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Computer Controlled Glucoregulation in the Diabetic Dog

G. HETENYI JR., B. PAGUREK, G. FLUKER, J. ANTHONY,
I. POPESCU, AND K. H. NORWICH

The Department of Physiology and the Computer Centre of the University of Ottawa, Ottawa, Ontario, Canada, the Department of Systems Engineering, Carleton University, Ottawa, Ontario, Canada and the Department of Physiology of the University of Toronto, Canada

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Based on a model of the experimentally validated glucoregulatory system operating in the normal dog, an automatic control system has been developed that restores and maintains the normal concentration of glucose in blood in nonanesthetized pancreatectomized dogs. The relative success of the experiments largely validates the model of the disturbed glucoregulatory system.

INTRODUCTION

A system capable of reaching and holding an elevated blood glucose level in normal dogs, a "glucose clamp," has been described earlier (Norwich *et al.*, 1975). This system is based on a model of the canine glucoregulatory system, a model which relates the rates of hepatic glucose release and overall glucose utilization to the changes in glucose concentration in the blood. Clamping is achieved by continuously monitoring the concentration of glucose in blood, and using the accumulated information every 7 min to calculate and (re-) set the optimal glucose infusion rate. The optimal glucose infusion rate is that constant rate which, if maintained, would produce the desired elevated level of glucose in the blood. The equations defining the glucose clamp, which are designed to operate in normal dogs, lack a function which explicitly relates endogenous insulin release to the concentration of glucose in blood. Such a function is contained implicitly by the two parameters which characterize the model.

The purpose of the experiments to be described here is to develop an automatic system that is capable of reducing the elevated blood glucose level in diabetic dogs to a set point (e.g., the normal level) and to hold it there by the infusion of insulin or glucose at calculated rates. Evidently, an automatic system is required in such an equation, explicitly relating the required exogenous insulin infusion rate to the other variables, blood glucose concentration, time, etc. Only to this extent were the equations of the "glucose clamp" modified. The introduction of the insulin infusion rate into our equations necessitates the addition of an associated third parameter. This third parameter, too, must be updated during the course of the experiment since, with increasing amounts of

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infused insulin, the insulin sensitivity of the diabetic dog is expected to increase.

We emerge, then, with a complete, nonisomorphic or "lumped parameter" (Sheppard, 1962) model of the glucoregulatory system of the nonanesthetized dog; a model which is validated to the extent by which it permits the control of blood glucose levels.

METHODS AND MATERIALS

Thirteen experiments were carried out on nine pancreatectomized mongrel dogs weighing between 9.9 and 17.8 kg. The pancreas was removed under aseptic conditions as described by Markowitz *et al.* (1959) at least 8 days before the experiment. The dogs were kept on injections of 5–12 U of protamine zinc insulin per day to keep glycosuria below 1%. A pancreatic extract (Pancreatin, Fisher Scientific) was added to their diet. The injections of insulin were discontinued 60–72 hr prior to an experiment. On the day of the experiment the average blood glucose level of the animals was 2.60 mg/ml, ranging from 1.73 to 3.38 mg/ml. All animals were trained to stand quietly in a Pavlov stand during the experiment.

The method for the continuous monitoring of blood glucose has been described earlier (Norwich *et al.*, 1975). The conversion of blood glucose to plasma glucose concentration was omitted and the calculation of the values of the model parameters were based on blood glucose concentration directly.

In the early experiments the operation of the system was semiautomatic; i.e., the readings from the Auto-Analyzer were manually transmitted to the computer and the infusion pumps were set manually to the rate calculated by the computer. In later experiments the output from the Auto-Analyzer was transmitted directly to the computer. The output of the computer was converted by a digital–analog converter and was used to set the rate at which a Harvard pump (infusion–withdrawal pump Model 950) delivered glucose when required. The infusion of insulin was given by a Sage pump set manually to the rate requested by the computer.

An IBM 360/65 computer has been used to carry out the necessary computations. The method of the transmissions of information to and from the computer has been described (Norwich *et al.*, 1975).

THEORY

It was shown as a result of many experiments performed in normal, fasted dogs that the effect of an intravenous glucose infusion is to produce a change in glucose pool, $V(dC/dt)$, which is described for the hyperglycemic state (very nearly) by the differential equation

$$V(dC/dt) = A + BC + R_g, \tag{1}$$

where V is the volume of distribution of glucose, C is the plasma glucose concentration, A and B are constants, $A > 0$ and $B < 0$, and R_g is the rate of exogenous glucose infusion.

