Mathematical modeling of the unsteady state glucose and insulin concentrations in blood for normal subjects and diabetics

Tung Shih
New Jersey Institute of Technology

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MATHEMATICAL MODELING OF THE UNSTEADY STATE GLUCOSE AND INSULIN CONCENTRATIONS IN BLOOD FOR NORMAL SUBJECTS AND DIABETICS

BY

TUNG SHIH

A THESIS
PRESENTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE IN CHEMICAL ENGINEERING AT
NEW JERSEY INSTITUTE OF TECHNOLOGY

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Newark, New Jersey
1983
APPROVAL OF THESIS

MATHEMATICAL MODELING OF THE UNSTEADY STATE GLUCOSE AND INSULIN CONCENTRATIONS IN BLOOD FOR NORMAL SUBJECTS AND DIABETICS

BY

TUNG SHIH

FOR

DEPARTMENT OF CHEMICAL ENGINEERING

BY

FACULTY COMMITTEE

APPROVED: ____________________________

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NEWARK, NEW JERSEY

APRIL, 1983
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Permanent address:

Degree and date to be conferred: Master of Science, 1983

Date of birth:

Place of birth:

Secondary education: Feng Chia University, 1977

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Major: Chemical Engineering
Title of thesis: Mathematical Modeling of The Unsteady State Glucose and Insulin Concentrations in Blood for Normal Subjects and Diabetics

Name: Tung Shih, Master of Science

A mathematical model of the blood-glucose regulatory system has been developed. This model describes an oral glucose tolerance test adequately and simulates the behavior of the real physiological system using computer techniques.

Regression of the rate constants involved have been effected by conforming the theoretical functions to the data from glucose tolerance test in nonobese normal subjects, obese normal subjects, nonobese mild diabetics, obese mild diabetics, nonobese moderate diabetics and obese moderate diabetics measured by continuous sampling after oral ingestion. Most of the data were conformed within the limits of experimental error. The result of optimal parameters lead to a criterion for separating normal subjects from mild diabetics and moderate diabetics.

The significance of the model conformation is discussed in view of the goals of modeling and the extension of knowledge of blood-glucose mechanism in the human body.
ACKNOWLEDGMENTS

Deep appreciation and thanks are extended to my advisor, Dr. C. R. Huang, whose assistance and guidance were invaluable and helped make this thesis a reality.

The assistance of Dr. Kristol for searching the literature is acknowledged.

The author would like to thank Mr. Bill Snyder Jr. for his help of setting up this research model.

Also the author is especially grateful to his wife, May, for her encouragement and assistance in the preparation of this thesis.
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CHAPTER I
INTRODUCTION

Studies of blood glucose dynamics have attracted the interest of persons with a variety of backgrounds. Glucose plays a 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, criterion, regulation, and control of blood glucose levels are an essential function of the organism.

The body's ability to maintain blood glucose at a relatively constant concentration results from the complex interrelationships between carbohydrate, lipid, and protein-metabolism and various hormones. For the past several years, several various simulations of the blood glucose regulatory system have been performed. Mathematical models of such a complex system represents an abstraction and a lumping of many parameters into a relatively small number of empirically determinable ones. The significance of the model conformation to glucose metabolism is discussed in view of kinetic dynamics and process control. In 1961, V. Bolie suggested a one-compartment model to illustrate the mathematical relationship between the kinetics of glucose and of insulin in plasma. In 1964, E. Ackerme et. al. effectively adopted Bolie's model and by the judicious selection of a mathematical
function to simulate gastro-intestinal absorption endeavoured to apply the model clinically in the interpretation of the oral glucose tolerance test.

Ackerme's model gives a general valuation of the glucose-tolerance curve for diagnostic purpose than the morphological or semiquantitative criteria employed. Current physiologic knowledge about glucose-insulin homeostasis in liver, brain, pancreas, kidney, peripheral tissues, and central vascular organs has been synthesized to form more accurate dynamics. So, we attempt to develop a mathematical model to include all available knowledge as possible and to map this in a fashion which can represent the overall action of the system. The model developed here is a set of simultaneous nonlinear differential equations which cannot be solved analytically.

In our theoretical investigation we had three aims in view,

1. To develop criteria (by the parameters of the model) to distinguish the difference between normal and abnormal responses.

2. To find out how much information could be extracted from the results of the test data as it is often carried out clinically.

3. To model and extend the knowledge of blood glucose dynamics that enable us to understand the physiological mechanism and control system.

Indeed, our initial interest arose from a desire to combine the blood-glucose levels during the oral glucose-
tolerance test in a kinetic model which would lead to a criterion for separating normals from diabetics.

The results support the hypothesis that the natural period measured can be used to distinguish health from disease. The success of our mathematical model to distinguish the losing function of the dynamic mechanism between normals and diabetics through the judgment of parameters leads to determine the physiological sensitivity domination. It is quite possible that such a criterion might have clinical utility.
CHAPTER II
DEVELOPMENT OF THE MATHEMATICAL MODEL

In originally selecting a mathematical model, the criteria used included simplicity and agreement with experimental oral glucose-tolerance data both in magnitude and form. In the oral glucose-tolerance test, the subject eats a large dose of glucose. The fasting concentration of blood glucose is measured before the glucose is administered. Models for glucose and insulin distribution in man were developed. These are referred to as the Ackerman et al., 1964 and Norwich et al., 1969 respectively. In addition these, a book by W. F. Ganong named "Review of Medical Physiology" describe the mechanism of glucose and insulin in chapter 19. Figure 1 depicts in the form of a block diagram the response of the body to added glucose. It is further apparent that these are interlocked in a feedback loop, thereby making oscillations possible. The diagram contain 16 physiological parameters, a few of which are uncertain. However, this number 16 is a minimum quantities since one would like to indicate, for example, a different rate of glucose utilization in each tissue and also the roles of other hormones and of the nervous system. The basic assumptions used in formulating this overall description of the blood-glucose regulatory system are simplifications of known interactions between glucose, insulin, and other regulatory hormones to take explicit
account of the role of the adrenal cortical and medullary function in glucose economy and of the heterogeneity of pancreatic insulin.

