DYNAMIC ANALYSIS OF MATHEMATICAL MODEL OF GLUCOSE, INSULIN CONCENTRATION, AND BETA SELECT CYCLES OF DIABETES MELLITUS DISEASE

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ABSTRACT

This study examines the relationship between the components of glucose (G), insulin (I) and beta cells (β) in the body by looking at the genetic predisposition (ϵ). The three components are very important for the body. The body requires glucose from food which is then converted into energy and partially stored in muscle or liver. Excess glucose in the blood will be balanced by insulin from beta cells in the pancreas.
The focus studied is the dynamic analysis of the three components. The benefit of this research is know the stability behavior for glucose, insulin and beta cells. The results of this study obtained an equilibrium point consisting of three things: the point of pathological equilibrium, susceptible to disease and physiological. And stability analysis is consist of stable and unstable. And the behavior of glucose, insulin and beta cells of the model can be known through phase and simulation fields. For further research is expected to analyze the model by changing the initial value.

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1. INTRODUCTION

One of the diseases of human metabolic disorders due to the pancreas does not produce enough insulin or the body can not use effectively produced insulin is diabetes mellitus. On this issue there is competition between glucose (G), insulin (I) and beta cells (β). The body requires glucose from food to be converted into energy and partly stored in muscle or liver. Insulin acts to balance glucose in the blood. This insulin production occurs by beta cells.
From the above exposure interesting to analyze the behavior of the three components namely glucose, insulin and beta cells. The three components are interrelated and change based on time so it can be said as a system. One tool to assess the behavior of this system is a mathematical analysis with dynamic system so that can be known stability for this system. Research on diabetes mellitus has been widely practiced, one of which is Topp, et al, (2000) that model the dynamics of glucose, insulin and beta cells. The model incorporates the Bergman et al, (1979) model that only models glucose and insulin. And there are also other scientists Boutayeb, et al, (2014) who developed the Topp model and only research on mathematical models by looking at the effects of genetic predisposition (ε) in diabetes. This study attempted to analyze the behavior of mathematical models of glucose, insulin, and beta cells. The model refers to Boutayeb, et al, (2014).

2. RESEARCH METHOD

Linier and Nonlinier Differential Equation System

The linear differential equation is a one-dimensional differential equation in the free variable and its derivatives, the differential equation in the form:

$$a_n(x)\frac{d^n y}{dx^n} + a_{n-1}(x)\frac{d^{n-1}y}{dx^{n-1}} + \cdots + a_1(x)\frac{dy}{dx} + a_0(x)y = f(x) \quad (1)$$

Defined $a_0, a_1, \ldots, a_n$ and $f(x)$ are continuous functions and the first coefficients $a_n(x) \neq 0, \forall x \in I$. According to the above definition, equation (2.1) is a linear differential equation, since it is a single rank in the free variable and its derivative (Waluyo, 2006). While the non linear differential equation is a differential equation whose variables are interrelated. The system of non linear or linear differential equations is a nonlinear or linear equation consisting of more than one interrelated equation.

Equilibrium Point

The fixed point of a mapping $T: M \rightarrow M$ of a set M on itself is a $m \in M$ point mapped to itself by that mapping. In other words fixed by the mapping T and denoted as follows: $Tm = m$ (Musta'adah, 2004). The balanced state of population growth or the number of ordinary cells is called the equilibrium point. Equilibrium point is a solution that remains constant despite the time of change. Then the equilibrium point of the above equation is obtained if $dx / dt = 0$. The other terms of equilibrium point are equilibrium point, fixed point, stationary point, rest point, singularity, critical point, or steady state.

Linierisasi

To find the linear result of nonlinear differential equation system can use Jacobian matrix (Maryam, 2009).

$$\text{Jacobian} = \begin{pmatrix} \frac{\partial \mathrm{k}_1}{\partial \mathrm{x}_1} & \frac{\partial \mathrm{k}_2}{\partial \mathrm{x}_2} & \cdots \frac{\partial \mathrm{k}_\mathrm{m}}{\partial \mathrm{x}_\mathrm{n}} \\ \vdots & \vdots & \cdots \vdots \\ \frac{\partial \mathrm{k}_\mathrm{m}}{\partial \mathrm{x}_1} & \frac{\partial \mathrm{k}_\mathrm{m}}{\partial \mathrm{x}_2} & \cdots \frac{\partial \mathrm{k}_\mathrm{m}}{\partial \mathrm{x}_\mathrm{n}} \end{pmatrix} \quad (2)$$