It seemed reasonable, therefore, that when insulin was being infused intravenously into a pancreatectomized dog, the rate of change of the glucose pool should be approximated by an equation of the form

$$V(dC/dt) = A + BC + \epsilon \cdot |R_i|^Q, \tag{2}$$

where R_i is the rate of insurion of insulin and $|R_i|$ is the absolute value of R_i, ϵ is a constant, always less than zero, which relates the rate of insulin infusion to the rate of change of glucose concentration. Q is some exponent, taken variously at 1.0, 2.0, or 3.0, and the value of Q has been decided arbitrarily prior to the experiment and has not been altered during its course. Since R_i will be related approximately to the Qth root of $(A + BC)/\epsilon$ (in Eq. (2)), insulin will be infused at a relatively higher rate if blood glucose is much above the set point. Lesser deviations will call for a disproportionally smaller rate of insulin infusion. The overall effect of selecting $Q > 1$ will be discussed. For ease in computation (see Appendix A) we chose R_i as a negative quantity.

For convenience let us represent both Eqs. (1) and (2) by

$$V(dC/dt) = A + BC + R, \tag{3}$$

where R may be either R_g or $\epsilon \cdot |R_i|^Q$.

The experiments were begun by arbitrarily defining a "set point" or desired blood glucose level (80 mg/dl in all the experiments to be reported), by infusing insulin at a known but arbitrary rate, and reading blood glucose at intervals of 7 min. Thus, six readings spanned 35 min and we call this period a "window." Equation (3) was solved or integrated (see Appendix A), and by fitting the integrated form to the experimental concentration–time curve over the window, numerical values for the parameters A, B, and ϵ were obtained. The question was then asked: What types of infusion, if applied steadily, would reduce (or raise) the blood glucose level smoothly and progressively to the set point? Calculation of this desired infusion rate is quite simple. When blood glucose is held constant at the set point C_s, the derivative on the left-hand side of Eq. (3) vanishes and we are left with the equation

$$R = -(A + BC_s). \tag{4}$$

If $(A + BC_s)$ is greater than zero, R must then be negative, and the magnitude of the insulin infusion required is found by replacing R in Eq. (4) by $\epsilon \cdot |R_i|^Q$ and solving algebraically for R_i. In the experiments the rate R_i was not allowed to exceed -2000 mU/min. If the calculated value of R_i was above this, the computer automatically set $R_i = -2000$ mU/min. If $(A + BC_s)$ is less than zero, R must then be positive, and the magnitude of the glucose infusion required is found by replacing R in Eq. (4) by R_g and solving algebraically for R_g. Theoretically, one should not require a glucose infusion for control. But very frequently we found that some initial overloading with insulin did occur, and a compensatory glucose infusion was required.

Each 7 min a new reading is taken, the 35-min window is advanced 7 min, the curve fitting procedure is repeated, and a revised estimate for R is obtained. In

TABLE 1

Summary of 13 Experiments

Experiment	Time limits (min) of set point recorded	Concentration attained ($\bar{C}$) (mg/dl)[a]	SD (±)	Regression coefficient (C vs t)
22	84–154	74	17.0	+0.532
23	49–154	81	22.0	+0.530
24	84–154	71	12.9	−0.164
25	70–133	107	5.6	+0.118
26	70–168	78	5.8	+0.094
30	35–168	90	14.9	+0.144
31	77–196	100	13.0	+0.016
32	42–210	82	16.4	+0.035
33	77–154	76	4.8	+0.0035
35	245–301	100	13.1	−0.636
36	168–224	68	7.1	−0.124
37[b]	157–220	76	3.0	−0.118
38	161–259	78	12.3	−0.344

[a] The attained concentration of glucose in plasma, $\bar{C}$, was calculated as the mean of successive readings made at 7-min intervals between the time limits shown in column 2. The set point was 80 mg/dl in all experiments.

[b] Values for blood glucose concentrations transmitted to the computer at irregular intervals because of technical problems.

this way the blood glucose level is guided steadily to the set point. The mathematical and computational details are given in the Appendices.

