptoms. Thus regulation and control of blood glucose levels are an essential function of the organism. Nonetheless, there remains a rather wide range within which blood glucose levels normally vary. Certain abnormalities of the dynamics of this variation lead to pathological conditions as will be discussed in the paper. Accordingly, the blood glucose regulatory system is a very suitable one for illustrating the use of deterministic models of physiological control systems.

Within the current paper, a more general discussion of models and simulation precedes the presentations relative to the modeling of the dynamics of blood glucose. This is followed by a description of specific models emphasizing the rationale of our choices. These models are applied first to a discussion of responses to glucose tolerance tests and second to responses to intravenous infusion tests. Throughout the paper we have sought to emphasize our approach and philosophy rather than mathematical or experimental detail.

MODELS AND SIMULATION

Mathematical models

We have regarded the use of mathematical models as an integral part of an overall research program. We have tried to avoid on the one hand allowing our interests in modeling and simulation to capture our entire attention, thereby neglecting the underlying empirical basis of biological and medical sciences. On the other hand, we have just as strenuously opposed the view that only the immediate, individual measurements were of value. Rather than this, our group has emphasized joint efforts involving to varying degrees the skills, knowledge and techniques

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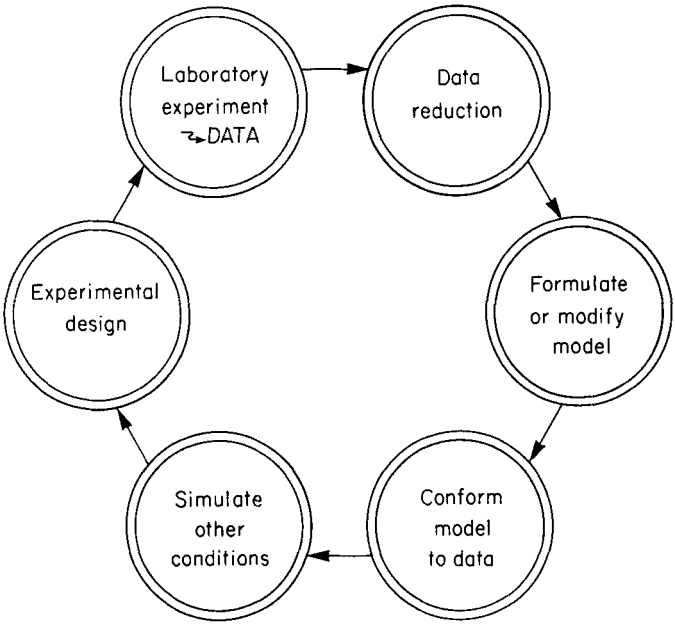

FIG. 1. Cyclic interactions in scientific investigation between laboratory experiments and the applications of mathematical models. From Ackerman et. al. (1966) with permission.

matical biologist, the statistician, and the health computer scientist.

It might be maintained that every biological study uses, at least implicitly, some type of mathematical model. Certainly this is the case whenever biostatistical maneuvers such as averaging are employed. However, mathematical biology has been concerned with the use of explicit mathematical models. In this paper, we emphasize deterministic models of a dynamic physiological system.

A general overview of such an approach is illustrated by the diagram in Figure 1. This represents the continual, evolutionary nature of knowledge in a specific field (Ackerman et al., 1966). One could consider starting at any of the circles in the diagram. Assuming success one would move clockwise to the next circle. In a complete cycle, the investigation moves through experiment, data reduction and verification, mathematical model construction and testing, simulation and the design of new experiments. The numerous fail and repeat routes are not shown but rather left to the viewers' imagination. Nonetheless the authors believe that by the failure of a proposed experimental protocol or a cherished hypothesis one may learn more than by everything happening in the anticipated patterns.

Control systems

Among the mathematical models and modeling techniques which may be employed in executing the various boxes of Figure 1 are those of the control systems engineer. Historically, this was not the initial approach of our group to studies of dynamic models of blood glucose regulation. Nonetheless there is a considerable overlap of interest. Accordingly it appears worthwhile to examine this approach here at least superficially.

As noted in the Introduction, it is customary in such engineering studies to use black boxes, one of which is illustrated in Figure 2. Some input variable $i(t)$ is supplied to the system which produces a response $o(t)$. The performance of the box can be described by a transfer function which describes the changes which occur in $o(t)$ due to an impulse added to i at time zero.

By and large the approach of the systems engineer has been to design black boxes or better combinations of black boxes which

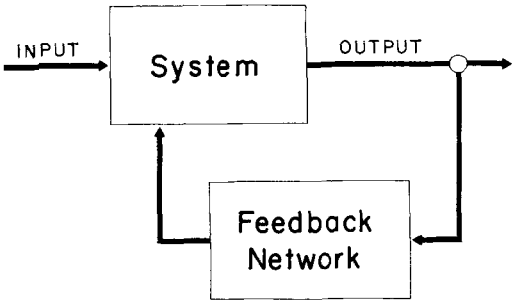

FIG. 2. Schematic diagram of a control system with feedback modifying the system input as a function of the output.

will behave in some desired fashion. Instead of maintaining o constant it is often desired to have it follow some more complicated pattern which may or may not be related to i.

In most cases o is called the controlled variable and the mechanism for producing the desired feedback is called the controller. The mathematical problem of selecting parameters for the transfer functions for these boxes in such a fashion as to optimize a group of performance and cost criteria is not a simple one. Much learned material has been written on the subject.

Although engineering control theory works extremely well and is a highly developed area, its applications to physiological systems are often less than satisfactory. This results from a number of causes. Grodins (1963) has pointed out that the physiologist does not have the opportunity to optimize the system being studied but rather wants to optimize estimates of its characteristics. In spite of this major difference, a certain amount of control theory can be applied to sensory physiology. However, for metabolic systems there are added complications. There may be several inputs combined in a complicated fashion. Worst of all it is often unclear what is the controlled variable and what is the controller. These latter difficulties are epitomized by the glucose-insulin interrelationships.