In chemicals and in physical mechanics, the technique of lumping parameters has proved very useful. Figure 2 presents a system of our model in which the parameters of Figure 1 have been lumped into two dependent variables, \(G\) and \(I\), seven rate constants. The blood-glucose level \(G\) can be increased either by glucose from the intestines or intravenous source, or by release of glucose from the liver. The blood-glucose level is decreased by removal of glucose by the liver or other tissues of storage or metabolism. The insulin \(I\) is assumed to promote the effect of accelerating glucose depletion. The simultaneous nonlinear differential equations of which imply the lumped parameters for blood glucose and insulin concentration are

\[
\frac{d(G)}{dt} = -K_1(G)(I) - K_2(G) + K_3 + M_1(t)
\]  

(1)

\[
\frac{d(I)}{dt} = -K_4(I) + K_5(I) + M_2(t)
\]  

(2)

\(G\) = Glucose concentration
\(I\) = Insulin concentration
\(K_1(G)(I)\) = Mass transfer of glucose to peripheral tissue which is dependent of insulin. This is a nonlinear term.
\(K_2(G)\) = Average rate of glucose transfer to brain or to red cells which is independent of insulin.
$K_3$ = A constant of average rate of release of glucose into blood plasma from tissue or liver, (if $G$ is much lower than the fasting glucose concentration $G_0$, the extra glucose may be added by breaking down of glycogen in liver or tissue)

$M_1(t) = \text{Input of glucose from glucose-insulin adsorption (gastro-intestinal), and}$

$$M_1(t) = \begin{cases} 1.8 & 0 \leq t \leq t_1 \\ 0 & t_1 < t \end{cases}$$

t_1 : \text{The time at which glucose concentration is maximum.}$

$K_4(I) = \text{Mass transfer of insulin removal which is independent of glucose due to breakdown in plasma by enzyme in 7 to 10 minutes.}$

$K_5(G) = \text{Extra secretion of release of insulin due to glucose by a feedback mechanism coming from pancreas.}$

$$M_2(t) = \begin{cases} K_6 + K_7 & 0 \leq t \leq t_1 \\ K_6 & t_1 < t \end{cases}$$

Where $K_6$ represents insulin coming from $\beta$-cells of pancreas to maintain constant influx of insulin and $K_7$ represents a feedback due to step input of $M_1(t)$.

So, we can therefore express equations (1) and (2) as:

(a) During oral glucose input or meal, $0 \leq t \leq t_1$

$$\frac{d[G]}{dt} = -K_1(G)(I) - K_2(G) + K_3 + 1.8 \quad (3)$$

$$\frac{d[I]}{dt} = -K_4(I) + K_5(G) + K_6 + K_7 \quad (4)$$
(b) After a step function of glucose input, \( t_1 < t \)

\[
\frac{d[G]}{dt} = -K_1[G][I] - K_2[G] + K_3 \tag{5}
\]

\[
\frac{d[I]}{dt} = -K_4[I] + K_5[I] + K_6 \tag{6}
\]

There are few important notes we should discuss here:

1. Glucose metabolizes by cycles in tissue (i.e. kerbs, glycolysis, etc.), so we assume that no disappearance due to reaction in plasma.
2. Assuming \( M_1(t) \) as a step function.
3. Assuming \( I \) in equal with \( I \) ads which is adsorbed on the surface of tissue especially on the liver.

There is wide variation in the values assumed by the rate constants. These parameters in general fall into the "physiological" range and are all positive as required. Accordingly, \( K_1 \) represents the lumped effect of the change of liver set-point for glucose absorption and of the change of the rate of glucose removal by the other tissues due to change in insulin. Similarly, \( M_2 \) represents the tendency of the system to return the blood glucose concentration towards its fasting value. \( K_3 \) represents the extra glucose secretion to keep the fasting glucose level. \( K_4 \) represents the tendency of the system to return the net insulin towards the fasting value. \( K_5 \) represents the lumped effects of the stimulation of the endocrine system protection of insulin from metabolic removal. The constants \( K_3, K_6, \) and \( K_7 \) are already explained previously.
Figure 1. Block-diagram representation of feedback loop involved in glucose tolerance test. Question mark indicate uncertain reactions.
- $K_4(I)$; insulin breakdown in plasma by enzyme in 7-10 minutes.

$K_5(G)$; extra secretion of insulin by a feedback mechanism coming from pancreas.

$K_6$; insulin coming from $\beta$-cells of pancreas to maintain constant influe of insulin.

$K_7$; feedback mechanism due to step input of $M_1(t)$

$M_1(t)=1.8$; input of glucose from glucose-insulin adsorption (gastro-intestinal).

$K_1(G)(I)$; glucose transfer to the tissue (insulin dependence).

$K_2(G)$; glucose to brain or to red cells (non-insulin dependence).

$K_3$; average rate of release of glucose into blood plasma from the tissue or the liver.

Figure 2. Simplified block diagram representation of the mechanism of glucose tolerance test.
CHAPTER III
EXPERIMENTS AND CURVE FITTING

Glucose tolerance tests are well-known examples of experiments 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. (Gatewood et. al., 1968)

In the oral glucose test, the subjects eat normal meals for several days, as extreme diets can affect the results. After an overnight fast, a blood sample is drawn. This is the zero time taken as the instant of cessation of loading. The subject then drink a glucose-enriched drink and several intermittent blood samples are obtained at 0, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes afterward. The data published by H. S. Seltzer and colleagues who desired quantitative comparison of oral and intravenous glucose administration in different kinds of subjects. The glucose and insulin concentrations were classified in Table 1 and 2. This test reveals the functioning of the overall physiological system, but abnormalities detected may be due to the patterns of intestinal glucose absorption.

After we set up the mathematical model, the first goal is data description. If we use parameters of our model to reduce a mass of data to a small number of constants which
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TABLE 2
Blood insulin concentrations during oral glucose tolerance test

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</table>

μU/ml

Normal subjects

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<tr>
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<th>40</th>
<th>93</th>
<th>111</th>
<th>129</th>
<th>122</th>
<th>103</th>
<th>93</th>
<th>89</th>
<th>70</th>
<th>52</th>
<th>45</th>
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<td>±7</td>
<td>±8</td>
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<td>±14</td>
<td>±16</td>
<td>±15</td>
<td>±8</td>
<td>±8</td>
<td></td>
</tr>
</tbody>
</table>

Obese(11)

| Mean | 33 | 68 | 137 | 193 | 269 | 274 | 216 | 199 | 160 | 117 | 72 | 33 |
| SEM  | ±2 | ±14| ±16 | ±18 | ±37 | ±35 | ±39 | ±37 | ±31 | ±23 | ±18 | ±4 |

Mild diabetics

<table>
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<tr>
<th>Nonobese(10)</th>
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<th>9</th>
<th>27</th>
<th>67</th>
<th>113</th>
<th>138</th>
<th>195</th>
<th>233</th>
<th>228</th>
<th>178</th>
<th>140</th>
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<th>61</th>
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<td>SEM</td>
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<td>±21</td>
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<td>±39</td>
<td>±31</td>
<td>±36</td>
<td>±34</td>
<td>±27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Obese(11)

| Mean | 22 | 38 | 77 | 116 | 155 | 165 | 200 | 200 | 202 | 181 | 167 | 158 | 138 |
| SEM  | ±2 | ±5 | ±8 | ±15 | ±20 | ±30 | ±27 | ±23 | ±20 | ±19 | ±17 |     |     |

