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Qualitative Study of Parkinson's Disease Model

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Abstract: Parkinson's disease (PD) is a heterogeneous disorderwith common age of onset. In this paper we will present a mathematical model for Parkinson's disease using delay differential equations, we study the stability of two models, one of which is to address the problem of positive feedback resulting from taking levodopa for a long time, and converting this delay differential equation into ordinary differential equation for small delays using Taylor series. Stability of the new equation was studied. Equations are solved and a comparison is made between the use of matlab codes dde23, ode45 and the use of the step method.

keywords: Parkinson's disease (PD), Simulation, Taylor series

1.Introduction

Parkinson's disease (PD) is a neurodegenerative movement condition characterized by hallmark motor manifestations caused by gradual depletion of dopaminergic neurons in the substantiate nigra pars compacta. It is currently projected that PD will impact upwards of 6 million people globally, with prevalence rates predicted to double in the coming years.

There is currently no treatment for PD, though dopaminergic therapies such as levodopa and dopamine agonists frequently control motor symptoms well. Unfortunately, to maintain the same degree of control over motor effects, these treatments need higher dosages over time [1].

Parkinson's disease has been studied mathematically by G. Austin in 1961 and expressed the amplitude in hand tremor by a second-order differential equation, using the Van der Pol model [2]. In 2009 Claudia expresses another symptom using nonlinear two-delay differential equation in [3]. We know the effect of the psychological and emotional state on the tremor, but it is worth noting that after a period of taking Parkinsonism drugs present a combination of symptoms, sometimes increased tremor. These symptoms appear as a result of the fact that only 5–10% of the drug crosses blood-brain barrier [4]. E.Ahmed suggests a modification to this model in [3] for solve the problem of positive feedback to be stable [5].

In this paper we will study the models in [3-5], and assume small delays. In Parkinson's disease, the time delay is small, whether we express the defect in signal transmission or the defect in the repetition of handwriting.

We will use the Taylor for the two models in [3-5] in the case of small delays, and then we will solve a set of numerical examples and compare them by the step method with the solution after approximating the model by using Taylor series with the solution using Matlab code DDE 23.

1. Stability for delay differential equation model

Parkinson's disease has been studied mathematically in [3] as in the following delay differential equations:

$$\frac{dx(t)}{dt} = a_1\, x(t-\tau_1) + a_2\, x(t-\tau_2) + a_3\, x(t-\tau_1)x(t-\tau_2),$$

$$x(t) = h\,,\ t>0 \ \text{and} \ -\tau_2 < -\tau_1 < t < 0. \qquad (1)$$

Where, a_1, a_2, a_3 are constant coefficients, $x(t)$ function for defect in Parkinson's disease and h constant history for $x(t)$.

The fixed points for the system in (1) are,

$$x^* = 0, \quad x^* = -\frac{a_1+a_2}{a_3}.$$

If

$$f\left(x(t-\tau_1),x(t-\tau_2)\right)=a_1\,x(t-\tau_1)+a_2\,x(t-\tau_2)+a_3\,x(t-\tau_1)x(t-\tau_2) \quad (2)$$

Then:

$$\frac{\partial f\left(x(t-\tau_1),x(t-\tau_2)\right)}{\partial x(t-\tau_1)}=a_1+a_3x, \quad (3)$$

$$\frac{\partial f\left(x(t-\tau_1),x(t-\tau_2)\right)}{\partial x(t-\tau_2)}=a_2+a_3x. \quad (4)$$

- Stability for zero fixed point ($x^*=0$)

By substituting into equations (3) and (4) for $x^*=0$,

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_1)}=a_1,$$

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_2)}=a_2.$$

Then the linear model corresponding to the model in (1) can be written as follow:

$$\frac{dx(t)}{dt}=a_1\,x(t-\tau_1)+a_2\,x(t-\tau_2),$$
$$x(t)=h,\ t>0\ \ and\ \ -\tau_2<-\tau_1<t<0. \quad (5)$$

By substituting into equation (5) for $x(t)=e^{-\lambda t}$, then the characteristic equation for the model in (5),

$$\lambda=a_1\,e^{-\lambda\tau_1}+a_2\,e^{-\lambda\tau_2}.$$

- For small delays $\tau_1<<1,\ \tau_2<<1$.

$$\lambda=a_1+a_2$$

Then the fixed point $x^*=0$ is asymptotically stable if,

$$a_1+a_2<0. \quad (6)$$

- For large delays $\tau_1>1,\ \tau_2>1$.