The advantage of the Jacobian method is a simple settlement step compared to the inverse and determinant matrix and method of L-U composition, while its limitation is the slow iteration process. Especially for high-order linear equations. This method can only be used to solve high-order homogeneous equations that satisfy the equation

Eigen Value and Eigen Vector

If A is matrix $n \times n$, so a vector is not zero x at R^n called eigen vector from A. If Ax is a scalar multiple of x, that is $Ax = \lambda x$. Scalar λ called eigen value from A and x called eigen vector associated with λ (Anton, 2004). To obtain the eigen values of matrix A sized $n \times n$ then write back $Ax = \lambda x$ as $Ax = \lambda\, I\, x$ or euivalently $det(A - \lambda I)x = 0$.

Stability Analysis

According to Finnizio and Ladas, the determination of fixed point stability can be obtained by looking at its eigenvalues, ie $\lambda_i, i = 1,2,3, \ldots, n$ obtained from the characteristic equation of A, is $(A - \lambda I) = 0$. The stability of the fixed point and the type of stability based on the eigenvalues resulting from the characteristic equation. Fixed point conditions have two states that are stable and unstable. Stability is a very common term to describe the dynamics of a system not experiencing turbulence (Ladas, 1988).

Phase Portrait

Behavior of the system of differential equations can be seen from the direction field, orbit and phase field / phase portrait of the system. A collection of all orbits or in other words the portrait phase is also a projection of the solution graph in the xy-plane. In phase portrait also given directed arrow. To analyze the system is needed is to know the eigenvalues and eigennya vector. So it will be known the stability and behavior of the mathematical model (Barnes & Fulford, 2002).

3. RESULTS AND DISCUSSION

Description of the Mathematical Model

The mathematical model used in this thesis is taken from the journal *Boutayeb, et al* (2014:331-332). The variables used are as follows:

$G(t)$: The amount of glucose on time t (mg/dl)

$I(t)$: The amount of insulin concentration on time t $(\mu U/ml)$

$\beta(t)$: The amount of beta cell on time t (mg)
The following parameters used in the formation of mathematical models are also taken from the journal *Boutayeb, et al* (2014):

Table 1 Table parameter values Boutayeb,et al (2014)

Parameter	Information	Value	Unit
a	Glucose production rate by liver when $G = 0$	864	$\frac{mg}{dl \cdot d}$
b	Glucose clearance rate independent of insulin	1.44	$\frac{1}{d}$
c	Insulin induced glucose uptake rate	0.72	$\frac{ml}{\mu U \cdot d}$
δ	Beta cell maximum insulin secretory rate	43.2	$\frac{\mu U}{ml.mg \cdot d}$
e	Gives inflection point of sigmoidal function	20,000	$\frac{mg^2}{dl^2}$
f	Whle body insulin clearance rate	432	$\frac{1}{d}$
g	Beta cell natural death rate	0.06	$\frac{mg}{d}$
h	Determines beta cell glucose tolerance range	0.00084	$\frac{dl}{mg \cdot d}$
i	Determines beta cell glucose tolerance range	0.0000024	$\frac{dl^2}{mg^2 \cdot d}$
K	Environment capacity	900	mg
r	Growth rate of the beta cell	0.01	$\frac{1}{d}$
α	Inverse of half saturation constant	0.01	$\frac{dl}{mg}$

The mathematical model used This is taken from the journal *Boutayeb, et al.* (2014: 331-332), as follows:

$$\begin{aligned} \frac{dG(t)}{dt} &= a - bG(t) - \frac{cI(t)G(t)}{\alpha G(t) + 1} \\ \frac{dI(t)}{dt} &= \delta\beta(t)\frac{G(t)^2}{e + G(t)^2} - fI(t) \\ \frac{d\beta(t)}{dt} &= (1-\epsilon)r\beta(t)\left(1 - \frac{\beta(t)}{K}\right) + \epsilon(-g + hG(t) - iG(t)^2)\beta(t) \end{aligned} \quad (3)$$