Goals of modeling

The preceding discussion emphasized the need for clarity in the goals one may hope to achieve by modeling the dynamics of systems. Five such goals are listed in Table I. It is our belief that any one of these is sufficient justification for undertaking a study which explicitly applies mathematical models to biological problems.

TABLE I

APPLICATIONS OF MATHEMATICAL MODELS

Data Description
Diagnostic Classification
Hypothesis Testing
Experimental Design
Isomorphic Mapping

The first goal is data description. If one merely uses parameters of a model to reduce a mass of data to a small number of constants which are more amenable to human discussion, then the application serves a real purpose. This activity, sometimes referred to as curve fitting, was the initial approach of our group to models of blood glucose dynamics. For this purpose one asks that the selected functional form, or model, be capable of predicting curves which pass within the limits of experimental error of the observed values. It is also desirable that such curves involve as few constants as possible and that no trends occur in the deviations of the observed points from the model-based curves.

The second goal which our group looked for in its studies of models of blood glucose regulation was the possibility of using the derived parameters for diagnostic classification. This goal also is independent of whether the model can be used in any of the other fashions referred to in Table I. If the derived parameters can separate normal from abnormal, or can help to characterize quantitatively disease states, then the model need not even produce an acceptable description of the empirical data.

Another use of mathematical models is to test alternate hypotheses. If several conceptually acceptable hypotheses exist then it may be possible by model studies to eliminate some of the alternatives. Even if one reduces the possible hypotheses from say five to three the model studies have been useful. An alternative method of meeting this goal is to test questions using the model, such as

if proposition A is true, what results would be expected.

For some of our colleagues, the most important goal in mathematical modeling of physiological systems, is to design new experiments. These experiments may test the range of validity of the model and incidentally the intuitive knowledge of the investigator concerning the physiological system. Such studies and such new experiments will be most gratifying if they support the investigator's preconceived notions but will result in the maximum increase in knowledge if they prove these notions to be false. Although unwilling to assign more importance to this goal than to the others, nonetheless we regard it as comparably important.

Finally, others regard an isomorphic mapping of the physiological system as the ultimate goal of mathematical modeling. While not denying the intuitive appeal of such a goal, one should recognize its inherent unrealizability. No model, whether it be of a physical, engineering, or physiological system ever reproduces all the facets of the original system. No matter how small pieces one chooses there always seem to be smaller ones; no matter how many details one models there are always others. This fifth goal also carries with it a contradiction of the other four. While they all imply simplifying and abstracting the real system to emphasize its most important features, isomorphic mapping suggests giving attention to even the least significant detail. Accordingly, the models of blood glucose regulation discussed in this paper are not isomorphic maps.

Simulation

In all cases, no matter which goal is selected the mathematical model simulates the physiological system. The model may be presented in the form of a group of boxes with various inter-connections. This may then be translated in some cases into algebraic and transcendental relationships between time and the measured quantities. Displaying these relationships for various values of the system parameters allows one to simulate the dependence of system behavior on system characteristics.

In other cases, it proves less convenient or impossible to represent the model which simulates the physiological system in terms of algebraic and functional relationships. In a study of the dynamics of a physiological system it is however always possible to represent the behavior in terms of differential (i.e. rate) equations (Berman and Schoenfeld, 1956, Ackerman and Hazelrig, 1964). In this case, it is necessary to solve these equations at least numerically for each set of characteristics selected.

TABLE II

EXAMPLES OF COMPUTER SIMULATION METHODS

Digital Computer	Analog Computer
FORTRAN Simulation and Display	Integration and Display
FORTRAN Iterative Conformation	Analog Circuitry with Patchable Logic
Simulation Languages (MIMIC, CSMP, etc.)	"Hybrid" Operations

In either case, for most models of dynamic systems, relating the parameters of the model to the observed variables requires lengthy, repetitive numeric operations. The only possible way of completing such studies today is through the use of electronic computers. Table II presents in outline form some of the fashions in which such simulations may be accomplished. In most cases, it has been the experience of our group that the most severely limited resource was the time of the scientific investigators. Accordingly, we have used as proved convenient all of the methods in Table II, seeking in each instance to optimize the scientific output per man hour invested, subject of course to the varying financial, hardware, and software restraints.

Conformation

Having selected by one means or another a mathematical model and having simulated its description of the observed system, one will usually find little resemblance between model simulation and natural observations. It is then necessary to try to make the model simulations conform to the empiric observations. We have referred to this process as conformation. Its success guarantees that the

first goal in Table I, data description, has been achieved. This indicates nothing about the uniqueness of the model, the relationship to underlying physiological phenomena, or whether this is the simplest model which can be used to describe the data. However a failure to be able to conform the model does produce definite proof of the inadequacy of that model.

The problem of conformation is comparatively easy for problems in which the parameters of the model are linearly related to the observed quantities. Such cases are treated in detail by statisticians who emphasize not only finding the best estimates of the parameters but also measures of the uncertainty of those estimates (e.g. confidence intervals). However, no comparable general theory exists for models which lack these linear relationships. Accordingly, we have most frequently followed a direct search strategy in which a grid of values of the model parameters is selected (Hazelrig et al., 1963). For each point on the grid, the model is simulated and the sum of the squared deviations between the model and the observed points is calculated using preassigned weighting factors. The point on the grid giving the lowest sum of squared derivations is then the best estimate of the model parameters. Studies of variations of this sum at neighboring points indicates the sensitivity of the model to the parametric values. In some cases several local minima may exist on the grid.

It is usually impractical to simulate the model at all points on the grid, so that various schemes have been developed to search for a global least squares minimum. One which our group has used will be described here only for the case of two non-linear parameters. An initial point plus a cluster of points surrounding it is guessed. The point with the least sum of squared deviations is then selected for the center of another cluster taking care not to recompute previously discarded points. This process is iterated until the central grid point is the best and then a tighter cluster is used. The entire process is reiterated until a preset terminal condition is reached. The entire process is easily generalized to more than two non-linear parameters. In this fashion we have conformed models of blood glucose dynamics to the responses of individual humans to various challenges (tolerance tests).