Then the fixed point $x^*=0$ is asymptotically stable if,

$$a_1+a_2<0,\ |a_1|<1 \text{ and } |a_2|<1. \quad (7)$$

If $a_1<0$ and $a_2>0$, the negative term affect as a negative feedback to reduce the motor defect, and positive term affect as a positive feedback to increase the motor defect.

If the negative feedback $|a_1|$ is greater than the positive feedback $|a_2|$, the defect tends to zero fixed point, see Fig. (1).

Under the positive feedback conditions

($a_1>0, a_2>0$ and $a_3>0$), $\lambda>0$

So, the zero fixed point is unstable.

The non-zero fixed point is negative.

Stability for non-zero fixed point

($x^*=-\dfrac{a_1+a_2}{a_3}$)

By substituting into equations (3) and (4) for

($x^*=-\dfrac{a_1+a_2}{a_3}$),

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_1)}=-a_2,$$

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_2)}=-a_1.$$

Then the corresponding linear model for the model in (1) can be written as follow:

$$\frac{dx(t)}{dt}=-a_2\,x(t-\tau_1)-a_1\,x(t-\tau_2),$$
$$x(t)=h,\ t>0\ \ and\ \ -\tau_2<-\tau_1<t<0. \quad (8)$$

By substituting into equations (8) for $x(t)=e^{-\lambda t}$, then the characteristic equation for the model in (8),

$$\lambda=-a_2\,e^{-\lambda\tau_1}-a_1\,e^{-\lambda\tau_2}$$

- For small delays $\tau_1<<1,\ \tau_2<<1$

$$\lambda=-a_2-a_1$$

Then the non-zero fixed point is asymptotically stable if,

$$a_1+a_2>0,\ a_3<0 \quad (9)$$

- For large delays $\tau_1>1,\ \tau_2>1$

Then the non-zero fixed point is asymptotically stable if,

$$a_1+a_2>0,\ |a_1|<1,\ |a_2|<1,\ a_3<0. \quad (10)$$

In the case of negative feedback $a_1<0$ and positive feedback $a_2>0$, If the positive feedback is greater than the negative feedback, the model will be stable at the non-zero fixed point see Fig. (2).

For small delays, by using Taylor series the system in (1) written as follows:

$$\frac{dx(t)}{dt} = a_1\left(x(t) - \tau_1 \frac{dx(t)}{dt} \right) + a_2\left(x(t) - \tau_2 \frac{dx(t)}{dt} \right) + a_3\left((x(t))^2 - (\tau_1+\tau_2)\frac{dx(t)}{dt} \right),$$

$$x(0) = h. \qquad (11)$$

$$\frac{dx(t)}{dt} = \left(\frac{a_1 + a_2}{1 + (a_1 + a_3\tau_1) + (a_2 + a_3\tau_2)} \right) x(t) + \frac{a_3}{1 + (a_1 + a_3\tau_1) + (a_2 + a_3\tau_2)} (x(t))^2,$$

$$x(0) = h \; . \qquad (12)$$

The critical points for the system in (12) are,

$$x^* = 0, x^* = -\frac{a_1 + a_2}{a_3}$$

Then the fixed point $x^* = 0$ is asymptotically stable if,

$$\frac{a_1 + a_2}{1 + (a_1 + a_3\tau_1) + (a_2 + a_3\tau_2)} < 0 \; . \qquad (13)$$

