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APPLICATION APPROACH FOR DIABETES DELAY DIFFERENTIAL EQUATIONS

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ABSTRACT

Diabetes is a rapidly growing chronic disease among people in Malaysia and other countries. This disease does not have a cure, especially for type 2 diabetes. Diabetes is a disease where the body does not produce or properly use insulin. Since the focus is on type 2 diabetes, suitable alternatives should be introduced to help maintain the glucose level. In this paper, we chose type 2 diabetes equations with glucose and insulin interaction where the equations involved the delay differential equation method. The objective of this project is to solve and analyze the numerical solution of the diabetes delay differential equations by using dde23 in MATLAB®.

Keywords*: Diabetes, delay differential equations, dde23*

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1. Introduction

Diabetes mellitus is a disease where the body does not produce or correctly use insulin; a hormone that is required to transform sugar, starches, and various types of food into energy that is necessary for daily life. This disease also had been classified into two main categories, namely type 1 (insulin dependent) and type 2 (non-insulin dependent). The type 1 of diabetes which happens about 10 percent of all cases is usually the result of an autoimmune process whereby the insulin that produce the pancreatic b-cells is damaged and can no longer produce adequate amount of insulin. This type of diabetes usually develops earlier in life. Meanwhile, the type 2 diabetes which is the remaining 90 percent of diabetes cases, results from the lowest level of the insulin sensitivity in peripheral tissues and more often develops later in life (“Facts about Diabetes and Insulin,” , 2009).

Garcia et al (2020) and Chalishajar et al (2016) state that Type 2 Diabetes Mellitus (T2DM) led by a combination of two main causes which are defective insulin secretion by pancreatic β-cells and the incapability of insulin-sensitive tissues to adequately respond to insulin. Obesity is one of major cause that most of the time are related to the family history. Development of the symptom is slow over time and mostly happened to people that age more than 40. Improper management of diabetes patients can cause heart disease, blindness, kidney disease, and non-traumatic limb amputations. Hence, researchers have been actively studies the glucose-insulin endocrine metabolic regulatory system hoping that they can understand the mechanistic functions factor that cause the dysfunction of the metabolic system.

A resolution in strengthening prevention and control of diabetes agreed by the World Health Assembly in May. Five global diabetes coverage and treatment aims to be obtained by 2030 (WHO, 2023). There are many mathematical models that have been developed in studying problems related to diabetes. In this paper, we use the model that was developed by Švitra et al., (2010). The general model for diabetes is shown as below:

$$I'(t) = r_I \left[\frac{G(t)}{K_G} - \frac{I(t-h)}{K_I} \right] I(t)' \tag{1}$$

$$G'(t) = r_G \left[I + c \left[a - \frac{I(t)}{K_I} \right] - \frac{G(t)}{K_G} \right] G(t) \tag{2}$$

where, $I'(t)$ is the level of active insulin in blood at the time moment t , K_I is the average value of insulin in blood,h is the time necessary for the production of insulin in pancreas β-cells. $G'(t)$ is the level of glucose in blood (glycaemia), K_G is the average value of glucose in the blood. Glycemic self-regulatory relations are interpreted as a "predator-victim" task, where the insulin is a "predator" and sugar is a "victim". r_I , r_G are positive values characterizing the linear rate of production of insulin and sugar concentration in bloodline growth, and c is a parameter (Švitra et al., 2010).

Many types of models have been developed to have clear view about the insulin-glucose regulatory system role, including ordinary differential equations, and delay differential equation. (Chalishajar et al., 2016). However, in this paper the focus is on delay differential equation (DDE). DDE is an equation where the evolution of the system at a certain time, t depends on the state of the system at an earlier time, $t - \tau$. The most obvious dissimilarity among ODEs and DDEs is the initial data (Shampine & Thompson, 2000). ODEs are the derivatives that only depend on the current value of the independent variable. While, solution of DDEs is not only required to know about the current value, but also have to state about the previous time. Most of DDEs solution has been started with the equation below:

$$y'(t) = f\left(t, y(t), y\left(t - \tau\big(t, y(t)\big)\right)\right) \tag{3}$$

$$y(t) = \varphi(t) \tag{4}$$

where, the function $y(t)$ represents the physical quantity that evolves over time. The derivative $y'(t)$ depends on past values of $y(t)$, $\varphi(t)$ represents the initial function, and τ s the delay. There are several ways to find the numerical solutions to Equation (1) and Equation (2). This includes the direct application of linear multi-step methods and Runge-Kutta methods for ODEs. If the delay is non-constant, the methods will combine with interpolation. Moreover, interpolation is handled in the modern Runge-Kutta solvers which are Hermite interpolation and continuously imbedded methods. Hermite interpolation requires both the value of the function and its derivative at each node (Burden & Faires, 2011).