Moderate diabetics

<table>
<thead>
<tr>
<th>Nonobese(7)</th>
<th>Mean</th>
<th>19</th>
<th>20</th>
<th>27</th>
<th>28</th>
<th>54</th>
<th>59</th>
<th>95</th>
<th>103</th>
<th>89</th>
<th>91</th>
<th>65</th>
<th>49</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEM</td>
<td>±5</td>
<td>±4</td>
<td>±11</td>
<td>±10</td>
<td>±18</td>
<td>±16</td>
<td>±25</td>
<td>±29</td>
<td>±32</td>
<td>±28</td>
<td>±20</td>
<td>±17</td>
<td></td>
</tr>
</tbody>
</table>

Obese(7)

| Mean | 19 | 20 | 36 | 47 | 55 | 69 | 102 | 99 | 111 | 94 | 78 | 62 |     |
| SEM  | ±7 | ±4 | ±11 | ±13 | ±17 | ±16 | ±33 | ±30 | ±27 | ±27 | ±17 | ±15 |     |
are more amenable to human discussion, then the application of the model serves a real purpose. This activity, sometimes referred to as curve fitting, was the initial approach of this thesis to models of blood glucose dynamics. For this purpose one asks that the selected model be capable of predicting curves which pass within the limits of experimental error of the observed values. The second goal which we looked for in the studies of our model of the blood glucose regulation is the possibility of using the derived parameters for diagnostic classification. 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.

Because our model is nonlinear differential equations, we cannot solve the equations analytically. So the fourth order Runge-Kutta method is used to integrate our nonlinear differential equations and gets the glucose and insulin concentrations for every minute. Then we use the least square curve fitting procedure with the Rosenbrock Hillclimb regression program to get the optimal parameters of the model.

The computer program used an iterative guessing technique which required initial guesses for $K_1$ to $K_7$. These parameters were adjusted by the computer until the cumulative sum of the squares of the derivation between the data points and the calculated points was a minimum.

The regression algorithm of Rosenbrock's theory varied all seven of the parameters in the neighborhood of the first
guess. The best neighboring point was then selected for the second guess, and so forth. When a given point was found to yield a lower cumulative square deviation than its neighbors, the step-sizes to the neighboring points were reduced and the entire process reiterated. When the step-size became sufficiently small, the process was terminated.

In this fashion the program always found an estimated set of values for the parameters yielding a least-square fit between the model and the data. It is needed to emphasize here, the initial guess of the parameters and the step-sizes is very important and very sensitive. Because in a case of bad guess, the program might converged to a local minimum with a large cumulative squared deviations, or the program was overflow, but suitable initial guesses enabled the model to be successfully conformed to all the data. On the other hand, a too large value of a step-size will lead to an overflow quickly due to the integration subroutine. We have to choose a suitable step-size in consistency with the size of the parameters which we guessed by trial. The optimization procedures are the most difficult part of this thesis.

The fitted parameters, which could then be used to describe each response qualitatively, and the glucose and insulin concentrations were printed out. Figure 3 to Figure 14 show the calculated curves and the data points. Most of the theoretical values were conformed within the limits of experimental error. The fitting of obese normal and nonobese mild diabetics have some small deviations between the simu-
lated curves and the actual data. These situations can be improved by a modified model.

All the parameters were checked for last twenty regression values to see if the parameters converge on the constant value eventually. The results of checking every parameter on every case show that the parameters do converge on the steady values (Appendix B).
FIG. 3. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on nonobese normals.
FIG. 4. Conformation of the mathematical model (curve) to data (points) obtained during an oral glucose tolerance test of insulin concentration on nonobese normals.
FIG. 5. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on obese normals.
FIG. 6. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on obese normals.
FIG. 7. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on nonobese mild diabetics.
FIG. 8. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on non obese mild diabetics.
FIG. 9. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on obese mild diabetics.
FIG. 10. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on obese mild diabetics.
FIG. 11. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on nonobese moderate diabetics.
FIG. 12. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on nonobese moderate diabetics.
FIG. 13. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of glucose concentration on the obese moderate diabetics.
FIG. 14. Conformation of the mathematical model (curves) to data (points) obtained during an oral glucose tolerance test of insulin concentration on obese moderate diabetics.
CHAPTER IV
RESULTS AND DISCUSSION

The result of the optimal parameters show the change of dynamic mechanisms from normals to diabetics. The final result are discussed as follow:

(I) Case of non-obese normal, non-obese mild diabetics and non-obese moderate diabetics

From Table 3, we can determine that:

(1) $K_1$ increases for diabetics. This means the glucose mass transfer, which is dependent on insulin, is higher in diabetics than in normals. On the other hand, since the diabetics have an insufficient supply of insulin, the high level glucose concentration thus goes to the tissue. Also, the difference of $K_1$ in these three cases is not very significant; therefore, it will not effect the mechanism much.

(2) $K_2$ decreases from normals to moderate diabetics. This is the reason why diabetics tire more easily than normals. Because the smaller the $K_2$ is the less glucose transfer to the brain or to the red cells, especially for mild diabetics.

(3) $K_3$ increases as the diabetic condition becomes more serious. From the mechanics, it shows the average rate of release of glucose to blood from liver or tissue was increased. It makes the diabetics have
more glucose in the blood plasma than in the normals due to abnormal release of glucose.

(4) $K_4$ is decreased from normals to moderate diabetics. This shows the rate of insulin breakdown in plasma by enzyme in diabetics is lower than in normals. If $K_4$ is small, as compared with normals, the metabolism of glucose in plasma will be slowed down and causes the concentration of glucose to increase steadily.

(5) $K_5$ decreased from top to bottom in Table 3 indicates that the diabetics do not get sufficient secretion of insulin by a feedback mechanism coming from the pancreas as normals. Therefore, the diabetics cannot metabolize the glucose in plasma by using the extra secretion from the pancreas.

(6) Table 3 also shows that mild diabetics have the largest value for $K_6$. This is a very special situation for us, because it show that mild diabetics secrete a lot of insulin from $\beta$-cells to maintain constant influe of insulin. This phenomena called hyperinsulinemia is due to the nature response of human body for attempting to keep the glucose concentration at normal level. For normals, they do not need more insulin secretion from $\beta$-cell because other mechanisms work in the normal conditions.

(7) $K_7$ is extremely high in the normal case. We can say that the feedback mechanism which, due to $M_1(t)$
step input, is very sensitive for normals and not for moderate diabetics. Since the feedback mechanism does not work well in diabetics, the diabetics will not be able to metabolize the glucose very effectively.