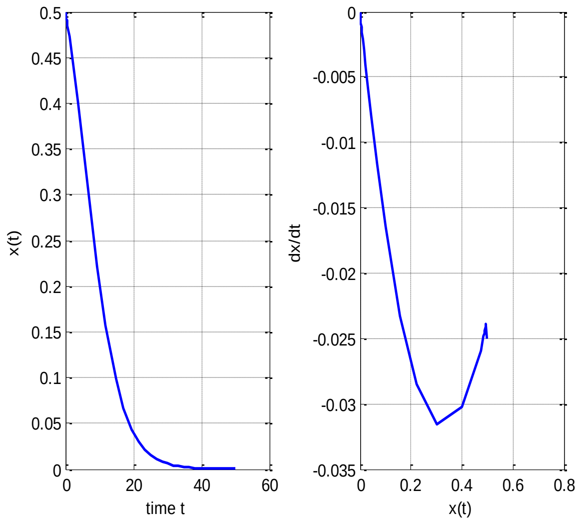

Fig. (1): negative feedback greater than the positive feedback

$a_1 = -0.6, a_2 = 0.4, a_3 = 0.3, h = 0.5, \tau_1 = 0.1 \, and \, \tau_1 = 0.2$

Then the non-zero fixed point is asymptotically stable if,

$$\frac{a_1 + a_2}{1 + (a_1 + a_3\tau_1) + (a_2 + a_3\tau_2)} > 0 \qquad (14)$$

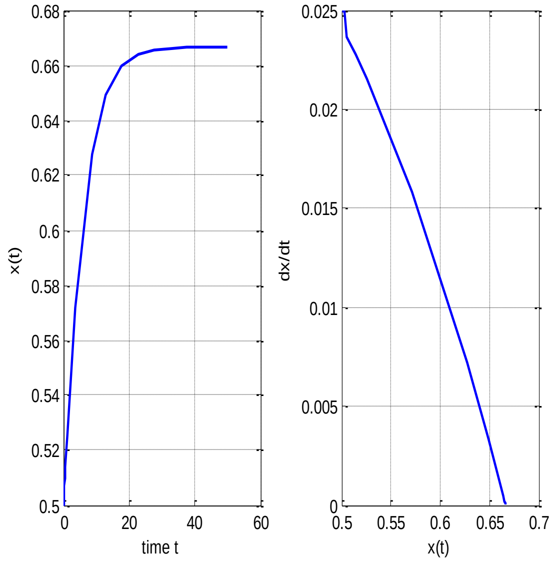

Fig. (2): negative feedback smaller than the positive feedback

$a_1 = -0.4, a_2 = 0.6, a_3 = -0.3, h = 0.5, \tau_1 = 0.1 \, and \, \tau_1 = 0.2$

So if we consider,

$$1 + (a_1 + a_3\tau_1) + (a_2 + a_3\tau_2) > 0 \; .$$

Then the zero fixed point is asymptotically stable if, $a_1 + a_2 < 0$, and the non-zero fixed point is asymptotically stable if, $a_1 + a_2 > 0$ which coincides condition in (6-7).

2. Stability for delay differential equation model with positive feedback

E.Ahmed in [5] discussed the model in (1) and have endorsed that it is unbounded and unstable for the case of positive coefficients, but this is not true for the biodynamic systems. Moreover, E.Ahmed in [5] suggests a modification for the model in (1) to be bounded for this case as follows:

$$\frac{dx(t)}{dt} = a_1 x(t-\tau_1) + a_2 x(t-\tau_2) + a_3 x(t-\tau_1) x(t-\tau_2) - x^2,$$

$$x(t) = h, \; t > 0 \; and \; -\tau_2 < -\tau_1 < t < 0. \quad (15)$$

Where $a_1 + a_2 + a_3 < 1$

For study stability in (16) assumes that:

$$g(x, x(t-\tau_1), x(t-\tau_2)) = a_1 x(t-\tau_1) + a_2 x(t-\tau_2) + a_3 x(t-\tau_1) x(t-\tau_2) - (x(t))^2$$

(16)

The model in (17) has critical points if $g(x, x(t-\tau_1), x(t-\tau_2)) = 0$.

The equilibrium points, $x^* = 0$, $x^* = \dfrac{a_1 + a_2}{1 - a_3}$.

By linearization the model to analysis the stability:

$$\frac{\partial g(x, x(t-\tau_1), x(t-\tau_2))}{\partial x(t-\tau_1)} = a_1 + a_3 x \quad , (17)$$

$$\frac{\partial g(x, x(t-\tau_1), x(t-\tau_2))}{\partial x(t-\tau_2)} = a_2 + a_3 x \quad , (18)$$

$$\frac{\partial g(x, x(t-\tau_1), x(t-\tau_2))}{\partial x(t)} = -2x \quad . \quad (19)$$

Stability for zero fixed point ($x^* = 0$)

By substituting into equations (17), (18) and (19) for $x^* = 0$,

Then the corresponding linear model for the model in (16) can be written as the previous system in (5), see Fig. (3).