SPECIFIC MODELS

Complexity

Some of the known physiological correlates of blood glucose are diagrammed in Figure 3. Here the blood glucose is shown as one compartment with three subdivisions, hepatic portal, systemic, and a heart-lung mixer. The tissues in which glucose is metabolized are also shown. Liver depots are examined separately since glucose can be stored and released or degraded. The kidney is represented as an overflow leaking function. Each hormone known to affect blood glucose is shown with its parent organ, including many effects that are postulated but not yet clearly identified. In addition the role of several intermediary metabolic factors is indicated such as ketones and free fatty acids.

In spite of the apparent complexity of Figure 3, it is nonetheless a gross oversimplification. Isotope studies can readily show at least two glucose pools and at least two insulin pools are required (Waterhouse and Kemperman, 1966; Silver et al., 1969). The number of hormones affecting blood glucose levels and their complicated non-linear interrelationships are only partially presented in this diagram. It has been estimated that hundreds of kinetic constants would be needed to simulate this oversimplified system and still more would be needed for a more complete system.

Each of these kinetic constants requires at least one measurement which implies that to study the system to the detail shown in Figure 3 would require hundreds of experiments. Moreover, since there exists a broad range of values for many of these constants, it would be necessary to perform all the experiments on any given individual within a fairly short time span. This contrasts quite dramatically with clinical practice in testing for mild cases of diabetes by taking four to seven measurements of blood glucose levels as part of an oral glucose tolerance test. It implies that a far simpler model should be used.

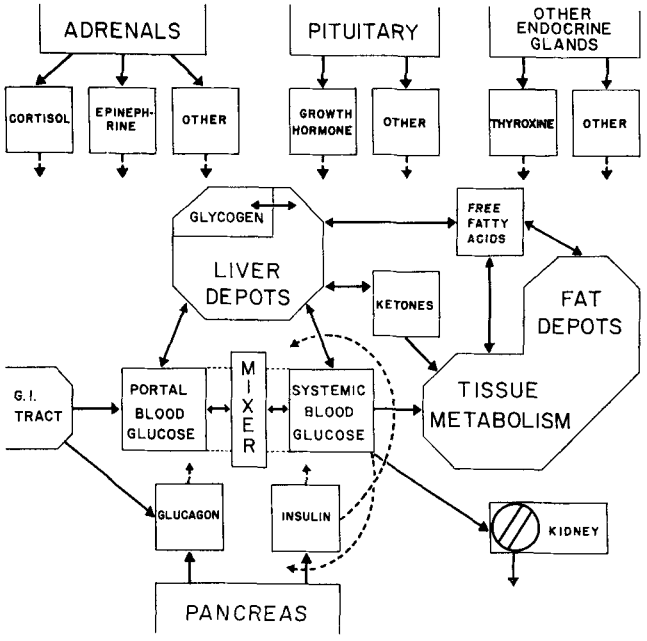

FIG. 3. Schematic diagram of the overall physiological control system regulating blood glucose. Glucose is represented as entering the blood from the G.I. tract, where it is accordingly affected by various hormones and other metabolic factors. The solid lines represent direct transfer; the dotted lines indicate changes in rate constants mediated by the various blood pools (square boxes). From Ackerman et. al. (1969) with permission of Marcel Dekker, Inc.

Simplified basic model

A simplified model which we have used is illustrated in Figure 4 (Ackerman et al., 1965). The heart of this model are two pools which are lumped representations of the factors controlling blood glucose dynamics. The first of these pools labeled G represents glucose in the blood and in spaces which exchange with the blood. Provision is included for the absorption of glucose from the intestines, transfer into or out of the liver, and destruction in the tissues. The second of these pools labeled H represents the net hypoglycemic promoting hormone. It is a composite of all the hormones in the previous figure, those promoting hyperglycemia being considered negative. Disappearance rates of isotope-labeled glucose and hormones indicated the need for several pools with different kinetic properties. However, our studies and those of others have shown that only the lumped pools G and H can be uniquely related to the responses to most tolerance tests. Moreover, we find that changes in H can be associated almost completely with changes in plasma insulin during glucose and insulin *tolerance tests*.

Figure 4 is also meant to illustrate the interrelationships between G and H. These are not simple mass transfers as occur in many compartmental studies. Rather as shown by the dotted lines, H may alter the value of G at which the liver changes from absorbing to releasing glucose, and may also alter the rate of removal of glucose to the other tissues. Correspondingly, G may modulate the release of H by the endocrine system and, although not shown, may also alter the rate of removal of H by the tissues. If significant circulating amounts of proinsulin are present its conversion to active insulin automatically will be lumped with the direct release of H by this simplified model.

In the various tests to be considered, the above model system is thought of as initially being in a steady-state. This situation is perturbed by the addition of an exogenous load of glucose, insulin, or other substance. Figure

4 illustrates the case of an oral load of glucose. However the basic simplified model is by no means restricted to discussions of oral glucose tolerance tests. It may be readily modified to include other tests such as intravenous glucose tolerance tests and insulin infusion tests.

Significance of model parameters

In order to simulate the model in Figure 4 using electronic computers it is necessary to assign functional forms at least to the differential relationships. It is convenient to work with the differences of G and H from their fasting (steady-state) volumes (Ackerman et al., 1964). Thus one may define

$$g = G - G_0$$

$$h = H - H_0$$

where the subscript 0 represents the fasting value. A much more drastic assumption which we have found useful is that the differential relationships between g and h can be linearized (Ackerman et al., 1965; Cerasa et al., 1968) as:

$$\frac{dg}{dt} = -m_1 g - m_2 h + J(t)$$

$$\frac{dh}{dt} = -m_3 h + m_4 g + K(t)$$

where m_1, m_2, m_3 and m_4 are positive constants, J and K represent the entry rates of exogenous glucose and insulin respectively and t is time.