TABLE 3
Non-obese normal (A), Non-obese mild diabetics (B), and Non-obese moderate diabetics (C)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$K_1$</th>
<th>$K_2$</th>
<th>$K_3$</th>
<th>$K_4$</th>
<th>$K_5$</th>
<th>$K_6$</th>
<th>$K_7$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x10^{-5}</td>
<td>x10^{-4}</td>
<td>x10^{-1}</td>
<td>x10^{-2}</td>
<td>x10^{-2}</td>
<td>x10^{-3}</td>
<td>x10^{-2}</td>
</tr>
<tr>
<td>A</td>
<td>3.59</td>
<td>6.57</td>
<td>0.28</td>
<td>6.18</td>
<td>6.39</td>
<td>0.0096</td>
<td>159.81</td>
</tr>
<tr>
<td>B</td>
<td>4.90</td>
<td>2.03</td>
<td>5.40</td>
<td>4.17</td>
<td>5.49</td>
<td>1.01</td>
<td>2.44</td>
</tr>
<tr>
<td>C</td>
<td>5.84</td>
<td>3.39</td>
<td>9.35</td>
<td>2.99</td>
<td>0.96</td>
<td>0.16</td>
<td>3.83</td>
</tr>
</tbody>
</table>

(II) Case of Obese normal, Obese mild diabetics, and Obese moderate diabetics

For obese case, the general discussions of the dynamic mechanisms are almost the same as we have discussed for non-obese case. However, we note that $K_2$ does not follow the tendency of decrement. $K_2$ in mild diabetics is higher than in moderate diabetics. This means the transportation rate of glucose to the red cells in mild diabetics is faster than in moderate diabetics. The other significant changes are $K_4$, $K_6$, and $K_7$. On the contrary, the non-obese normals and the obese normals have a lower breakdown rate of insulin by enzyme than
the obese mild diabetics. And, the parameter $K_6$ shows the obese normals have the highest hyperinsulinemia situation in all cases. Since $K_7$, the feedback mechanism to secrete the insulin, is much smaller in obese people than in non-obese people, we can say that the obese people have more glucose than the non-obese people in blood. Also, from the value of $K_6$, it seems that the efficiency of $\beta$-cells secretion in moderate diabetics cannot work out well.

**TABLE 4**

Parameter of Obese normal (D), Obese mild diabetics (E), and Obese moderate diabetics (F)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$K_1$</th>
<th>$K_2$</th>
<th>$K_3$</th>
<th>$K_4$</th>
<th>$K_5$</th>
<th>$K_6$</th>
<th>$K_7$</th>
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</thead>
<tbody>
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<td></td>
<td>x10^{-5}</td>
<td>x10^{-4}</td>
<td>x10^{-1}</td>
<td>x10^{-2}</td>
<td>x10^{-2}</td>
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<tr>
<td>D</td>
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<td>4.31</td>
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<td>4.10</td>
<td>7.94</td>
<td>6.62</td>
<td>266.85</td>
</tr>
<tr>
<td>E</td>
<td>3.52</td>
<td>3.40</td>
<td>6.06</td>
<td>4.27</td>
<td>4.81</td>
<td>5.72</td>
<td>84.86</td>
</tr>
<tr>
<td>F</td>
<td>4.74</td>
<td>3.09</td>
<td>7.08</td>
<td>2.94</td>
<td>0.99</td>
<td>0.047</td>
<td>38.37</td>
</tr>
</tbody>
</table>

(III) Case of Non-obese normal and Obese normal

The obese normals transfer less glucose to the tissue or to the red cells than the non-obese normal. The average rate of release of glucose into the blood from the liver are same for both subjects. In regard to the insulin, the insulin breakdown rate by enzyme decreases, and the insulin coming from $\beta$-cells or feed-
back mechanism increases for the obese people. The large difference in $K_6$ and $K_7$, between non-obese normal and obese normal, proves that large accumulation of insulin which comes from $\beta$-cells or feedback mechanism by $M_4(t)$ exists in obese normals. Totally, we might say that the obese normals have more glucose and insulin than the non-obese normals.

TABLE 5
Parameters of Non-obese normal (A) and Obese normal (D)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$K_1$</th>
<th>$K_2$</th>
<th>$K_3$</th>
<th>$K_4$</th>
<th>$K_5$</th>
<th>$K_6$</th>
<th>$K_7$</th>
</tr>
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<tbody>
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<td>$x10^{-1}$</td>
<td>$x10^{-2}$</td>
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<td>$x10^{-2}$</td>
</tr>
<tr>
<td>A</td>
<td>3.59</td>
<td>6.57</td>
<td>0.28</td>
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<td>6.39</td>
<td>0.0096</td>
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<tr>
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<td>4.10</td>
<td>7.94</td>
<td>6.62</td>
<td>266.85</td>
</tr>
</tbody>
</table>

(IV) Case of Non-obese mild diabetics and Obese mild diabetics

From Table 6, we see that $K_2$ in obese mild diabetics is larger than in non-obese diabetics. So, the transfer of glucose to the red cells will be larger in the obese case than in the non-obese case. $K_5$ shows that the extra secretion of insulin from pancreas in obese mild diabetics is less than in non-obese mild diabetics. These are different from the normal people. Generally, we may have the following discovery:

(1) Mild diabetics have the hyperinsulinemia phenomena
because of the body response for attempting to lower the glucose concentration.

(2) There are no differences in the rate of insulin breakdown by enzyme between non-obese mild diabetics and obese diabetics.

(3) Mild diabetics have the ability to metabolize the extra glucose which is caused by the abnormal mechanisms of $K_3$, $K_4$, $K_5$, and $K_7$.

TABLE 6

Parameters of Nonobese mild diabetics (B) and Obese mild diabetics (E)

<table>
<thead>
<tr>
<th>Subjects</th>
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<th>$K_2$ (x10⁻⁴)</th>
<th>$K_3$ (x10⁻¹)</th>
<th>$K_4$ (x10⁻²)</th>
<th>$K_5$ (x10⁻²)</th>
<th>$K_6$ (x10⁻³)</th>
<th>$K_7$ (x10⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>4.90</td>
<td>2.03</td>
<td>5.40</td>
<td>4.17</td>
<td>5.49</td>
<td>1.01</td>
<td>2.44</td>
</tr>
<tr>
<td>E</td>
<td>3.52</td>
<td>3.40</td>
<td>6.06</td>
<td>4.27</td>
<td>4.80</td>
<td>5.72</td>
<td>84.86</td>
</tr>
</tbody>
</table>

(V) Cases of Non-obese moderate diabetics and Obese moderate diabetics
Since the moderate diabetics in serious condition, Table 7 shows that there are no differences in $K_2$, $K_3$, $K_4$, and $K_5$ between the nonobese and the obese. All these mechanisms are under abnormal conditions. $K_7$ in the nonobese mild diabetics is larger than in the nonobese moderate diabetics. That is due to the total effects from $K_2$, $K_4$, $K_5$, $K_6$ on $K_7$. The $K_4$ in nonobese is larger
than obese. This is different from normal and mild diabetics cases. Thus, it means that non-obese moderate can get more insulin from $\beta$-cells than obese moderate diabetics. Therefore, we can conclude that the obese moderate diabetics are in the worst condition.