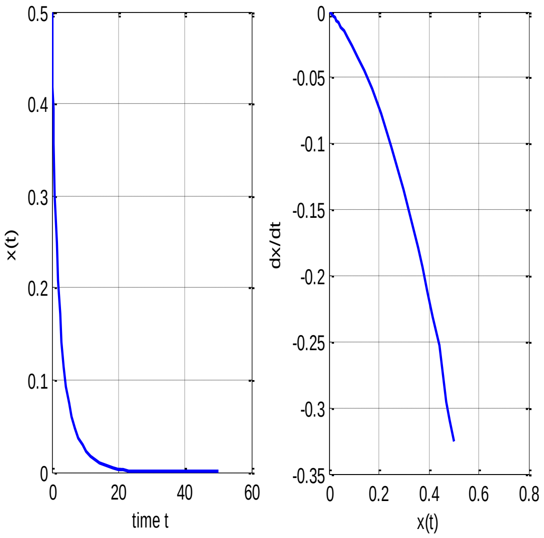

Fig. (3): $\tau_1 = 0.1$, $\tau_2 = 0.2$, $a_1 = -0.6$, $a_2 = 0.4$, $a_3 = 0.1$, $and\ h = 0.5$

In this case, the effect of negative feedback is greater than the effect of positive feedback. So the defect decreases until it reaches the zero fixed point.

Stability for non-zero fixed point

By substituting into equations (17), (18) and (19) for ($x^* = \dfrac{a_1 + a_2}{1 - a_3} = p$),

Then the corresponding linear model for the model in (16) can be written as follow:

$$\frac{dx(t)}{dt} = (a_1 + a_3 p)\, x(t-\tau_1) + (a_2 + a_3 p)\, x(t-\tau_2) - 2p x(t),$$
$$x(t) = h,\ t > 0\ \ and\ \ -\tau_2 < -\tau_1 < t < 0. \quad (20)$$

By substituting into equations (20) for $x(t) = e^{-\lambda t}$, then the characteristic equation for the model in (20),

$$\lambda = (a_1 + a_3 p)e^{-\lambda \tau_1} + (a_2 + a_3 p)e^{-\lambda \tau_2} - 2p$$

For small delays $\tau_1 << 1$, $\tau_2 << 1$

$$a_1 + a_2 - 2(1 - a_3)p < 0$$

$$a_1 + a_2 - 2(1 - a_3)\frac{a_1 + a_2}{1 - a_3} < 0$$

$$a_1 + a_2 > 0, a_3 \neq 1$$

Then the non-zero fixed point is asymptotically stable if,

$$a_1 + a_2 > 0$$

In Fig. 4, the condition $a_1 + a_2 > 0$ for stability is satisfied.

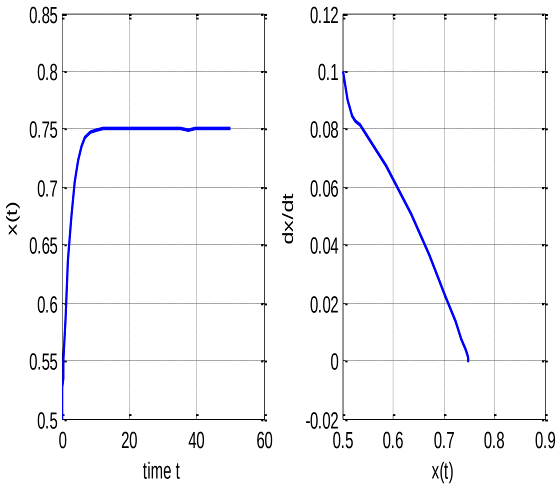

Fig. (4) : $\tau_1 = 0.1$, $\tau_2 = 0.2$, $a_1 = 0.2$, $a_2 = 0.4$, $a_3 = 0.2$, $and\ h = 0.5$

Small delays chosen, the coefficients a_1, a_2, a_3 are positive. The defect will increase until it reaches the non-zero equilibrium point $x^* = 0.75$.