Stability Analysis of Mathematical Model
System will reach a point of equilibrium if $dG(t)/dt = 0$, $dI(t)/dt = 0$, $d\beta(t)/dt = 0$. When the fixed point is obtained the rate of growth of each equation will remain. With a kat else there are many changes in the existing concentration in the equation system. In this case it will obtain some equilibrium points seen from the genetic predisposition (ϵ). If $\epsilon = 1, 0.5$ defined as a genetic predisposition. While $\epsilon = 0$ because there is no genetic predisposition. To search equilibrium point which was first held $f(x) = 0$, as follows:

$$0 = a - bG(t) - \frac{cI(t)G(t)}{\alpha G(t) + 1} \quad (4)$$

$$0 = \delta\beta(t)\frac{G(t)^2}{e + G(t)^2} - fI(t) \quad (5)$$

$$0 = (1-\epsilon)r\beta(t)\left(1 - \frac{\beta(t)}{K}\right) + \epsilon(-g + hG(t) - iG(t)^2)\beta(t) \quad (6)$$

Here is the equilibrium point table of the system of equations by substituting the parameters in table (1) when ϵ= 0, 0.5, dan $\epsilon = 1$. Where ϵ is a value that shows a genetic predisposition.

Under the system of equations above, we can see the first step to get a fixed point on glucose, insulin concentration and beta cells for diabetes mellitus. The initial step will be done to get a point of equilibrium is out of the equation (6), as follows:

$$\begin{aligned} 0 = \quad & (1-\epsilon)r\beta(t)\left(1-\frac{\beta(t)}{K}\right)+\epsilon(-g+hG(t)-iG(t)^2)\beta(t) \\ 0 = \quad & \beta(t)\left((1-\epsilon)r\left(1-\frac{\beta(t)}{K}\right)+\epsilon(-g+hG(t)-iG(t)^2)\right) \end{aligned} \tag{7}$$

From equation (7) is obtained

$$\beta(t) = 0 \tag{8}$$

or

$$(1-\epsilon)r\left(1-\frac{\beta(t)}{K}\right)+\epsilon(-g+hG(t)-iG(t)^2) = 0 \tag{9}$$

Equation (7) obtain an equilibrium point that beta cells $\beta(t) = 0$ in equation (8) and $\beta(t) \neq 0$ corresponding in equation (9). So the first step is to substitute $\beta(t) = 0$ in equation (5). hen we will get the equilibrium point of glucose and insulin at the moment $\beta(t) = 0$ without a genetic predisposition, as follows:
Equilibrium point $I(t)$, then obtained

$$\begin{aligned} 0 = \quad & \delta\beta(t)\frac{G(t)^2}{e+G(t)^2}-fI(t) \\ 0 = \quad & \delta(0)\frac{G(t)^2}{e+G(t)^2}-fI(t) \\ 0 = \quad & 0-fI(t) \\ 0 = \quad & I(t) \end{aligned} \tag{10}$$

Then substitute the equation (10) in equation (4) untuk mencari titik tetapto find fixed point $G(t)$, then it can be written as follows:

$$\begin{aligned} 0 = \quad & a-bG(t)-\frac{cI(t)G(t)}{\alpha G(t)+1} \\ 0 = \quad & a-bG(t)-\frac{c(0)G(t)}{\alpha G(t)+1} \\ 0 = \quad & a-bG(t)-0 \\ bG(t) = \quad & a \\ G(t) = \quad & \frac{a}{b} \end{aligned} \tag{11}$$

Based on the description, then generated the first fixed point that is

$$\begin{aligned} & G(t) = \frac{a}{b} \\ & I(t) = 0 \\ & \beta(t) = 0 \end{aligned} \tag{12}$$

Then the resulting fixed point as follows: $\{G(t), I(t), \beta(t)\} = \{a/b, 0,0\}$.
Table 2 Point Equilibrium Mathematical Model Glucose, Insulin Concentration, and Mass cycle Beta cells

Genetic Predisposition (ϵ)	Equilibrium Point (Glucose (mg/dl), Insulin($\mu U/ml$), Mass Beta cell (mg))
Absence of Genetic Predisposition ($\epsilon = 0$)	$T_1(600, 0, 0)$ $T_2(82.6, 23, 900)$
The existence of Genetic Predisposition ($\epsilon = 0.5$)	$T_1(600, 0, 0)$ $T_2(271.23, 8.9, 114.45)$ $T_3(93.67, 20.93, 686.51)$
The existence of Genetic Predisposition ($\epsilon = 1$)	$T_1(600, 0, 0)$ $T_2(250, 9.8, 129.36)$ $T_3(100, 20, 600)$

Having obtained a fixed point or equilibrium point at the time of value $\epsilon = 0, 0.5,$ and $\epsilon = 1$. Furthermore, stability analysis is performed around fixed point with the following procedure.