TABLE 7

Parameters of Non-obese moderate diabetics (C) and Obese moderate diabetics (F)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$K_1$</th>
<th>$K_2$</th>
<th>$K_3$</th>
<th>$K_4$</th>
<th>$K_5$</th>
<th>$K_6$</th>
<th>$K_7$</th>
</tr>
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<td>$10^{-1}$</td>
<td>$10^{-2}$</td>
<td>$10^{-3}$</td>
<td>$10^{-2}$</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>5.84</td>
<td>3.39</td>
<td>9.35</td>
<td>2.99</td>
<td>9.55</td>
<td>1.63</td>
<td>3.83</td>
</tr>
<tr>
<td>F</td>
<td>4.74</td>
<td>3.09</td>
<td>9.08</td>
<td>2.94</td>
<td>9.91</td>
<td>0.47</td>
<td>38.36</td>
</tr>
</tbody>
</table>

(VI) The research studies by Drs. Judith and Richard Wurtman shows low-carbohydrate diets are doomed to fail for many overweight people because they upset a chemical regulator in the brain that triggers a craving for sweet, bread and starches. When someone eats carbohydrates, insulin is release into the blood. This raises the body's level of an amino acid called tryptophan. In the brain, tryptophan is used to manufacture a chemical called serotonin. This, in turn, turns off the hunger for carbohydrates.

Referring the research done by Drs. Judith to our model, we find the obese normal subjects have the most
strong appetite for carbohydrates after a diet because they have the highest value of $K_5$ for extra secretion of insulin by a glucose feedback mechanism.
## TABLE 8
Summary of optimal parameters for different cases

<table>
<thead>
<tr>
<th>Subjects</th>
<th>$K_1$</th>
<th>$K_2$</th>
<th>$K_3$</th>
<th>$K_4$</th>
<th>$K_5$</th>
<th>$K_6$</th>
<th>$K_7$</th>
<th>Max. Time (G) of (I)</th>
<th>Max. Time (G) of (I)</th>
<th>mg/Max. uU/ml Max. 100ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonobese normals (21)</td>
<td>3.59</td>
<td>6.57</td>
<td>0.28</td>
<td>6.18</td>
<td>6.39</td>
<td>0.0096</td>
<td>159.81</td>
<td>118</td>
<td>32</td>
<td>120</td>
</tr>
<tr>
<td>Obese normals (11)</td>
<td>3.07</td>
<td>4.31</td>
<td>0.27</td>
<td>4.10</td>
<td>7.94</td>
<td>6.62</td>
<td>266.85</td>
<td>130</td>
<td>45</td>
<td>253</td>
</tr>
<tr>
<td>Nonobese mild diabetics (10)</td>
<td>4.90</td>
<td>2.03</td>
<td>5.40</td>
<td>4.17</td>
<td>5.49</td>
<td>1.01</td>
<td>2.44</td>
<td>188</td>
<td>74</td>
<td>217</td>
</tr>
<tr>
<td>Obese mild diabetics (11)</td>
<td>3.52</td>
<td>3.40</td>
<td>6.06</td>
<td>4.27</td>
<td>4.81</td>
<td>5.72</td>
<td>84.86</td>
<td>200</td>
<td>80</td>
<td>222</td>
</tr>
<tr>
<td>Nonobese moderate diabetics (7)</td>
<td>5.84</td>
<td>3.39</td>
<td>9.35</td>
<td>2.99</td>
<td>0.96</td>
<td>0.16</td>
<td>3.83</td>
<td>305</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Obese moderate diabetics (7)</td>
<td>4.74</td>
<td>3.09</td>
<td>7.08</td>
<td>2.94</td>
<td>0.99</td>
<td>0.047</td>
<td>38.37</td>
<td>320</td>
<td>104</td>
<td>105</td>
</tr>
</tbody>
</table>
CHAPTER V

CONCLUSIONS

The mathematical model presented has been a successful and effective way to average the measure point into several parameters. Through the comparison of parameters, it has enabled diagnostic classification, hypothesis testing, and extension of knowledge of blood glucose dynamics for normals and diabetics.

It is believed that this research can be utilized to determine the effect on the different designed parameters of the glucose dynamics and also can help to characterize quantitatively disease states; the model need not even produce an acceptable description of the empirical data.
CHAPTER VI

RECOMMENDATIONS

Some terms of the mathematical model represented can be modified as follows:

(1) $K_1(G)(I)$ should be $K_1(G)(I)_{ads}$ which $(I)_{ads}$ is the concentration of insulin adsorbed on the surface of tissue.

(2) If $(G)$ is much lower than the fasting glucose concentration $(G_0)$, $K_3$ will not be a constant. $K_3$ should increase faster than a constant when $(G)-(G_0)$ is a large negative quantity.

(3) The step function $M_1(t)$ should be modified as a distribution function.

(4) $K_4(I)$ should be modified as $K_4(I)(Enzyme)$. $(Enzyme)$ may be a function of time and follows the Michaelis-Menten kinetics.

(5) $K_5(G)$ can be expressed as $K_5((G)-(G_0))$ or a feedback control model.

(6) If $(I)$ is much lower than the fasting insulin concentration $(I_0)$, $K_6$ should increase faster than a constant.

(7) The same studies can be developed for thyroid gland and iodine balance.
APPENDIX A

OPTIMIZATION PROGRAM FOR NONLINEAR SIMULTANEOUS EQUATIONS

REAL LC
INTEGER PR
INTEGER P
INTEGER R
INTEGER C

DIMENSION XX(10,10), XCEN(10,10), XREF(10,10),
IZ(10), XCEN(10,10), XEX(10,10)
DIMENSION X(10), E(8), V(8,8), S(8), B(8), G(8),
H(8), AL, B(8), PH(8), A(8,8), B(8,8), EX(8), DA(8),
VV(8,8), EINT(8), VM(8), Y(10)

COMMON EXP(50,50), TR(50)
DATA ITMAX, IPRINT, L, ALFA, BETA, GAM, ACC, A
/40, 10, 7, 1.0, 0.5, 2.0, 0.01, 0.0001/
DATA M, P, LOOPY, PR, ND, NDATA, NSTEP /-1, 7, 7, 1,
11, 0, 0, 0/
READ (5, 35) (E(J), J = 1, L)
READ (5, 35) (XX(1,J), J = 1, L)
35 FORMAT (7F10.2)

DATA NVAR, NDATA /2, 24/
READ (5, 45) (Y(J), J = 1, NVAR)
45 FORMAT (2F10.1)

FORMAT (2F10.1)
READ (5, 43) (EXP(IL, 1), IL = 1, NDATA)
READ (5, 47) (EXP(IL, 2), IL = 1, NDATA)
43 FORMAT (8F10.1/8F10.1/8F10.1)
47 FORMAT (8F10.1/8F10.1/8F10.1)