It seems reasonable that these two equations might approximate the system close to steady-state and with slowly changing values of g and h. Independent experimental evidence indicates that both the constants m_2 and m_4 are indeed constant over quite wide ranges of g and h provided neither g nor h changes too rapidly (Campbell and Abbrecht, 1968). The four m parameters are best defined merely as linear proportionality constants. Nonetheless, it is intuitively pleasing to describe them in words. Thus m_1 represents the average hormone-independent rate at which the system tends to return the blood glucose concentration towards its fasting value. It seems probable that four different values should be measureable for m_1, depending on the signs of g and h. However simulation studies not yet reported indicate that these differences would not be observable during a tolerance test.

Similarly m_2 represents the lumped effect of the change of the liver set-point for glucose absorption or release, and of the change of the rate of glucose removal by the other tissues due to changes in h. The constant m_3 represents the glucose-independent rate at which the system tends to return the net hormone towards the fasting values. Finally the constant m_4 represents the lumped effects of the stimulation of the endocrine system by departures of glucose from its fasting values and possibly the protection of insulin from metabolic removal.

It is possible to estimate values for the four m-parameters for normal individuals. If glucose is measured in mg per 100 ml of blood, hormone in net immunoreactive insulin microunits per ml of plasma, and time

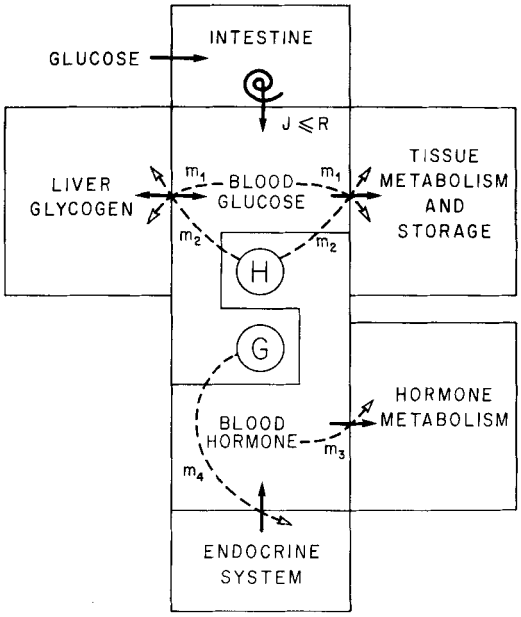

FIG. 4. Schematic diagram of a simplified model of the blood glucose regulatory system. The two compartments, blood glucose G and the net hormones affecting blood glucose H, are interrelated by the dashed arrows indicating control of the rate constants. Transfer from the intestines and to the tissues occurs via the solid arrows. The symbols are defined in the text. From Ackerman et. al. (1965) with permission of N. Rashevsky.

of the internist, the biochemist, the mathe- in minutes, all four m-parameters tend to be about 0.05. However quite wide ranges exist of perhaps a factor of ten or more in normals. Accordingly other presentations of these parameters may be convenient. One which we have used is to combine the two previous equations as

$$\ddot{g} + 2\propto \dot{g} + \omega_0^2 g = S_1(t)$$

$$\ddot{h} + 2\propto \dot{h} + \omega_0^2 h = S_2(t)$$

where:

$$\begin{aligned} \propto &= \tfrac{1}{2}(m_1 + m_3) = \text{damping constant} \\ \omega_0^2 &= m_1 m_3 + m_2 m_4 \\ &= \text{natural frequency squared} \\ S_1(t) &= m_3 J - m_2 K + \dot{J} \\ &= \text{glucose driving function} \\ S_2(t) &= m_1 K + m_4 J + \dot{K} \\ &= \text{hormone driving function.} \end{aligned}$$

Since $\propto$ and ω_0 will be most easily determined from the shape of the curve these seem to be convenient derived parameters to use to characterize the dynamics of blood glucose regulation. If only a few observations are made then the estimate of ω_0 is less sensitive to experimental error than is $\propto$. Accordingly, we have frequently used the related term

$$2\pi/\omega_0$$

which we have called the natural period T_0. Normal individuals are characterized by natural periods less than about four hours (Ackerman et al., 1964). (However, it should be noted that the term

$$\omega^2 = \omega_0^2 - \propto^2$$

or ω itself can be used to characterize the dynamics of blood glucose regulation.) The parameters $\propto$ and ω_0 have the added advantage of implying that two numbers are sufficient to describe normal and abnormal blood glucose dynamics.

Exogenous inputs

In addition to the differential relationships described in the preceding section, one needs a form for the exogenous inputs in order to simulate the model in Figure 4. These may be described in terms of the input rates J and K or in terms of the driving functions S_1 and S_2. Note that the units of J are mg glucose per 100 ml of blood increase per minute and of S_1 mg glucose per 100 ml of blood increase per minute squared. The units for K and S_2 have a corresponding form except they involve immuno-reactive insulin microunits per ml of plasma.

For glucose tolerance tests K is zero. For intravenous glucose tolerance tests, J is usually a step function representing input at a constant rate for a certain period of time. For the oral glucose tolerance test however a more complicated form is needed to represent the variation of J with time. The form of an integrated impulse function was used in several of our earlier studies. However the exact form of J for the oral glucose tolerance test has little effect on the resulting curves provided it rises quite rapidly to a maximum and falls to almost zero in less than two hours (Gatewood et al. 1968*b*). Under these latter circumstances it is possible to approximate the driving function S_1 by a constant times an impulse function. Then one can solve exactly for the blood glucose as a function of time.

For more detail, more complicated absorption patterns are needed. To come still closer to the physiological system, we have also used a carrier-limited model for intestinal absorption since this added little to the complexity of either analog or *MIMIC* simulation. While this leads to esthetically more pleasing blood-glucose and plasma-insulin simulated curves, it is not possible through tolerance tests to distinguish between the various absorption models described (Gatewood et al., 1968*b*).