1. Determine the Jacobian matrix of the system of equations with value:
2. Determine the Jacobian matrix of the system of equations with value.
3. Determine the eigenvalues (λ), by solving the characteristic equation $\det(J - \lambda I) = 0$.

To determine the Jacobian matrix then linear the system of equations first. Suppose that equation (3) to the equation (5) is written as follows:

$$\begin{aligned} A &= a - bG - \frac{cIG}{\alpha G + 1} \\ B &= d\beta \frac{G^2}{e + G^2} - fI \\ C &= (1 - \epsilon) r\beta \left(1 - \frac{\beta}{K}\right) + \epsilon(-g + hG - iG^2)\beta \end{aligned} \quad (13)$$

To determine the Jacobian matrix then linear the system of equations first, is written as follows:

$$J = \begin{pmatrix} \frac{\partial A}{\partial G} & \frac{\partial A}{\partial I} & \frac{\partial A}{\partial \beta} \\ \frac{\partial B}{\partial G} & \frac{\partial B}{\partial I} & \frac{\partial B}{\partial \beta} \\ \frac{\partial C}{\partial G} & \frac{\partial C}{\partial I} & \frac{\partial C}{\partial \beta} \end{pmatrix} \quad (14)$$

$$J = \begin{pmatrix} -b - \frac{cI}{\alpha G + 1} + \frac{c\alpha GI}{(\alpha G + 1)^2} & -\frac{cG}{\alpha G + 1} & 0 \\ \frac{2\delta\beta G}{G^2 + e} - \frac{2\delta\beta G^3}{(G^2 + e)^2} & -f & \frac{\delta G^2}{G^2 + e} \\ \epsilon(-2iG + h)\beta & 0 & s \end{pmatrix} \quad (15)$$

where $s = (1 - \epsilon) r \left(1 - \frac{\beta}{k}\right) - \frac{(1-\epsilon) r\beta}{k} + \epsilon(-iG^2 + hG - g)$

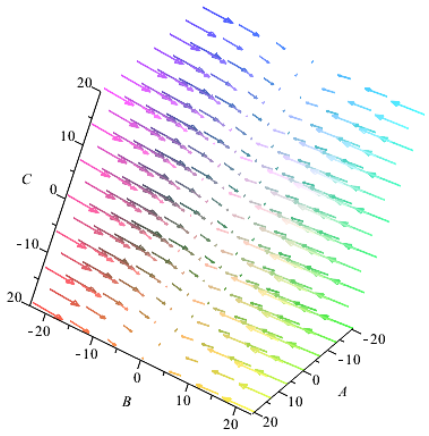
The stability of an equilibrium point can be checked from system eigen value equation mathematical model itself. The stability character of the equilibrium point is divided into three parts: stable, stable asymptotic, and unstable. So from the eigen value that has been obtained can be known whether or not a stable point of equilibrium. Here is a table of stability analysis of glucose mathematical model, insulin concentration and beta cell cycle related to the genetic predisposition and when there is no genetic predisposition.

Table 3 Table Stability

ϵ	Eigen Values	Stability
0	$T_1(\lambda_1 = -1.44, \lambda_2 = -432, \lambda_3 = 0.01)$	Unstable
	$T_2(\lambda_1 = -20.51, \lambda_2 = -417.87, \lambda_3 = -0.01)$	stable
0.5	$T_1(\lambda_1 = -1.44, \lambda_2 = -432, \lambda_3 = -0.205)$	Stable
	$T_2(\lambda_1 = -2.701, \lambda_2 = -431.24, \lambda_3 = 0.039)$	Stable
	$T_3(\lambda_1 = -16.7, \lambda_2 = -420.74, \lambda_3 = -0.012)$	Unstable
1	$T_1(\lambda_1 = -1.44, \lambda_2 = -432, \lambda_3 = -0.42)$	Stable
	$T_2(\lambda_1 = -3.06, \lambda_2 = -431.01, \lambda_3 = 0.059)$	Unstable
	$T_3(\lambda_1 = -14.96, \lambda_2 = -422.05, \lambda_3 = -0.017)$	Stable