RESULTS

Table 1 presents the summary of the experiments. The set point, 80 mg/dl has been approximated within ±10 mg/dl in 9 out of the 13 experiments completed. In the remaining 4 a plateau was attained at 68, 100, 100, and 107 mg/dl. The standard deviation of the blood glucose concentrations taken at 7-min intervals during the plateau varied between 3.0 and 22.0 mg/dl. No significant regression was found in the concentration vs time curve in any experiment, indicating that a true plateau in the concentration of blood glucose had been reached.

Figures 1 and 2 show two typical experiments. Figure 3 shows the variations in the values of the parameters A, B, and $\log \epsilon$ in the experiment shown on Fig. 1. The relatively long time required to reach the set point in some experiments (e.g., #35 and #37) was due to the relative insensitivity to insulin of these animals. Thus relatively large amounts of insulin had to be infused which, because of the constraint of R_i (maximal) = −2000 mU/min slowed down the attainment of the set point. Two experiments had to be abandoned because of the breakdown of the computer and a third one because of other technical difficulties. No reference to these experiments is made in Table 1.

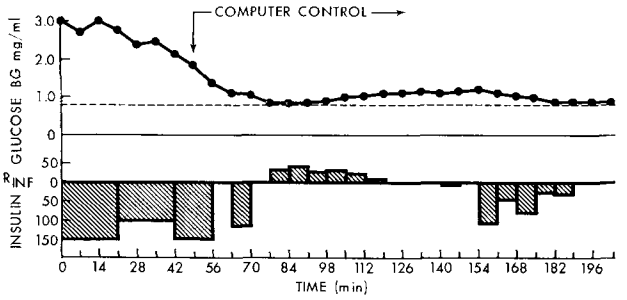

FIG. 1. Changes in blood glucose concentration and rates of glucose or insulin infusion in experiment #31 on Table 1. Abscissa time in minutes. Upper ordinate: concentration of blood glucose (milligrams per milliliter). Lower ordinate: The rates of glucose infusions (milligrams per minute) shown above the zero line and the rates of insulin infusions (mU/min) below the zero line. The interrupted line on the upper panel represents the set point.

DISCUSSION

If the closeness of the agreement between the set point and the level of blood glucose attained is a measure of the validity of the model, the current computer controlled glucoregulator involves a less precise model of the system than the "glucose clamp" (Norwich *et al.*, 1975). In the case of the glucose clamp the parameters of the model could be clearly related either to the rate of overall glucose utilization (R_d) or to the rate of the hepatic glucose production (R_a). Furthermore, since blood glucose was raised in the experiment, reducing R_a to near zero, the model involved only R_d and its two associated parameters. The model underlying the glucoregulator is less precisely defined. In Eq. (1), A has the dimensions of a rate (milligrams glucose per minute), B that of a metabolic clearance (milliliters per minute), while R_g and $\epsilon \cdot |R_i|^Q$ have similar dimensions to A. In a dynamic steady state ($dC/dt = 0$) maintained in a diabetic dog by an infusion of insulin but no glucose, A can be associated with R_a and $BC + \epsilon|R_i|^Q$ associated with R_d. This latter notation is of interest since it distinguishes be-

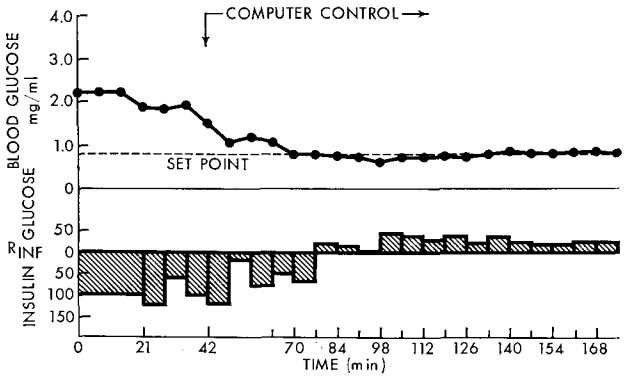

FIG. 2. Changes in blood glucose concentration and rates of glucose or insulin infusions in experiment #26 in Table 1. See legend to Fig. 1.