NP1 = L+1
Q = (AA/(L*(2.**.5)))**((L+1.)**.5-1.)
P1 = (AA/(L*(2.**.5)))**((L+1.)**.5+L-1.)
MM = L+1
DO 139 I = 2, MM
AP = 1.0
DO 121 J = 1, L
AP = AP + 1
IF (I .EQ. AP) GO TO 135
XX(I, J) = XX(1, J) + Q
GO TO 121
135 XX(I, J) = XX(1, J) + P1
121 CONTINUE
139 CONTINUE
IF (ALFA .EQ. 0.) ALFA = 1.
IF (BETA .EQ. 0.) BETA = .5
IF (GAM .EQ. 0.) GAM = 2.
IF (ACC .EQ. 0.) ACC = 0.1
WRITE (6, 23)
23 FORMAT (1H1, 10X, 28HNEDELD AND MEAD OPTIMIZATION)
WRITE (6, 24)
24 FORMAT (/, 2X, 10H PARAMETERS)
WRITE (6, 25) L, ACC, ALFA, BETA, GAM
25 FORMAT (/, 2X, 25H NUM OF COEFF OPTIMIZED = , I2, 14X, 11H ACCURACY = , E10.4, /, 2X, 8H ALPHA = , E10.4, 4X, 8H BETA = , E10.4, 4X, 8H GAMMA = , E10.4)
WRITE (6, 29)
29 FORMAT (///, 10X, 16H STARTING SIMPLEX)
DO 141 I = 1, NP1
WRITE (6, 28) (I, J, XX(I, J), J = 1, L)
28 FORMAT (/, 4(2X, 2H X(I, J) = V(I), PE12.5))
141 CONTINUE
ITR = 0
DO 155 I = 1, NP1
CALL FUNC (I, XX, Z, Y, FNC)
155 CONTINUE
ITR = ITR + 1
IF (ITR .GE. ITMAX) GOTO 145
IF (IPRINT) 158, 162, 158
158 WRITE (6, 37) ITR
37 FORMAT (///, 2X, 17H ITERATION NUMBER, I3)
DO 161 J = 1, NP1
WRITE (6, 28) (J, I, XX(J, I), I = 1, L)
GO TO 162
161 WRITE (6, 28) (J, I, XX(J, I), I = 1, L)
GO TO 162
162 ZHI = AMAX1(Z(1), Z(2), Z(3), Z(4), Z(5), Z(6), Z(7), Z(8))
ZLO = AMIN1(Z(1), Z(2), Z(3), Z(4), Z(5), Z(6), Z(7), Z(8))
DO 165 I = 1, NP1
IF (ZHI .EQ. Z(I)) GOTO 171
165 CONTINUE
K = I
EN = L
DO 181 J = 1, L
SUM = 0.
DO 175 I = 1, NP1
IF (K .EQ. I) GOTO 175
SUM = SUM + XX(I, J)
175 CONTINUE
181 XCEN(K, J) = SUM / EN
I = K
CALL FUNC (I, XCEN, Z, Y, FNC)
ZCEN = Z(I)
SUM = 0.
DO 185 I = 1, NP1
IF (K .EQ. I) GOTO 185
SUM = SUM + (Z(I) - ZCEN) * (Z(I) - ZCEN) / EN
185 CONTINUE
EJ = SQRT(SUM)
IF (EJ .LT. ACC) GOTO 998
DO 191 J = 1, L
XREF(K, J) = XCEN(K, J) + ALFA*(XCEN(K, J) - XX(K, J))

CONTINUE
I = K
CALL FUNC (I, XREF, Z, Y, FNC)
ZREF = Z(I)
DO 200 I = 1, NP1
IF (ZLO .EQ. Z(I)) GOTO 205

200 CONTINUE

205 LL = I
IF (ZREF .LE. Z(LL)) GOTO 241
DO 207 I = 1, NP1
IF (ZREF .LT. Z(I)) GOTO 208
207 CONTINUE
GO TO 215

208 DO 211 J = 1, L
211 XX(K, J) = XREF(K, J)
GO TO 150

215 DO 221 J = 1, L
221 XCEN(K, J) = XCEN(K, J) + BETA*(XX(K, J) - XCEN(K, J))
I = K
CALL FUNC (I, XCEN, Z, Y, FNC)
ZCEN = Z(I)
IF (ZCEN .LT. Z(K)) GOTO 231
DO 225 J = 1, L
DO 225 I = 1, NP1
GO TO 150

231 DO 235 J = 1, L
235 XX(K, J) = XCEN(K, J)
GO TO 150

241 DO 245 J = 1, L
245 XEX(K, J) = XCEN(K, J) + GAM*(XREF(K, J) - XCEN(K, J))
I = K
CALL FUNC (I, XEX, Z, Y, FNC)
ZEX = Z(I)
IF (ZEX .LT. Z(LL)) GOTO 255
DO 251 J = 1, L
251 XX(K, J) = XREF(K, J)
GO TO 150

255 DO 261 J = 1, L
261 XX(K, J) = XEX(K, J)
GO TO 150

145 WRITE (6, 10) ITMAX
10 FORMAT (///, 10X, 20H 'DID NOT CONVERGE IN', 1I5, 11H ITERATIONS.)

998 WRITE (6, 39) ZLO
39 FORMAT (///, 2X, 21H 'OPTIMUM VALUE OF F = ', E16.8)
WRITE (6, 19)
19 FORMAT (///, 2X, 'OPTIMUM VALUE OF VARIABLE')
DO 301 I = 1, L

-41-
301 WRITE (6,26) I,XX(NP1,I)
26 FORMAT (/2X,2H(I2,4H) = ,1PE16.8)
   WRITE (6,21) EJ
21 FORMAT (/2X,'EJ = ',F10.5)
   DO 610 J=1,L
610 X(J)=XX(NP1,J)
   WRITE (6,13)
13 FORMAT (1H1,10X,'ROSENTHALE HILLCLIMB PROCEDURE')
C
C
   IF (ND-1) 30,20,30
20   DO 300 KA=1,NDATA
      READ (NI,2) DA(KA)
      2 FORMAT (1E10.4)
500 CONTINUE
C
30   LAP=PR-1
   LOOP=0
   ISW=0
   INIT=0
   KOUNT=0
   TERM=0.0
   DELY=0.001
   F1=0.0
   NPAR=NDATA
   N=L
   DO 40 K=1,L
40   AL(K)=(CH(X,DA,N,NPAR,K)-CG(X,DA,N,NPAR,K))*0.0001
   DO 60 I=1,P
      DO 60 J=1,P
         V(I,J)=0.0
      IF (I-J) 60,61,60
61      V(I,J)=0.0005
60 CONTINUE
   DO 65 KK=1,P
      EINT(KK)=E(KK)
65 CONTINUE
C
C
1000 DO 70 J=1,P
      IF (NSTEP .EQ. 0) E(J)=EINT(J)
      SA(J)=2.0
70     D(J)=0.0
     FBEST=F1
80     I=1
      IF (INIT .EQ. 0) GOTO 120
90     DO 110 K=1,P
110    X(K)=X(K)+E(I)*V(I,K)
     DO 50 K=1,L