A common approach to solve DDEs is by extending one of the methods that being used to solve ODEs. Most of the codes are based on explicit Runge-Kutta methods. *dde23* takes this approach by extending the method of the MATLAB ODE solver, *ode23*. The idea is similar as the "method of steps" for solving DDEs (Shampine and Thompson, 2000). According to Shampine and Thompson (2000), a MATLAB program, *dde23* had been developed with the aim to make it easy as possible to solve the wide range of DDEs with constant delays that happened in practice, thus, it numerically solves the DDEs in order to get the approximate results for diabetes equations.

Besides, the other solution for solving DDEs based on Ishak and Ahmad (2011), it also can be solved by using the predictor-corrector multistep method where it is iterated until its convergence. Basically, a general invocation of *dde23* has the form as below:

sol = dde23(ddefile,lags,history,tspan),

where, the input argument *tspan* is the interval of integration. The *history* argument is the name of a function that evaluates the solution at the input value of *t* and returns it as a column vector. Most of the time history acts as a constant vector. The easiest way to set the history then is to supply the vector itself as the *history* argument. The delays are set to be the vector *lags, where* in here $\left[\frac{\pi}{2}\right]$. *dde23* is the function's name to evaluate the DDEs.

The most popular type of diabetes suffered by Malaysian was type 2 diabetes. In this paper we choose in solving diabetes type 2 equations on interactions of glucose and insulin level in the body. However, the equations did not have analytical solutions. Type 2 diabetes shows that the body does not produce enough insulin and unable to use insulin properly which also known as insulin resistance. The main purpose of this study is to approximate the solution of delay differential equations on diabetes model.

2. Methodology

In this section, example of DDEs with exact solutions were solved numerically. The purpose of using examples is to verify that *dde23* will give acceptable approximation.

For

$$y'_1 = y_1(t-1) + y_2(t) \tag{5}$$

$t \geq 0$,

$$y'_2 = y_1(t) - y_1(t-1) \tag{6}$$

With the initial functions given as,

$$y_1 = e^t \tag{7}$$

$$y_2 = 1 - e^{-1} \tag{8}$$

And the exact solutions,

$$y_1 = e^t \tag{9}$$

$$y_2 = 1 - e^{(t-1)} \tag{10}$$

With the value of *t* in the interval [0,3].

The first M-file is created for the history function. Then, the second M-File is created for the delay function. After defining the equations both M-File, a complete program needs to be created to compute and plot the solution as shown in Figure 1.

```
function v=example2f(t,y,Z)


       v=zeros(2,1);
       ylag=Z;
       v(1)=ylag(1)+y(2);
       v(2)=y(1)-ylag(1);

function v=example2h(t)
       v(1)=exp(t);
       v(2)=1-(exp(-1));

function example2
       sol=dde23(@example2f,1,@example2h,[0,3]);
       Xint=0:3;
       Sxint=deval(sol,Xint)
       t=0:3;
       y_exact1=exp(t);
       y_exact2=exp(t)-exp(t-1);
       plot(sol.x,sol.y,t,y_exact1,'--r',t,y_exact2,'--b');
       title('y(t) against time, t');
       xlabel('Time, t');
       ylabel('y(t)');
       legend('y_1','y_2','yExact1','yExact2',4)
```

Figure 1. Mathlab code to plot the approximation and the exact solutions to verify the method.

After the code was written and saved, the last step is obtaining the solution by executing the command in the MATLAB command window.