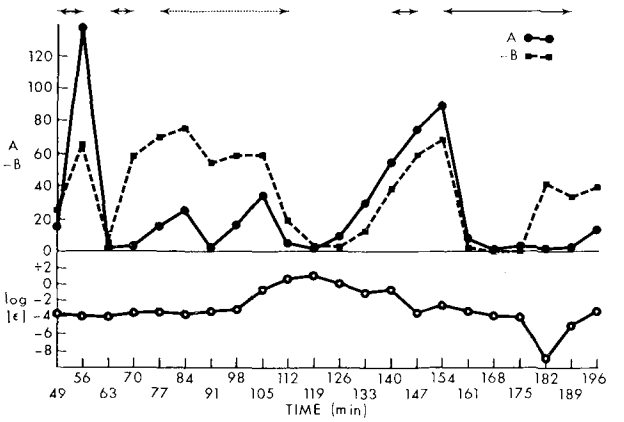

FIG. 3. The changes in the values of the three parameters A, B, and ϵ of Eq. (2). Q was set to 3. Abscissa: time (minutes). Top arrows indicate the periods of glucose (dotted line) or insulin (continuous line) infusions. Upper panel: A (○—○) and B (■- - -■). The panel is log $|\epsilon|$.

tween two components of R_d: one, BC, brought about by the mass action of glucose level in the blood, the other $\epsilon \cdot |R_i|^Q$ as dependent on insulin released into the circulation. These two components of glucose utilization were originally incorporated into Bolie's early model of blood glucose regulation (Bolie, 1961). Experimental support for this concept may be found in the published literature (Hetenyi, 1971). It does not follow rigorously, however, that under such or any circumstances A is indeed equal to R_a or that a true value for R_d, let alone its components, can be calculated from C_t, as is possible with the "glucose clamp." Indeed the three parameters in Eqs. (1) and (2) are just a set of figures that when applied to the model approximately predict R_i or R_g necessary to keep a steady $\bar{C}$ at the set point.

A few weaknesses in the construction of the model are apparent: (a) No true allowance for the delayed effect of insulin is made. Because of its effect on the synthesis of some enzymes, insulin is expected to alter the insulin sensitivity of the diabetic animal in the later phases of the experiment. Such changes in insulin sensitivity are of course reflected in the changes of A, B, and especially ϵ. Setting $Q > 1$ provides some crude compensation for this effect of insulin. Nevertheless it would improve the precision of the model if such changes could be predicted quantitatively. For example, the integral of the insulin infused from $t = 0$ to t could be used as a similar predictor in the calculation of ϵ. The relative success of the experiments on dogs of different insulin sensitivity proves the empirical worth of the equations. (b) Imagine that in some phase of the experiment dC/dt becomes very small; i.e., a plateau is reached at a blood glucose level above or below the set point with R transiently equal to zero. In such a case the computer will continue to recommend a value for R equal to zero (see Appendix B). Hence no infusion is given and C tends to stay constant. Such hang-ups may last quite some time and are resolved usually when dC/dt becomes positive, when as a rule the model calculates a large R_i and breaks the deadlock. This in turn may result in undershooting the set point. Serious hypoglycaemia, however, is pre-

vented by setting the maximal $R_i = -2000$ mU/min (see "Theory"). Nevertheless a considerable delay in attaining the set point can occur, as in, for example, experiment #35. (c) Could more frequent sampling result in improved accuracy? The perhaps surprising answer is: not likely. Sampling at too frequent intervals would lead to attempts to correct for very small changes in C by frequently altering R_g and R_i. Evidently an optimal sampling frequency exists but no attempt was made to find it for this system. The computer controlled glucoregulator has *not* been designed to bring down the concentration of glucose in the plasma to a set point *rapidly*. No attempt was made to introduce factors of "optimization" into the calculated value of R_i or R_g (Pontriagin *et al.*, 1962). Any increase in the speed of attainment of the set point by such means increases the risk of untoward gross hypoglycaemia if the parameters of the model are wrongly estimated. The *safety* of the design described in avoiding the possibility of hypoglycaemia is related to its relative slowness.