Having discussed the simplified, basic model in some detail it now appears desirable to restate the goals of modeling in terms of this specific model. First, and foremost, the goal is to represent blood glucose dynamics during a restricted time period of up to five hours. The individual whose blood glucose dynamics are thus simulated is assumed to start in a steady-state and to be subjected to the challenge of a load of glucose, insulin or other substance (such as glucagon or tolbutamide) which tends to disturb the initial state. (Alternately, the blood glucose or insulin could be suddenly displaced from its

steady-state and the return to that state could be simulated.) The representation should be described in terms of as few parameters as possible, where the latter may have, but are not required to have, physiological significance.

The model should describe the overall system. Accordingly, the model should be useful in setting up or describing quantitative, physiologically understandable bases for classifying individuals as normal, or abnormal, possibly also indicating quantitatively the severity of the diabetes of the abnormals.

The basic, simplified model should also allow the testing of hypotheses and should lend to the design of additional experiments. This model has proven successful in all of these regards while adding emphasis to the most important features of the overall system.

At the same time, it must be noted that this model is not useful for representing disappearance curves of isotope labelled glucose or insulin, for representing responses to meals except in a general fashion, or for describing the day by day changes which occur in an individual. Finally the model is expected to fail during short periods of time when the blood glucose or plasma insulin is changed very rapidly as part of the experimental protocol.

These limitations should not detract from the success of the simplified, basic model in fullfilling many goals of modeling under a variety of circumstances. Rather the limitations should emphasize that this model, as all other models, is a mental construct to help humans think about and discuss an actual system.

GLUCOSE TOLERANCE TESTS

Oral and intravenous tests

Glucose tolerance tests are a well known example of an experiment designed to classify individuals according to their response to a challenge load of glucose. These tests are also helpful to evaluate the assumptions made in formulating the basic model concerning the regulation of blood glucose levels (Gatewood et al., 1968*a*). In the oral test, the subject eats normal meals for several days, as extreme diets can affect the results. After an overnight fast, a blood sample is drawn. The subject then drinks a glucose-enriched drink and several intermittent blood samples are obtained, perhaps at 30, 60, 90, 120, 180 and 240 minutes afterward. The analysis of these 4 to 7 samples for glucose is used to classify the individual as normal or diabetic (Frethem, 1963). This test reveals the functioning of the overall physiological system, but abnormalities detected may be due to the patterns of intestinal glucose absorption.

Intravenous glucose tolerance tests are used to examine the blood glucose dynamics alone without the mediation of intestinal absorption. Rapid injections are used to test the effect of a sudden glucose load upon the system. Our basic model fails to describe the initial rise during this type of response as the linearizing assumptions no longer hold. However, the fall from this rise in blood glucose can be conveniently described by this model (Adam, 1968). Data from slow glucose infusion tests, when the infusion rate is a more physiological one comparable to the rate of entry of glucose from the intestines, can be conformed to the basic model (Gatewood et al., 1968*a*). Different combinations of parameters may be determined than with the oral test alone. Thus the intravenous and oral tests complement each other in describing more fully blood glucose dynamics after a glucose load.

Simulation studies

Simulation studies were performed conforming the simplified model to a variety of data obtained during glucose tolerance tests. In applying the model to these data, the basic features desired were that the blood glucose should rise relatively rapidly, fall (perhaps) to levels below the fasting baseline, and return to this baseline within 2 to 4 hours. The initial success with this model in describing glucose responses during oral and intravenous tests led us to test several hypotheses concerning blood glucose regulation. Can this simplified model represent the detailed glucose response after a glucnse load? Can the parameters obtained from such conformations be used to separate normals from mild diabetics? Can the changes in the net effective blood hormone H be iden-

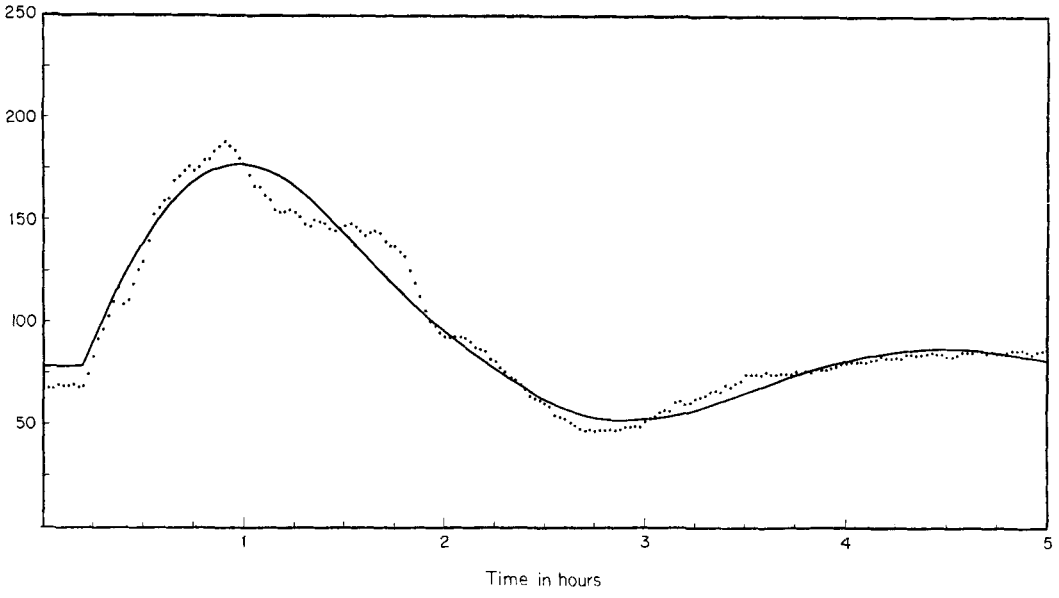

FIG. 5. Conformation of the simplified mathematical model (curve) to a series of blood glucose measurements (data points) obtained during continuous monitoring of an oral glucose tolerance test on a normal person. From Gatewood et. al. (1968b) with permission of Academic Press, Inc.

tified with a specific hormone such as insulin? Several types of experiments including data from other investigators were used to answer these questions.

