Stability Analysis of Two-delay Differential Equation for Parkinson's Disease Models with Positive Feedback

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***Abstract*—**Parkinson's disease (PD) is a heterogeneous movement disorder that often appears in the elderly. PD is induced by a loss of dopamine secretion. Some drugs increase the secretion of dopamine. In this paper, we will simply study the stability of PD models as a nonlinear delay differential equation. After a period of taking drugs, these act as positive feedback and increase the tremors of patients, and then, the differential equation has positive coefficients and the system is unstable under these conditions. We will present a set of suggested modifications to make the system more compatible with the biodynamic system. When giving a set of numerical examples, this research paper is concerned with the mathematical analysis, and no clinical data have been used.

***Keywords*—**Parkinson's disease, stability, simulation, two delay differential equation.

I. INTRODUCTION

PD is a sort of disorder of movement. It occurs when the brain's nerve cells do not contain enough of a brain chemical called dopamine. Gait and balance disorders like PD have a common effect on the geriatric population. It is inherited at times, but most cases do not seem to occur within families. Environmental exposure to chemicals may play a part. Dopamine plays a key function in controlling body movement. A decrease in dopamine is responsible for many of the PD symptoms. It is unknown exactly what causes the loss of nerve cells. Most experts agree that blame rests on a combination of genetic and environmental factors [1].

PD was modeled mathematically in 1961 [2]), after it was observed that the tremors were affected by the emotional state of the patient. In this model, the Van der Pol model was used. This model relied on two parts, one of which acts as a positive feedback and the other as negative feedback, or the two terms act as negative feedback for the tremor [2].

In 2009, Lainscsek et al. used delay differential equations to describe PD and used time series analysis to estimate the constants in the differential equation, which were two delays, one for the control - on and the other for the control – off state [3].

Claudia [3] noticed repeated tapping movements of the finger and assumed a periodic function as:

$$x(t) = cos(ft)$$

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Then, the velocity:

$$\dot{x}(t) = -f\,sin(ft)$$

$$\dot{x}(t) = -f\,cos\left(f\left(t - \frac{\pi}{2f}\right)\right)$$

$$\dot{x}(t) = a\,cos\left(f(t-\tau)\right)$$

$$\dot{x}(t) = ax(t-\tau)$$

Hence, the model was deduced from this symptom of PD. In the end, any symptoms of the disease are caused by a defect in the transmission of the nerve signal to the locomotor system.

From the results of [2] and [3], it can be assumed that the defect in Parkinson's patients can be expressed by the delay differential equation with positive and negative feedback [4] as:

$$\frac{dx(t)}{dt} = a_1\, x(t-\tau_1) + a_2\, x(t-\tau_2) + a_3\, x(t-\tau_1)x(t-\tau_2) \quad (1)$$

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

where a_1, a_2, a_3 are constants, $x(t)$ the positive function that describes the defects in the locomotor system in Parkinson's patients, in [2] $x(t)$ express the amplitude of the tremor, h the initial value for function $x(t)$, τ_1 the delay of control-on and τ_2 the delay of control-off, $\tau_i = \frac{\pi}{2f_i}, i = 1,2$, f_i the frequency of the Oscillatory movement. Delays depend on the time the drugs take effect on and off and the emotional state of the patient. The nonlinear part adjusts for any perturbation in the model.

In the second section, we will do a simple analysis of the stability of this assumed model and determine the equilibrium points.

In 2019, Ahmed [5] assumed that all the constants are a_1, a_2, a_3 positive with a positive initial value h, depending on a set of positive values that appeared when Claudia's estimation of the constants a_1, a_2, a_3 [3]. Ahmed presented modification to make the system stable at a non-zero equilibrium point. In the third and fourth sections, we will present other modifications with a simple stability analysis for these modifications.

We will show some numerical examples that illustrate the stability process for these proposed modifications by MATLAB code dde23. Agiza solve the nonlinear delay differential equation in (1) by using step method with comparison to the solution using MATLAB Code dde23 [6]. In this paper, we will simply analyze the stability of Model in (1) and the proposed modifications to this model in (1) without addressing the solution.

II. Stability Analysis

Assume that:

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

The model in (1) has critical points if:

$$f(x,x(t-\tau_1),x(t-\tau_2))=0$$

The critical points are $x^*=0$ and $x^*=-\frac{a_1+a_2}{a_3}$. By linearization the model to analysis the stability:

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_1)}=a_1+a_3x^*$$
$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_2)}=a_2+a_3x^*$$

Stability for Zero Fixed Point ($x^*=0$)

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_1)}=a_1$$
$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_2)}=a_2$$

The model is written as:

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

Then the characteristic equation:

$$\lambda=a_1e^{-\lambda\tau_1}+a_2e^{-\lambda\tau_2}$$

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

$$\lambda=a_1+a_2$$

The model is stable if $a_1+a_2<0$

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

If $a_1+a_2<0$, $|a_1|<1$ and $|a_2|<1$.