❖ For large delays $\tau_1 > 1$, $\tau_2 > 1$

The model in (21) at non-zero fixed point is stable if,

$a_1 + a_3 p < 1$, $a_2 + a_3 p < 1$ and $p < 1$

The condition of stability system

$$\frac{a_1+a_2}{1-a_3}<1 \quad \text{then} \quad a_1+a_2+a_3<1,$$

$$a_1+p<1, \quad a_2+p<1, \quad a_1+a_2+2p<2$$

For small delays, by using Taylor series the system in (15) written as follows:

$$\frac{dx(t)}{dt}=a_1\left(x(t)-\tau_1\frac{dx(t)}{dt}\right)+a_2\left(x(t)-\tau_2\frac{dx(t)}{dt}\right)$$
$$+a_3\left((x(t))^2-(\tau_1+\tau_2)\frac{dx(t)}{dt}\right)-(x(t))^2,$$
$$x(0)=h. \qquad (21)$$

So,

$$\frac{dx(t)}{dt}=\left(\frac{a_1+a_2}{1+(a_1+a_3\tau_1)+(a_2+a_3\tau_2)}\right)x(t)$$
$$+\left(\frac{a_3-1}{1+(a_1+a_3\tau_1)+(a_2+a_3\tau_2)}\right)(x(t))^2,$$
$$x(0)=h. \qquad (22)$$

The fixed points for the system in (22) are,

$$x=0, \quad x=\frac{a_1+a_2}{1-a_3}.$$

If,

$$f(x(t))=\left(\frac{a_1+a_2}{1+(a_1+a_3\tau_1)+(a_2+a_3\tau_2)}\right)x(t)$$
$$+\left(\frac{a_3-1}{1+(a_1+a_3\tau_1)+(a_2+a_3\tau_2)}\right)(x(t))^2,$$

$$\frac{df(x(t))}{dx(t)}=\left(\frac{a_1+a_2}{1+(a_1+a_3\tau_1)+(a_2+a_3\tau_2)}\right)$$
$$+2\left(\frac{a_3-1}{1+(a_1+a_3\tau_1)+(a_2+a_3\tau_2)}\right)x(t),$$

For zero fixed point, $\frac{df(x(t))}{dx(t)}>0$

Then zero fixed point is unstable.

For non-zero fixed point,

$$\frac{df(x(t))}{dx(t)}=-\frac{a_1+a_2}{1+(a_1+a_3\tau_1)+(a_2+a_3\tau_2)}<0$$

Then nonzero fixed point is asymptotically stable, which coincides with results of E.Ahmed in [5].

3. Numerical examples with comparison between dde23 ,ode45 and step method

In this section, we will present numerical examples to illustrate the previously inferred stability conditions for small delays with a comparison between the solutions by using matlab codes dde23, ode45 and step method.

Case 1: Consider the delay differential equation,

$$\frac{dx(t)}{dt}=-0.6x(t-0.1)+0.4\,x(t-0.2)$$
$$+0.3x(t-0.1)x(t-0.2)$$
$$x(t)=0.5,\ t>0 \ \text{ and } \ -0.2<t<0.$$

The corresponding initial value problem,

$$\frac{dx(t)}{dt}=\frac{-0.2}{0.89}x(t)+\frac{0.4}{0.89}(x(t))^2, \quad x(0)=0.5$$

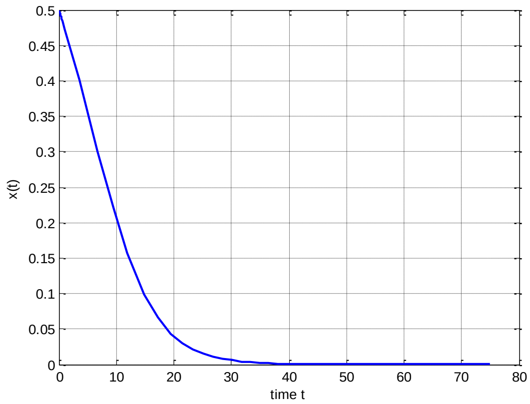

Fig. (5): solving by using matlab code dde23, zero fixed point is asymptotically stable