Figure 2 represents the numerical solutions along with the exact solutions. It consists of two solutions a shown in Figure 4. Its clearly shows that the numerical solution is approaching the results of the exact solution. Therefore, it can be defined that, this method is able to produce approximate solution for DDEs that will always be convergent. Hence, the method can be used to solve DDEs with no analytical solutions. For the next steps, the method is applied to solve Equation 3 and Equation 4 on diabetes delay differential equations.

```
function v=diabetes1f(t,y,Z)

   kI=7;
   kG=125;
   rG=21.6;
   c=0.14;
   rI=0.39;
   v=zeros(2,1);
   ylag=Z;
   v(1)=rI*(y(2)/kG-ylag(1)/kI)*y(1);
   v(2)=rG*(1+c*(1-y(1)/kI)-y(2)/kG)*y(2);

function v=diabetes1h(t)

    v(1)=20;
    v(2)=85;

function diabetes1

      sol=dde23(@diabetes1f,5.8,@diabetes1h,[6,72]);
      Xint=6:72;
      Sxint=deval(sol,Xint)
      plot(sol.x,sol.y);
      axis([6 72 0 240])
      title('The level of active insulin and the level of
      glucose at time t');
      xlabel('Time,t(hours)');
      ylabel('Insulin (pU/ml)   Blood glucose(mg/dl)')
      legend('y_1:Insulin level','y_2:Glucose level',2)
      hold on;
```

Figure 2. Code to plot the approximation and the exact solutions for DDE in diabetes

3. Result and Discussion

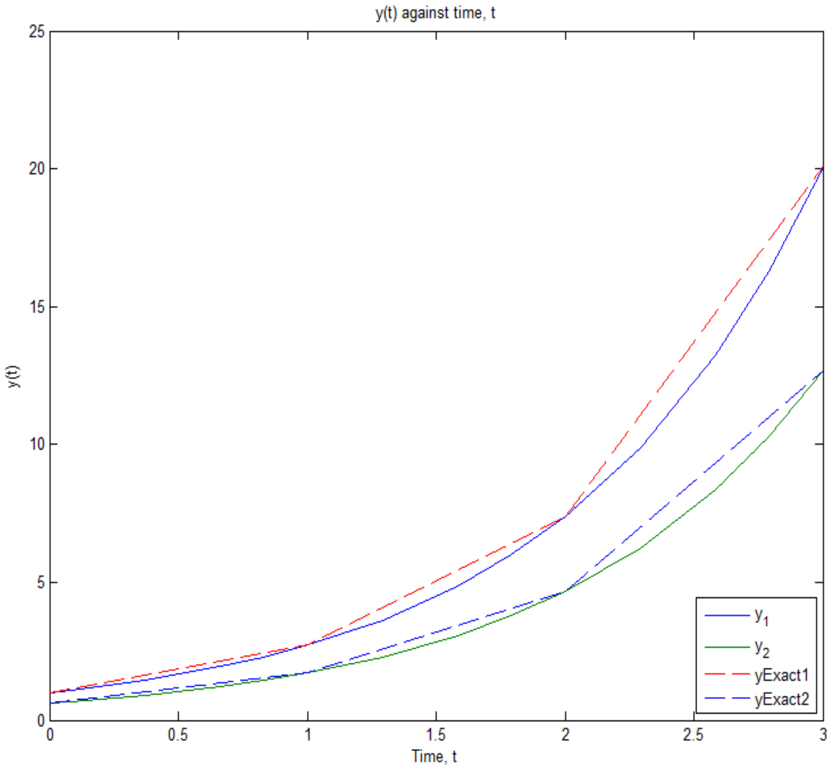

Figure 3. Graph for numerical solution and exact solution for the example

Figure 3 represents the numerical solutions along with the exact solutions for Equation (5) and Equation (6). It contains two solutions as shown in the figure. The numerical solution and the exact solutions are converging to each other. Therefore, it can be confirmed that this method is suitable in solving delay differential equations as the solutions is approaching the exact solution. On the next steps, Equation (1) and Equation (2) were solved using the same method. Table 1 shows the value of parameters used to solve the equation. It was taken from (Švitra et al., 2010). Assumption is made that the values are fixed for all the parameters.

Table 1. Parameter value for normal and diabetes case

Variable	**Normal case**	**Diabetes case**
r_G	12	21.6
r_I	0.39	0.39
K_G	100	125
K_I	8	7
h	6	5.8

c	0.14	0.14

Table 1 shows list of variables to be apply in Equation (1) and Equation (2) and also two different cases which is normal case and diabetes case. Normal case refering to healthy people and diabetes case refer to diabetic patients. It is clearly shown that certain values are the same for both cases and certain values are varied from one another. From the results in figure 2 and figure 3 the effect of the parameter will be shown.