-42-
50  \text{\textit{H}(\textit{K})=F_0}

\text{\textbf{C}}

120  \text{\textit{F1=F}(\textit{X},\textit{N},\textit{Y},\textit{FNC})}
\text{\textit{F1=M*F1}}
\text{IF (ISW .EQ. 0) F0=F1}
\text{ISW=1}
\text{IF (ABS(FBEST-F1)-DELY) 122,122,125}
122  \text{TERM=1.0}
\text{GO TO 450}
125  \text{CONTINUE}

\text{\textbf{C}}

\text{J=1}

\text{\textbf{C}}

130  \text{\textit{XC=\textit{CX}(\textit{X},\textit{DA},\textit{N},\textit{NPAR},\textit{J})}}
\text{\textit{LC=\textit{CG}(\textit{X},\textit{DA},\textit{N},\textit{NPAR},\textit{J})}}
\text{\textit{UC=\textit{CH}(\textit{X},\textit{DA},\textit{N},\textit{NPAR},\textit{J})}}
\text{IF (\textit{XC} .LE. \textit{LC}) GOTO 420}
\text{IF (\textit{XC} .GE. \textit{UC}) GOTO 420}
\text{IF (\textit{F1} .LT. \textit{FO}) GOTO 420}
\text{IF (\textit{XC} .LT. \textit{LC}+AL(J)) GOTO 140}
\text{IF (\textit{XC} .GT. \textit{UC}-AL(J)) GOTO 140}
\text{\textit{H(J)=F0}}
\text{GO TO 210}

\text{\textbf{C}}

140  \text{CONTINUE}

\text{\textbf{C}}

\text{\textit{BW=AL(J)}}

\text{\textbf{C}}

\text{IF (\textit{XC} .LE. \textit{LC} .OR. \textit{UC} .LE. \textit{XC})}
\text{GO TO 159}
\text{IF (\textit{LC} .LT. \textit{XC} .AND. \textit{XC} .LT. \textit{LC}+BW)}
\text{GO TO 160}
\text{IF (\textit{UC}-\textit{BW} .LT. \textit{XC} .AND. \textit{XC} .LT. \textit{UC})}
\text{GO TO 170}
\text{\textit{PH(J)=1.0}}
\text{GO TO 210}