Phase Portrait

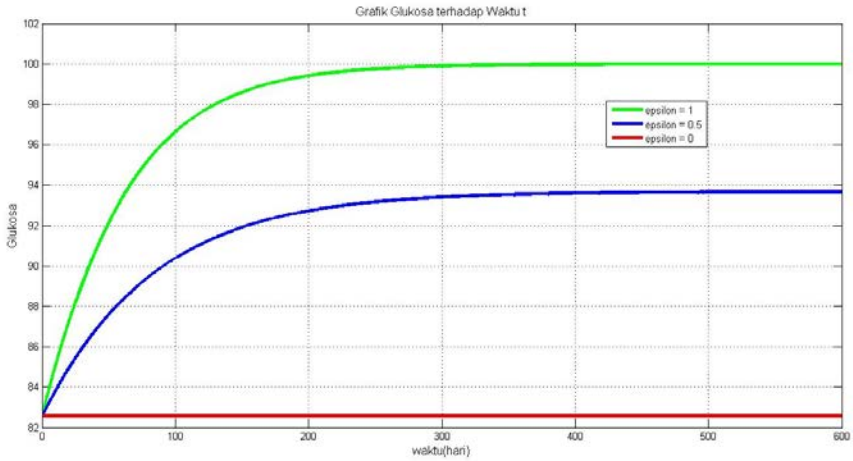
The behavior of the system of nonlinear differential equations of mathematical models of diabetes mellitus disease can be shown in the following figure:



Picture 1 Mathematical Model Trajectory Diabetes Mellitus with $\epsilon = 0, 0.5$, and $\epsilon = 1$

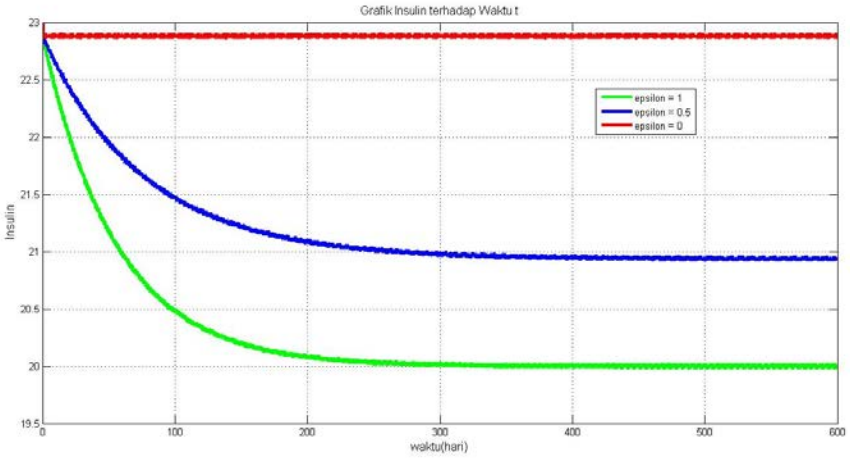
In the picture at above shows the areas of mathematical modeling phase symbolized glucose (A), insulin concentration (B) dan sel be and beta cellsa (C). T rayektori The move nearly zero with a genetic predisposition factors (ϵ), so that phase portrait is stable node point.

Solution Numerical and Interpretation Chart of Model
In this section will be displayed graphics system solutions of nonlinear ordinary differential equations of mathematical models of glucose, insulin concentration and beta cell cycle using Matlab program assistance. By providing the initial conditions $G(0) = 82.6(mg/ml)$, $I(0) = 23(\mu U/ml)$ and $\beta(0) = 900(mg)$ also uses these parameter values that have been presented in Table 1.



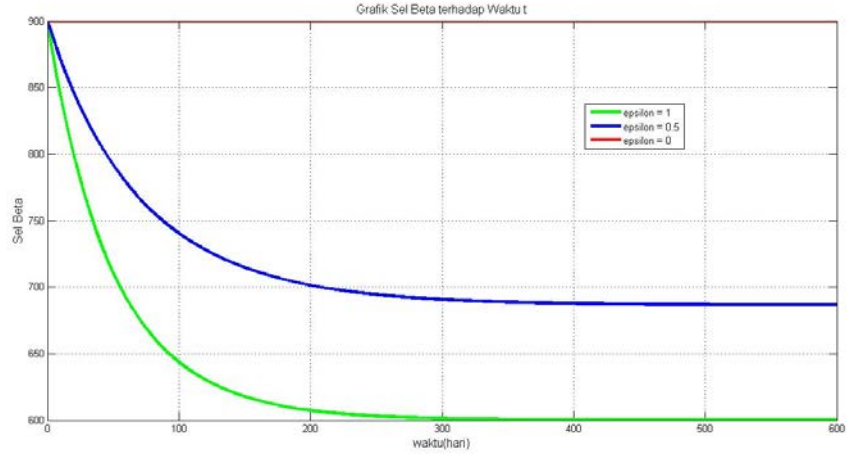
Picture 2 Chart amount glucose tp tim e t with $\epsilon = 0, 0.5$ and $\epsilon = 1$