Continuous blood glucose analysis

To answer the first of these questions, we used continuous blood glucose recordings. The continuous automated recording of blood glucose levels for varied time periods has considerably increased the knowledge of detailed blood glucose dynamics (Mirouze et al., 1962; Burns et al., 1965; Molnar et al., 1968). In this procedure a venous catheter is inserted into the subject's arm and blood glucose levels are continuously measured by an autoanalyzer. Data obtained in this fashion agreed with the shape of the glucose responses obtained from intermittent sampling, and demonstrated other patterns previously indicated only by computer simulations.

We conformed the simplified model to continuously sampled data supplied by Burns (Gatewood et al., 1968*a*). These data were originally obtained to monitor blood glucose responses during oral glucose tolerance tests. Venous blood was sampled for 5 hours after the subject swallowed 1.75 grams of glucose per kilogram of ideal body weight. In order to conform these data to the basic model, additional preprocessing was needed. First, the tracings were manually smoothed and digitized every 1.5 minutes of the tolerance test. After transgeneration of these 201 values from optical density to glucose units, the basic model was digitally conformed to the data using an iterative guessing technique. A more complicated form was needed for the rate of glucose absorption than was needed for conformation of the 4 to 7 intermittent measurements obtained from standard glucose tolerance tests. Such a conformation to a normal response is shown in Figure 5. Although the second hump in the glucose peak has been smoothed in the simulated curve, still the conformation is well within the limits of experimental error and reproducibility.

The use of this procedure has been extended (Molnar et al., 1968; Service et al., 1969) to monitor both normals and various types of diabetics for periods of up to 48 hours. A ten-foot catheter from the patient to the autoanalyzer permits the maintenance of a nearly normal regimen, including meals,

exercise, and sleep. Other metabolic factors were measured in intermittent blood samples, including free and total ketones, free fatty acids, cortisol, and immunoreactive insulin, growth hormone, and glucagon. Acute tolerance tests were also performed, using glucose, insulin, glucagon, epinephrine, arginine, and tolbutamide as the challenge factors. A study of the time-courses of the interrelated variables is currently being conducted to help determine some of the etiology of different types of diabetes.

Delineation of *H*

In an effort to see if the values obtained for the blood pool of net effective blood hormone, *H*, could be identified with those obtained for insulin during an oral glucose tolerance test, we conformed the model to published data (Yalow and Berson, 1960). In this study the subjects were given a large oral glucose load. Both blood glucose and plasma immunoreactive insulin were measured during the course of the four-hour test. Figure 6 shows the results of conforming the simplified model to data obtained from a mild diabetic. The model could be conformed to both data sets to give a reasonable representation of the responses observed. Changes in *H* could therefore be identified with changes in insulin, at least during the first several hours of such a tolerance test.

There are enough data points on either the blood glucose or plasma insulin curves to conform the model to each curve separately. However, if this is done, different values of α and ω are obtained. We therefore conformed the model to both curves at the

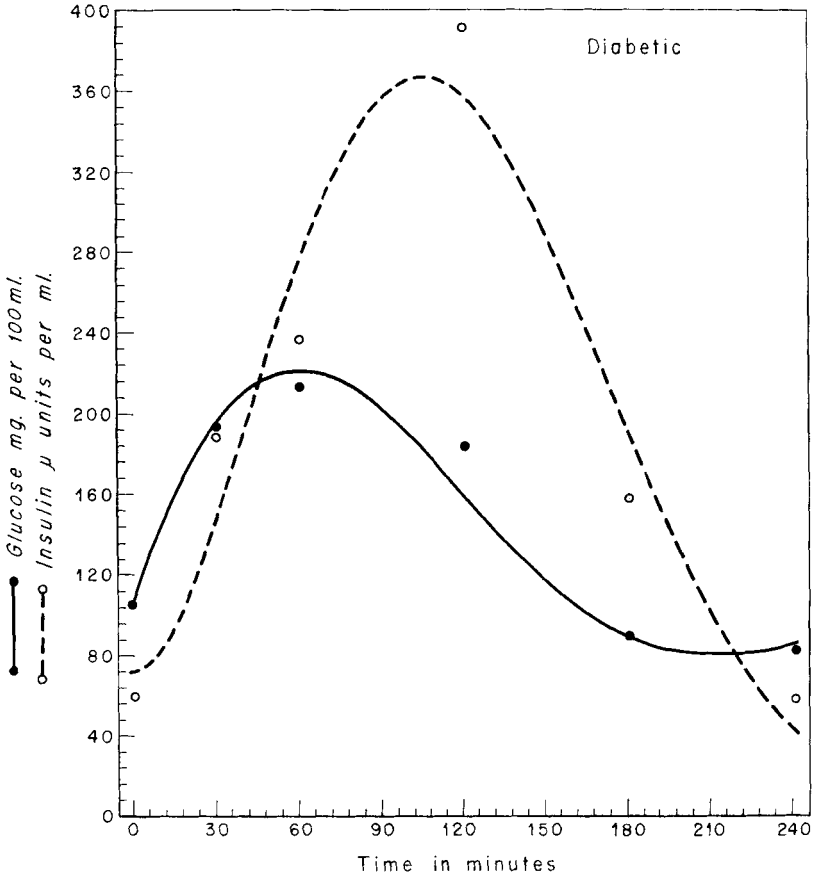

FIG. 6. Conformation of the simplified mathematical model (curves) to data (points) obtained during an oral glucose tolerance test on a mild diabetic. Glucose values are represented by the solid line and closed circles; immunoreactive insulin values by the dashed line and open circles.

same time, asking that the values of α and ω be the best fit for both data sets. From these types of conformations, where both glucose and insulin values have been measured, the parameters m_1 and m_3 can be defined. When only the blood glucose is measured, these m-parameters cannot be separated from their lumped relationships in the parameters α and ω_0^2.