\text{\textbf{C}}

159  \text{\textit{PH(J)=0.0}}
\text{GO TO 190}
160  \text{\textit{PW=(LC+BW-XC)/BW}}
\text{GO TO 180}
170  \text{\textit{PW=(XC-UC+BW)/BW}}
180  \text{\textit{PH(J)=1.0-\left(3.0*PW\right)+\left(4.0*PW*PW\right)-\left(2.0*PW*PW*PW\right)}}
\text{F1=H(J)+\left(F1-H(J)\right)*PH(J)}
C 210 CONTINUE
IF (J .EQ. L) GOTO 220
J=J+1
GO TO 130
C
220 INIT=1
IF (F1 .LT. FO) GOTO 420
D(I)=D(I)+E(I)
E(I)=3.0*E(I)
F0=F1
IF (SA(I) .GE. 1.5) SA(I)=1.0
C
230 DO 240 JJ=1,P
IF (SA(JJ) .GE. 0.5) GOTO 440
240 CONTINUE
C
C AXES ROTATION
C
DO 250 R=1,P
DO 250 C=1,P
250 VV(C,R)=0.0
DO 260 R=1,P
KR=R
DO 260 C=1,P
DO 265 K=KR,P
265 VV(R,C)=I(K)*V(K,C)+VV(R,C)
260 B(R,C)=VV(R,C)
BMAG=0.0
DO 280 C=1,P
BMAG=BMAG+(B(1,C)*B(1,C))
280 CONTINUE
BMAG=SQRT(BMAG)
BX(1)=BMAG
DO 310 C=1,P
310 V(1,C)=B(1,C)/BMAG
C
DO 390 R=2,P
C
IR=R-1
DO 390 C=1,P
SUMVM=0.0
DO 320 KK=1,IR
SUMAV=0.0
DO 330 KJ=1,P
330 SUMAV=SUMAV+VV(R,KJ)*V(KK,KJ)
320 SUMVM=SUMAV*V(KK,C)+SUMVM
390 B(R,C)=VV(R,C)-SUMVM
DO 340 R=2,P
BBMAG=0.0
DO 350 K=1,P
350 BBMAG=BBMAG+B(R,K)*B(R,K)
BBMAG=SQRT(BBMAG)
DO 340 C=1,P
340 V(R,C)=B(R,C)/BBMAG
LOOP=LOOP+1
LAP=LAP+1
IF (LAP .EQ. PR) GO TO 450
GO TO 1000
C
420 IF (INIT .EQ. 0) GOTO 450
DO 430 IX=1,P
430 X(IX)=X(IX)-E(I)*V(I,IX)
E(I)=-0.5*E(I)
IF (SA(I) .LT. 1.5) SA(I)=0.0
GO TO 230
C
440 CONTINUE
IF (I .EQ. P) GOTO 80
I=I+1
GO TO 90
C
450 WRITE (6,3)
3 FORMAT (//,2X,5HSTAGE,8X,8HFUNCTION,12X,
18HPROGRESS,9X,16HLATERAL PROGRESS)
WRITE (6,4) LOOP,F0,BMAG,BBMAG
4 FORMAT (1H,I5,3E20.8)
WRITE (6,14) KOUNT
14 FORMAT (/,2X,'NUMBER OF FUNCTION EVALUATIONS = ',I8)
WRITE (6,5)
5 FORMAT (/'2X,25HVALUES OF X AT THIS STAGE)
C
PRINT CURRENT VALUES OF X
C
WRITE (6,6) (JM,X(JM),JM=1,P)
6 FORMAT (/,2(2X,2HX(,I12,4H) = ,1PE14.6,4X))
C
LAP=0
IF (INIT .EQ. 0) GOTO 470
IF (TERM .EQ. 1.0) GOTO 480
IF (LOOP .GE. LOOPY) GOTO 480
GO TO 1000
C
470 WRITE (6,7)
7 FORMAT (///,2X,'THE START POINT MUST NOT VIOLATE')
480 CONTINUE
490 WRITE (6,8)
8 FORMAT (///,2X,'FINAL DIRECTION VECTOR MATRIX')
DO 500 J=1,P
500 WRITE (6,9) (J,I,V(J,I),I=1,P)
9 FORMAT (/,*2(2X,2HV(*,I2,1H, *I2,4H) = ,
       1F10.8,4X))
WRITE (*,11)
11 FORMAT (/,*2X,16HFINAL STEP SIZES)
WRITE (*,12) (J,E(J),J=1,P)
12 FORMAT (/,*2(2X,2HS(*,I1,4H) = ,F10.8,
       14X))
F7=F(X,N,Y,FNC)
DO 540 I=1,NDAT
   540 WRITE (*,17) TR(I),FNC(I,1),FNC(I,2)
   17 FORMAT (/,*2(,'T = ',F6.2,8X,
               'G = ',F7.2,8X,
               'I = ',F7.2)
STOP
END
FUNCTION F(XE,IA,Y,FNC)
DIMENSION XE(10),Y(10),G(10),FNC(50,50)
COMMON EXP(50,50),TR(50)
DATA NDAT,TMAX,H,KOUNT,NVAR,CMAX/24,240.,
       1.,0,2,75./
INTEGER RUNGE
T=0.
J=0.
SUM=0.
T1=0.
C CALL ON THE FOURTH-ORDER RUNGE-KUTTA NUMERICAL METHOD
   15 CALL RUNKU(RUNGE,2,Y,G,T,H)
C WHENEVER RUNGE=1 COMPUTE DERIVATIVE
   IF (RUNGE .NE. 1) GOTO 82
   IF (T-CMAX) 45,45,46
   45 G(1)=-(XE(1)*Y(1))*Y(2))-(XE(2)*Y(1))+XE(3)+1.8
   G(2)=-(XE(4)*Y(2))+(XE(5)*Y(1))+XE(6)+XE(7)
      GO TO 15
   46 G(1)=-(XE(1)*Y(1))*Y(2))-(XE(2)*Y(1))+XE(3)
   G(2)=-(XE(4)*Y(2))+(XE(5)*Y(1))+XE(6)
      GO TO 15
   82 IF (T-TMAX) 90,90,95
   90 DO 106 M=1,241,10
        T1=M-1.
        IF (T-T1) 15,53,106
   106 CONTINUE
   53 J=J+1
   TR(J)=T
   FNC(J,1)=Y(1)
   FNC(J,2)=Y(2)
      GO TO 15
   95 DO 100 IL=1,NDAT
        A1=EXP(IL,1)
        B1=FNC(IL,1)
        C1=(A1-B1)**2
        A2=EXP(IL,2)
        B2=FNC(IL,2)
   100 CONTINUE
C2=(A2-B2)**2
SUM=SUM+(C1+C2)
100 CONTINUE
F=SUM
 IF (KOUNT-25.) 120,140,140
140 WRITE (6,10) KOUNT
10 FORMAT (/,2X,'ITERATION NUMBER = ',I8)
WRITE (6,19) F
19 FORMAT (/,2X,'FUNCTION = ',F12.1)
WRITE (6,11) (J,XE(J),J=1,IA)
11 FORMAT (/,4(4X,2HX('I1,4H) = ,1PE14.6))
120 KOUNT=KOUNT+1
RETURN
END
FUNCTION CX (X,DA,N,NPAR,K)
DIMENSION X(N),DA(NPAR)
CX=X(K)
RETURN
END
FUNCTION CO (X,DA,N,NPAR,K)
DIMENSION X(N),DA(NPAR)
CG=0.0
RETURN
END
FUNCTION CH (X,DA,N,NPAR,K)
DIMENSION X(N),DA(NPAR)
GO TO (1,2,3,4,5,6,7),K
1 CH=X(1)*10.
   GO TO 9
2 CH=X(2)*10.
   GO TO 9
3 CH=X(3)*10.
   GO TO 9
4 CH=X(4)*10.
   GO TO 9
5 CH=X(5)*10.
   GO TO 9
6 CH=X(6)*10.
   GO TO 9
7 CH=X(7)*10.
9 RETURN
END
SUBROUTINE RUNKU(RUNGE,N1,Y,G,W,H2)
INTEGER RUNGE
DIMENSION PHI(50),SAVEY(50),Y(10),G(10)
DATA M1/0/
    M1=M1+1
GO TO (1,2,3,4,5),M1
1  RUNGE=1
   RETURN
2  DO 22 J=1,N1
   SAVEY(J)=Y(J)
   PHI(J)=G(J)
22  Y(J)=SAVEY(J)+0.5*H2*G(J)
    W=W+0.5*H2
    RUNGE=1
    RETURN
3  DO 33 J=1,N1
   PHI(J)=PHI(J)+2.0*G(J)
33  Y(J)=SAVEY(J)+0.5*H2*G(J)
    RUNGE=1
    RETURN
4  DO 44 J=1,N1
   PHI(J)=PHI(J)+2.0*G(J)
44  Y(J)=SAVEY(J)+0.5*H2*G(J)
    W=W+0.5*H2
    RUNGE=1
    RETURN
5  DO 55 J=1,N1
55  Y(J)=SAVEY(J)+(PHI(J)+G(J))*H2/6.
    M1=0
    RUNGE=0
    RETURN
END
SUBROUTINE FUNC (I,XX,Z,Y,FNC)
DIMENSION XX(10,10),Z(10),F(10),Y(10),FNC(50,50)
COMMON EXP(50,50),TR(50)
DATA NDAT,TMAX,H,NVAR,CMAX/24,240.,1.,2,75./
INTEGER RUNGE
X1=XX(I,1)
X2=XX(I,2)
X3=XX(I,3)
X4=XX(I,4)
X5=XX(I,5)
X6=XX(I,6)
X7=XX(I,7)
T=0.
J=0
SUM=0.
T1=0.
C CALL ON THE FOURTH-ORDER RUNGE-KUTTA NUMERICAL METHOD
15 CALL RUNKU(RUNGE,2,Y,F,T,H)
C WHENEVER RUNGE=1 COMPUTE DERIVATIVE VALUE
IF (RUNGE .NE. 1) GOTO 82
IF (T-CMAX) 45, 45, 46
45  \( F(1) = -(X1*Y(1)*Y(2)) - (X2*Y(1)) + X3 + 1.80 \)
    \( F(2) = -(X4*Y(2)) + (X5*Y(1)) + X6 + X7 \)
    GO TO 15
46  \( F(1) = -(X1*Y(1)*Y(2)) - (X2*Y(1)) + X3 \)
    \( F(2) = -(X4*Y(2)) + (X5*Y(1)) + X6 \)
    GO TO 15
82 IF (T-TMAX) 90, 90, 95
90  DO 106 M=1,241,10
    T1=M-1.
    IF (T-T1) 15,53,106
106 CONTINUE
53  J=J+1
    TR(J)=T
    FNC(J,1)=Y(1)
    FNC(J,2)=Y(2)
    GO TO 15
95  DO 100 L=1,NDAT
    A1=EXP(L,1)
    B1=FNC(L,1)
    C1=(A1-B1)**2
    A2=EXP(L,2)
    B2=FNC(L,2)
    C2=(A2-B2)**2
    SUM=SUM+(C1+C2)
100 CONTINUE
Z(I)=SUM
RETURN
END
FIG. 15. The last twenty values of $X_1$ of nonobese normal subjects.
FIG. 16. The last twenty values of $K_2$ of nonobese normals.
FIG. 17. The last twenty values of $K_3$ of nonobese normal subjects
FIG. 18. The last twenty values of $K_4$ of nonobese normal subjects.
FIG. 19. The last twenty values of $K_5$ of nonobese normal subjects.
FIG. 20. The last twenty values of $K_6$ of nonobese normal subjects.
FIG. 21. The last twenty values of $K_7$ of nonobese normal subjects.
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