Figure 2 is obtained that information within 600 days for the initial value $G(0) = 82.6\, mg/dl$ the three states related to genetic predisposition. It can be said of glucose in the normal condition for normal blood glucose ranges$70 - 200\, mg/dl$.



Picture 3 Chart amount insulin concentration against time t with $\epsilon = 0, 0.5$ and $\epsilon = 1$

Figure 3 explains the concentration of insulin within 600 days for baseline values $I(0) = 23\ \mu U/ml$ in three circumstances in which berkaita n with a genetic predisposition. Value normal insulin is $20 - 60\ \mu U/ml$. While from the three conditions can be seen that insulin is still in normal circumstances.



Picture 4 Chart amount beta cells against time t with $\epsilon = 0, 0.5$, and $\epsilon = 1$

Figure 4 describes the number of beta cells within 600 days for the initial value $\beta(0) = 900\ mg$ in three circumstances related to genetic predisposition. For $\epsilon = 0.5$ and $\epsilon = 1$ v $> 850\ mg$.Following this table value time (day) stable for glucose, insulin, beta cells with variation $\epsilon = 0, 0.5$ and $\epsilon = 1$.

Table 4 Value time t (day) Stable for Glucosa, Insulin, Beta Cell
With Variation $\epsilon = 0, 0.5$ and $\epsilon = 1$

ϵ	Glucosa	Insulin	Beta Cell
$\epsilon = 0$	$t = 0$	$t = 0$	$t = 0$
$\epsilon = 0.5$	$t = 400$	$t = 500$	$t = 400$
$\epsilon = 1$	$t = 400$	$t = 400$	$t = 400$

Can be known from the table above that in the moment $\epsilon = 0$ when there is no genetic predisposition, then glucose, insulin and beta cells have stabilized starting from $t = 0$ (day).

For $\epsilon = 0.5$ between genetic predispositions and when there is no genetic predisposition, glucose and beta cells are stable from time to time $t = 400$ (day). In contrast to insulin that stability begins when $t = 500$ (day). While $\epsilon = 1$ with genetic predisposition, glucose, insulin and beta cells have stabilized from time to time $t = 400$ (day).

CONCLUSION

Based on the explanation above, then obtained some conclusion, as follows:

1. Stability analysis on mathematical model of diabetes mellitus is to find the equilibrium point, eigenvalues and stability in the system of existing equations. From the equilibrium point value of the equation system by looking at its genetic predisposition (ϵ) it can be seen that there are three things to note: the point of pathological equilibrium (fixed point of disease), the point of equilibrium to the disease (the point remains disease vulnerable) with high glucose levels and physiological equilibrium points (fixed point of disease-free). Here is the chart of the equilibrium and stability analysis by finding the eigenvalues of the completion of the third Jacobian matrix system of equations exist, namely:

ϵ	Equilibrium point	Stability	Information
0	T_1(600, 0, 0) T_2(82.6, 23, 900)	Unstable stable	fixed point pathological fixed point physiological
0.5	T_1(600, 0, 0) T_2(271, 9, 114.5) T_3(93.7, 21, 686.5)	Stable Stable Unstable	fixed point pathological the point remains susceptible to disease fixed point physiological
1	T_1(600, 0, 0) T_2(250, 9.8, 129.36) T_3(100, 20, 600)	Stable Unstable Stable	fixed point pathological the point remains susceptible to disease fixed point physiological

2. Based on the results of the resulting numerical simulations show that the dynamic behavior of glucose and beta cells is very influential in determining patients with diabetes or non diabetes. And based on the results of the simulation of glucose mathematical models, the concentration of insulin and beta-cell cycle over time with changes in parameters that depend on whether or not there is a genetic predisposition can be known that about individuals who are hyperglycemic, hypoglycemia and complications against diabetes mellitus..

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