Conformational success

In these simulations, the model has been shown to characterize the responses of both the blood glucose and the plasma immunoreactive insulin to an oral glucose load. The model is not unique in predicting these responses, as more complicated models could have been used which could have been more closely conformed to the data. Nonetheless it does succeed in prediction with a minimum of parameters and complexities. Finer features, such as deviations noted in the blood glucose as double humps, small oscillations, and other small variations in the time-course, are not followed. Nevertheless, the model can be used to answer these questions regarding blood glucose dynamics. 1) The number of compartments is sufficient to represent the blood glucose response to an oral or intravenous load. 2) The parameters can be used for classification of normals and mild diabetics. The parameters α and ω are smaller in mild diabetics, but the values are sensitive to the fitting technique. The lumped parameter ω_0^2 is better as it is relatively insensitive to small variations in conformation. These parameters are most sensitive to the 30 minute value after glucose ingestion, although this is not usually obtained during the standard glucose tolerance test. 3) The changes in H during the first few hours are similar to changes in insulin. If several major hormones were released asynchronously with insulin, the model would not be conformable, so that theory can be discarded as unlikely. However, if one or more hormones were released or operated synchronously with insulin, this could not be seen.

INSULIN INFUSION TESTS

Glucose tolerance tests are performed on normals and mild diabetics, since they are easy to execute and yield significant information. However they are risky tests for a severe diabetic, and can not be well interpreted because of the pathologically high values which could result. Accordingly insulin infusion tolerance tests have been introduced to study glucose dynamics in severe diabetics, especially those exhibiting instability.

Diabetic instability

Unstable or brittle diabetics exhibit extensive fluctuations of the blood glucose level and frequent hypoglycemic episodes, even under conditions of apparently optimal therapy (Molnar et al., 1965). It was desired to quantitate the blood glucose swings in order to define the instability and to be able to design better treatment for such diabetics. Accordingly a number of studies in depth were performed on a group of normal and diabetic volunteers, where the types of diabetes ranged from stable to highly unstable.

These data were ideal for our model studies. The simplified model defines a primary control loop between glucose and insulin in the blood which is sufficient to predict responses to a normal pattern of living, including meals and activities. However, in severe insulin-taking diabetics who are supplied exogenous insulin each day, this primary control loop has been cut. The blood glucose level no longer controls pancreatic release of endogenous insulin. In this case secondary control systems must be postulated which enable such an individual to survive daily stresses. These secondary loops may involve other hormones such as glucagon or growth hormone as regulators of blood glucose levels, as well as metabolic factors which are biochemically convertible to glucose, such as glycogen, ketones, and free fatty acids. Model studies of acute tolerance experiments can be used to define more clearly the role of blood glucose without depot insulin interventions, and to separate these secondary loops and define their roles.

A confounding factor involved in these insulin infusion studies of insulin-taking diabetics is the presence in the blood of preformed insulin antibodies which bind insulin

into a biologically inactive form (Berson et al., 1956). These antibodies make the measurement of immunoreactive insulin difficult, and the results hard to assess. Since H of the model represents both free insulin and bound insulin, where only the free is physiologically active, the apparent model constants for diabetics with large amounts of insulin antibodies are significantly altered from those obtained in normal persons.

Insulin infusion tests

The insulin infusion tests studied (Fatourechi et al., 1969) were performed using continuous blood glucose analysis to permit ending the infusion at a specified level of hypoglycemia and to protect the patient from excessive blood glucose lowering. In addition a more complete record of time relationships during the experiment was obtained.

For this test, the diabetic patients were switched to short acting insulin for at least two days prior to the test to minimize the possible effects from previously administered depot insulins. In addition meals and insulin injections were stopped nine hours before the scheduled test. Normal patients also had their last meal at this time, but needed no other pretreatment.

The insulin was infused slowly at the rate of 0.1 units per kilogram per hour until the desired blood glucose nadir of 30 mgs% was reached. Since the continuous monitoring equipment involved a lag of at least 10 minutes before the blood glucose level could be recorded (Rosevear et al., 1969), separate termination procedures were developed for diabetics and normals. The infusion was stopped for normals at 60 minutes, since normals reached a blood glucose nadir of 30 mgs percent by this time. The diabetic infusion was terminated when visual interpolation of glucose values at 10 and 15 minutes intersected at 30 mgs percent.

A typical infusion test for a normal and an unstable diabetic are shown in Figure 7. The infusion beginning and end are indicated by the stipled area for each curve. The normal curve reached a nadir at 45 minutes and had reestablished a new equilibrium before the end of the infusion. The

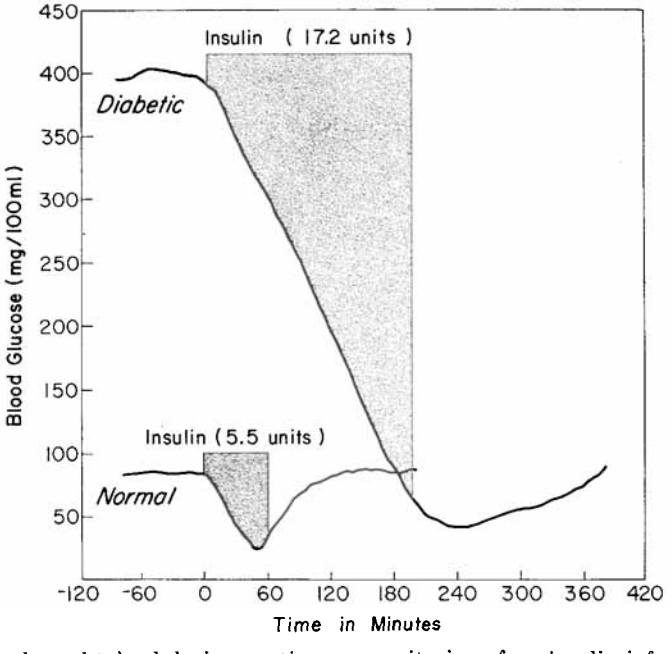

FIG. 7. Glucose values obtained during continuous monitoring of an insulin infusion test on an unstable diabetic (top) and a normal (bottom). The insulin infusion in each case occurred during the time period covered by the stipled area, starting at time zero.

diabetic curve continued to descend after the infusion was stopped. Only this termination of the infusion allowed the subject to recover from the hypoglycemic episode.