Figure 2 represents the numerical solution for Equation (1) in normal case. The graph is showing repeated curve for three consecutive days (72 hours).Based on the observation it can be said that the result will always be the same every day. Based on the graph it also can be concluded that the level of glucose drops each time the level of insulin increases. The level of insulin is increased during the end of each day.

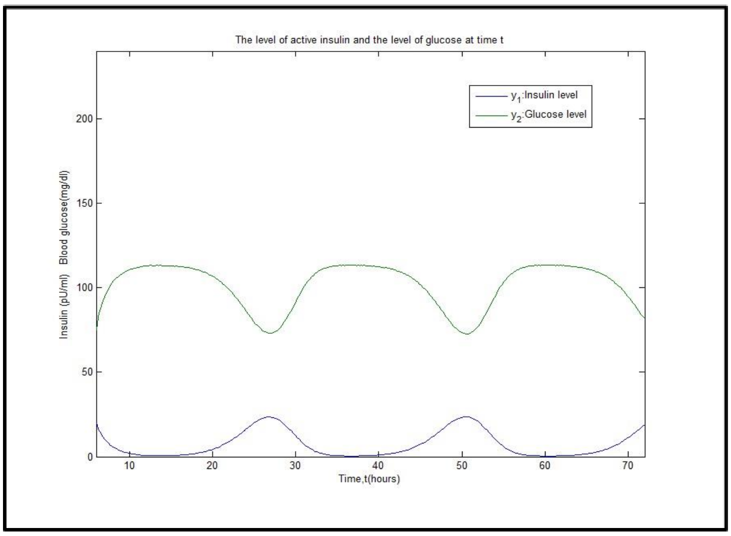

Figure 2. Time versus insulin level in normal case

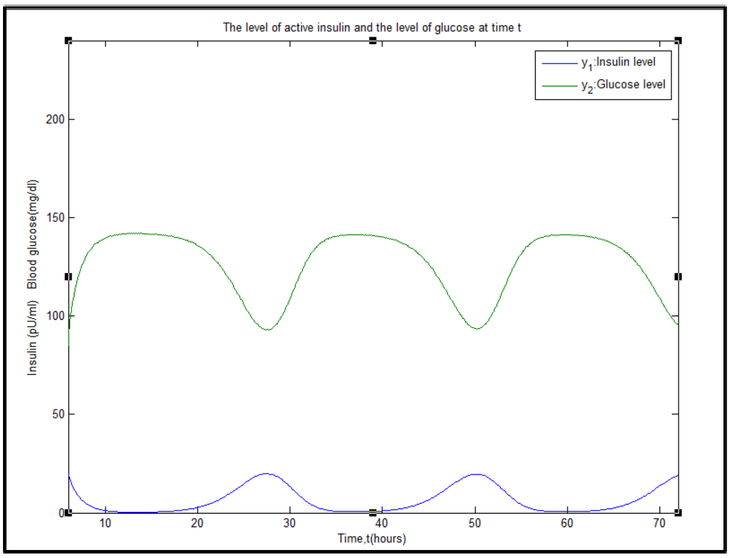

Figure 3. Time versus insulin level in diabetes case

Based on Figure 3, similar things happen to the graph for diabetes case. The curve is repeated for three consecutive days. Similar conclusion can be made that the same graph will continuously happen daily. It can be said that level of insulin for a diabetic patient is higher than level of insulin for a healthy person. Even with higher level of insulin the glucose level of a diabetic patients were almost similar to the level of glucose for a healthy person. The progression of type 2 happens over time which causing less insulin produce by the body. Some patients are needed to have more complex insulin regimen (Wexler, 2023).

4. Conclusion and Recommendation

It can be concluded that *dde23* gives acceptable approximate solution for delay differential equations based on the example. This method was verified to be used to solve delay differential equation for different problem or disease. Approximating solution of diabetes delay differential equation helps to provide solution numerically. It also helped to show the level of glucose and the effect of insulin on the glucose level for daily for both healthy person and diabetic patients. For future research, diabetes delay differential equation with factor such as exercise and control meal intakes can be used to be solve and analyse.

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7. Conflict of Interest

The authors have no conflicts of interest to declare.

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