The earliest successful attempts to hold a desired level of glucose concentration in blood, worked on the principle of injecting an amount of insulin and restoring the set point by a variable infusion of glucose (Kadish, 1964; Kline *et al.*, 1968). When the concentration of glucose surpassed the set point, another fixed amount of insulin was injected. In these experiments "insulin was used as an error input used to activate the glucose feedback trigger by creating a hypoglycemic condition and not as an opposite corrective factor to glucose" (Kline *et al.*, 1968). Pfeiffer *et al.* (1974) used a system which infused glucose or insulin according to the deviation of blood glucose from the set point and the rate of change of blood glucose concentration with time (proportional plus derivative control).

The "artificial pancreas" (Albisser *et al.*, 1974) has been constructed for the purpose of an automatic maintenance of a near normal blood glucose level in diabetic patients. The purpose of our experiments, in contradistinction to the above, was to test on diabetic dogs, a model of the canine glucoregulatory system by putting it into control of variable insulin and glucose infusions. This difference in purpose between the two groups of investigators accounts for the differences in the performance of the controlling devices. The "artificial pancreas" uses a smaller computer than the IBM 360/65 used in our experiments. We were able to reach the set point faster and hold it more precisely than reported for the "artificial pancreas," but our experiments were of much shorter duration than those reported by Albisser *et al.* (1975) on humans. None of the control systems previously described by others worked on an adaptive principle in which the individual subject is modeled in order to adjust the system automatically.

APPENDIX A

The differential equation $V(dc/dt) = A + BC + R$ (Eq. (3)) was integrated to give $C(t)$, the blood glucose concentration at any time, t, in terms of some fixed value $C(t_n)$, the concentration at time t_n. Integrating (3) we obtain

$$C(t) = C(t_n)e^{-(B/V)(t_n-t)} + [(A + R)/B][e^{-(B/V)(t_n-t)} - 1]. \qquad (A.1)$$

The function $C(t)$ was fitted to the experimental data points over a 35-min

window with the fixed point $C(t_n)$ taken as the final (most recent) point in the window. In this way, the fitted curve was constrained to pass through the most recent data point. The curve fitting was carried out initially using the computer searching technique described by Hazelrig *et al.* (1963) using a minimum sum of squares deviations criterion. Beginning with experiment #32, curve fitting was executed using Zangwill's (1967) modification of Powell's optimization program, which required substantially less execution time.

The 35-min "window" over which the curve fitting took place contained six sample points. Each of the six sample points consisted of a set of three measured values for time, t, concentration, C, and infusion rate, R. The variable R represents either an insulin infusion $\epsilon \cdot |R_i|^Q$ or glucose infusion R_g. Therefore some of the six sample points may have contained values for R_i and some may have contained values for R_g. We entered all R_g values as positive numbers and all R_i values as negative numbers, so the computer would "know" whether insulin or glucose was being infused at a given time. If glucose was given throughout an entire window (six data points), function (A.1) was fitted with $R = R_g$, and the parameters A and B only (not ϵ) were optimized. If, however, insulin was infused at one or more of the six data points, function (A.1) was curve fitted with $R = \epsilon \cdot |R_i|^Q$ or $R = R_g$, each over the appropriate time interval, and all three parameters A, B, and ϵ were optimized. This distinction was necessary when using the swifter Powell–Zangwill algorithm, although not with the slower searching process described in our previous paper.

APPENDIX B

The Problem Associated with a Transient Plateau in Blood Glucose Concentration

Suppose that glucose concentration levels off temporarily at some value C_p when infusion rate R_p is equal to zero. The problem is that instead of instituting a nonzero value of R immediately, the computer will replicate the situation of $R = 0$. This is for the following reason. Setting $dC/dt = 0$ and $R = 0$ in Eq. (4),

$$A + B \cdot C_p = 0,$$

or

$$C_p = -A/B. \tag{B.1}$$

Comparing Eqs. (B.1) and (1) we see that they are compatible only if A, $B \to 0$. The recommended (or set) value of the rate of infusion, R, is obtained from Eq. (4) as

$$R = -(A + BC_s),$$

where C_s is the set point. But A and B are very small, so that the computer sets

$$R = 0; \tag{B.2}$$

which is quite inappropriate. The deadlock will be broken because in the absence of any exogenous infusion the blood glucose level has to rise sooner or later in a diabetic animal. Thus the "plateau" at C_p is destroyed and $R < 0$ is set by the

computer. The situation could be avoided by introducing a design to recognize the presence of a plateau at a level different from the set point, and in such case set B to any level other than zero and solve Eq. (B.1) for A.

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