Simulation assumptions

In order to simulate the blood glucose response of a severe diabetic to insulin infusion, several further assumptions were made in the description of the simplified model. Since these diabetics have no way to release endogenous pancreatic insulin, the parameter m_4 was set to zero. The initial (fasting) values of glucose and insulin were set very high and low respectively to represent the fasted diabetic without a recent insulin injection. A lower value of m_1 was used to represent the slower rate of return to this fasting setpoint. Finally, m_2 and possibly m_3 should be reduced if there are appreciable preformed antibodies.

In both the normal and diabetic simulations, the exogenous input J, representing the rate of glucose input to the blood, was set to zero. The rate of insulin input to the blood, K, was set to a constant while infusion continued and to zero at its termination. In addition the values for G and H were both constrained to be positive, since concentrations of blood glucose and net effective blood hormone identified as insulin could not be negative.

Simulation results

In order to simulate this model most efficiently, it was decided to try *MIMIC*, the higher level continuous model simulation language available on the Control Data 6600 at the University of Minnesota. The conditions to simulate an insulin infusion with the simplified model were set up with a minimum of statements. Different constants and conditions of termination were used for the diabetic and normal examples. The integration method used by the program is a fourth-order Runge-Kutta which proved sufficient in most cases. The statements are executed in parallel fashion giving analog capacity to examine each data value as a function of time. Blood glucose and plasma insulin values were listed and graphed for every five minutes of the simulated test.

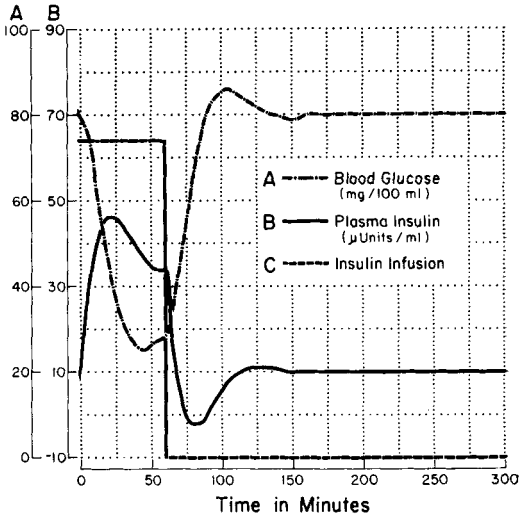

FIG. 8. Output from a *MIMIC* computer program simulating a normal response to an insulin infusion test. The negative values for the simulated insulin concentration indicate an error in the computer integration techniques and represent zero values.

The computer output is shown in Figures 8 and 9 for a normal and a diabetic response to an infusion under the conditions mentioned in the preceeding section. As can be seen in Figure 8, the normal blood glucose has turned before the end of the insulin infusion and is oscillating around a new equilibrium. At the end of the infusion, glucose values then return rapidly to the fasting level. The opposite is seen in Figure 9, where the simulated blood glucose continues to descend in the diabetic and only plateaus at the end of the insulin infusion. The glucose then returns very slowly to the fasting level.

Simulation methods

Other simulation methods mentioned in Table II could have been used to produce the same type of curves. In all cases the scientific investigator must operate within the constraints of computer hardware and software, physical location, and ease of access. The analog computer, especially with patchable logic, offers more "hands-on" control and manipulation of the simulation parameters. Hybrid operation, with the pair-

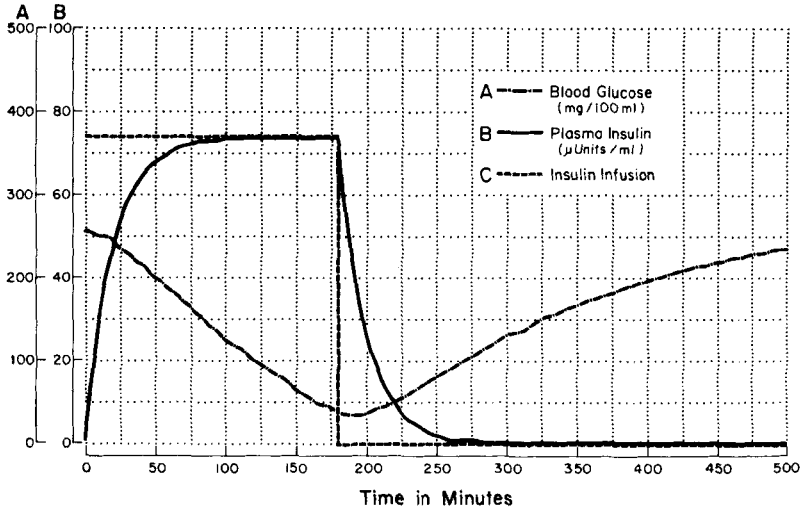

FIG. 9. Output from a MIMIC computer program simulating a diabetic response to an insulin infusion test.

ing of an analog to a small digital computer, could be programmed to try many values for these parameters and logically choose a best one. However hybrid operation is less convenient to use, as it combines many undesirable features of both types of computers.

Within the present milieu *MIMIC* has proven very helpful in obtaining information of the nature of simulation of an insulin infusion test with the basic simplified model. One study not expanded here dwelt with the significance of the parameter m_3, the rate constant determining insulin degradation. These simulations allowed a choice of two different interpretations with different expansions and manipulation of the original mathematical functions. These studies also indicated that there was no need to introduce other existent modulating factors into the basic model when describing the response to an insulin infusion test.

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In the eighteenth century and since, Newton came to be thought of as the first and greatest of the modern age of scientists, a rationalist, one who taught us to think on the lines of cold and untinctured reason.

I do not see him in this light. . . . Newton was not the first of the age of reason. He was the last of the magicians, the last of the Babylonians and Sumerians . . . the last wonder-child to whom the Magi could do sincere and appropriate homage.

LORD KEYNES