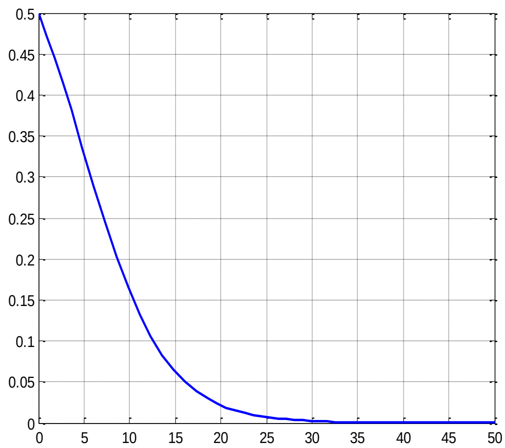

Fig. 6, solving by using matlab code ode45

By comparing the solutions using the Matlab dde23 and ode45 codes, we find that, same behavior.

Case 2: Consider the delay differential equation,

$$\frac{dx(t)}{dt} = -0.4x(t-0.1) + 0.5\,x(t-0.2)$$
$$-0.1x(t-0.1)x(t-0.2)$$
$$x(t) = 0.5\,,\ t > 0\ \ and\ \ \ -0.2 < t < 0.$$

The corresponding initial value problem,

$$\frac{dx(t)}{dt} = \frac{0.1}{1.07}x(t) + \frac{0.1}{1.07}\left(x(t)\right)^2, \quad x(0) = 0.5$$

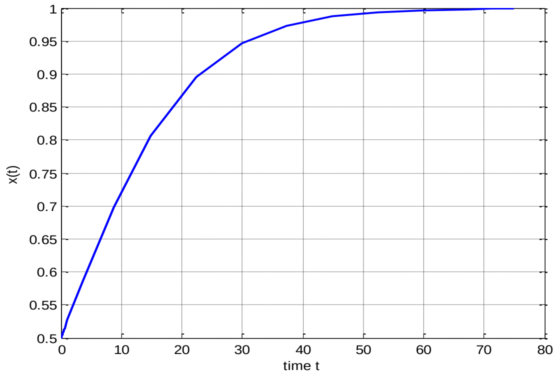

Fig. 7, solving by using matlab code dde23, non-zero fixed point is asymptotically stable.

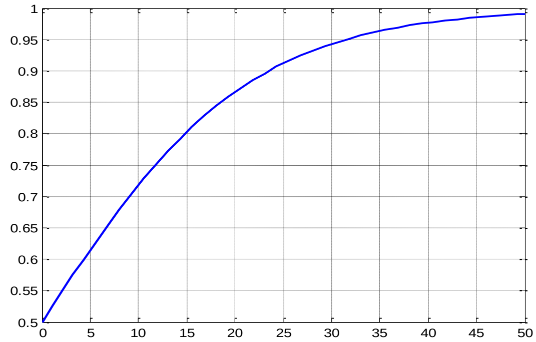

Fig. 8, solving by using matlab code ode45

By comparing the solutions using the Matlab dde23 and ode45 codes, we find that, same behavior.

Case 3: Consider the delay differential equation,

$$\frac{dx(t)}{dt} = 0.1x(t-2) + 0.2\,x(t-4) + 0.3x(t-2)x(t-4),$$
$$x(t) = 0.5\,,\ t > 0\ \ and\ \ \ -4 < t < 0.$$

(24)

In this case we will use the step method to solve the delay differential equation, explain the stability, and solve it by using the matlab code dde23

First step $[0,2]$

$$\frac{dx_1(t)}{dt} = 0.225, x_1(0) = 0.5.$$

Second step $[2,4]$

$$\frac{dx_2(t)}{dt} = 0.25x_1(t-2) + 0.1, x_2(2) = x_1(2).$$

Third step $[4,6]$

$$\frac{dx_3(t)}{dt} = 0.1x_1(t-2) + 0.2x_1(t-3) + 0.3x_1(t-2)x_1(t-3), x_3(4) = x_2(6).$$

$$\frac{dx_4(t)}{dt} = 0.1x_2(t-2) + 0.2x_1(t-3) + 0.3x_2(t-2)x_1(t-3), x_4(6) = x_3(8).$$

Fourth step $[6,8]$

By solving the initial value problem to every step.

$$x(t) = \begin{cases} \frac{1}{2} & ,-4 \le t \le 0 \\ \frac{9t}{40} + \frac{1}{2} & ,0 \le t \le 2 \\ \frac{9t^2}{320} + \frac{9t}{80} + \frac{49}{80} & ,2 \le t \le 4 \\ \frac{243}{512000}t^4 + \frac{69}{64000}t^3 + \frac{63}{1600}t^2 + \frac{27}{400}t + \frac{211}{500} & ,4 \le t \le 6 \\ \text{..........} & \end{cases}$$

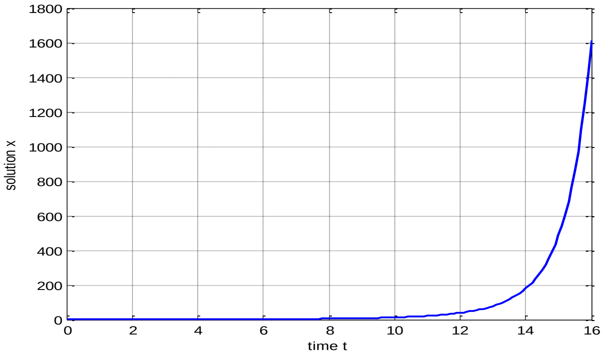

Fig. 9: step method for model in (24) where, $a_1 = 0.1, a_2 = 0.2, a_3 = 0.3, h = 0.5, \tau_1 = 2, \tau_2 = 4$

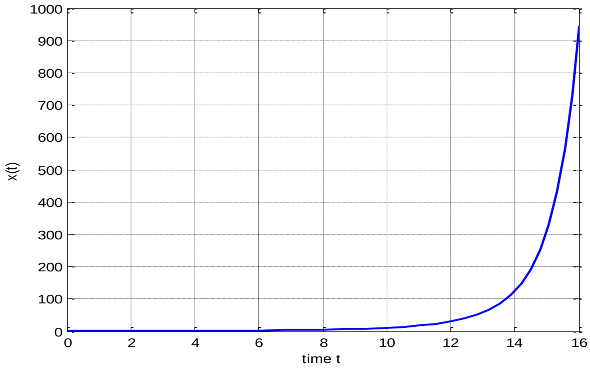

Fig. 10: Matlab code dde23 for model in (24) where,
$a_1 = 0.1, a_2 = 0.2, a_3 = 0.3, h = 0.5, \tau_1 = 2, \tau_2 = 4$

The corresponding ordinary differential equation,

$$\frac{dx(t)}{dt}=\frac{0.3}{3.1}x(t)+\frac{-0.7}{3.1}(x(t))^2, \quad x(0)=0.5$$

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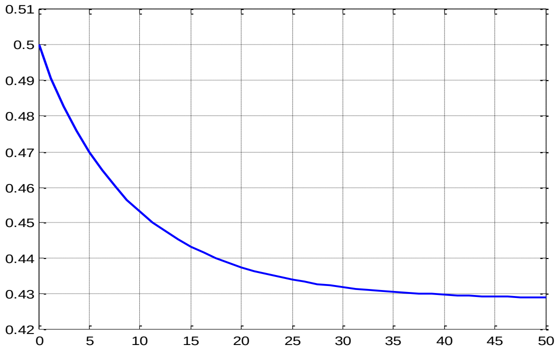

Fig. 11: Matlab code ode45 for corresponding model in (24) where, $a_1=0.1$, $a_2=0.2$, $a_3=0.3$, $h=0.5$, $\tau_1=2$, $\tau_2=4$

By comparing the figures 9, 10 and 11 we find a great match between the Matlab code dde23 and the solution using the steps method. The solution is completely different from using the Taylor series because the delays are not small

4. Conclusion

The delays with Parkinson's disease in the control state and the non-control state are often very small and this is the reason for using the Taylor series to convert the delay differential equation into ordinary differential equation. The stability conditions that were deduced in [4-6] in the case of small delays matched the conditions that were inferred. The solution to the delay differential equations matches the solution by converting to the normal differential equations in the case of small delays. Solving differential equations using Taylor series Good and simple in case of small delays and the directional behavior matches when using the Taylor series, the step method is effective when the delays are small or large.

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