If the negative feedback is greater than the positive feedback, the model will be stable at the zero fixed point.

Stability for Non-Zero Fixed Point ($x^*=-\frac{a_1+a_2}{a_3}$)

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_1)}=-a_2$$
$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_2)}=-a_1$$

The model is written as:

$$\frac{dx(t)}{dt}=-a_2\,x(t-\tau_1)-a_1\,x(t-\tau_2) \tag{3}$$
$$x(t)=h,\ t>0\ \ and\ \ -\tau_2<-\tau_1<t<0$$

Then the characteristic equation:

$$\lambda=-a_2e^{-\lambda\tau_1}-a_1e^{-\lambda\tau_2}$$

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

$$\lambda=-a_2-a_1$$

The model is stable if $a_1+a_2>0$

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

If $a_1+a_2>0$, $|a_1|<1$ and $|a_2|<1$

If the positive feedback is greater than the negative feedback, the model will be stable at the non-zero fixed point with condition positive non-zero fixed point.

❖ *Numerical Example*

Example1. If $\tau_1=0.1, \tau_2=0.2$, $a_1=-0.6$, $a_2=0.4$, $a_3=0.3$ *and* $h=0.5$ see Fig. 1.

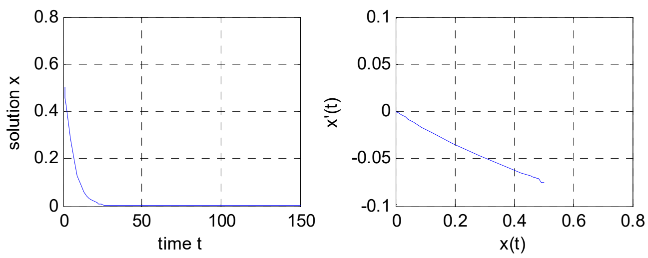

Fig. 1 Negative feedback greater than the positive feedback and fixed point equal zero

Example2. If $\tau_1=0.1, \tau_2=0.2$, $a_1=-0.4$, $a_2=0.6$, $a_3=-0.1$ *and* $h=0.5$ see Fig. 2.

III. B-Modification Model

Ahmed [5] suggests some modifications for the model in (1) under the positive condition for a_1, a_2, a_3 and h to be bounded as:

$$\frac{dx(t)}{dt} = a_1\, x(t-\tau_1) + a_2\, x(t-\tau_2) + a_3\, x(t-\tau_1)x(t-\tau_2) - x^2 \quad (4)$$
$$x(t) = h\,,\ t > 0 \ \text{and} \ \ -\tau_2 < -\tau_1 < t < 0$$

with stability conditions: $a_1 + a_2 + a_3 < 1$ and $a_1 + a_2 + 2\frac{a_1 + a_2}{1 - a_3} < 2$. Here, we suggest that the model in (1) and (4) can be modified in the following form:

$$\frac{dx(t)}{dt} = a_1\, x(t-\tau_1) + a_2\, x(t-\tau_2) + a_3\, x(t-\tau_1)x(t-\tau_2) - bx^2$$
$$x(t) = h\,,\ t > 0 \ \text{and} \ \ -\tau_2 < -\tau_1 < t < 0 \quad (5)$$

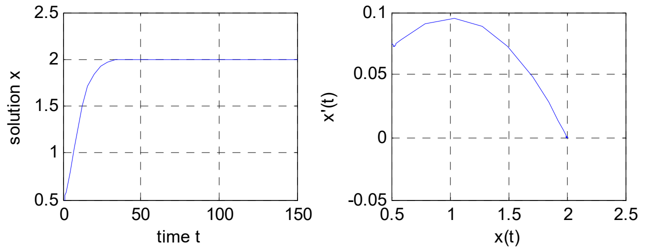

Fig. 2 Positive feedback greater than the negative feedback and fixed point $x^* = 2$

Let:

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

The system in (5) has critical points:

$$x^* = 0 \ \text{and} \ x^* = \frac{a_1 + a_2}{b - a_3}$$

By linearization, the model in (5) as:

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_1)} = a_1 + a_3 x^*$$
$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_2)} = a_2 + a_3 x^*$$
$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t)} = -2bx^*$$

The equivalence linear system will be for $x^* = 0$ unstable point with positive conditions.

The equivalence linear system will be for $x^* = \frac{a_1 + a_2}{b - a_3} = l$ in the form:

$$\frac{dx(t)}{dt} = (a_1 + a_3 l)\, x(t-\tau_1) + (a_2 + a_3 l)\, x(t-\tau_2) - 2bl x(t) \quad (6)$$
$$x(t) = h\,,\ t > 0 \ \text{and} \ \ -\tau_2 < -\tau_1 < t < 0$$

The characteristic equation

$$\lambda = (a_1 + a_3 l)e^{-\lambda\tau_1} + (a_2 + a_3 l)\, e^{-\lambda\tau_2} - 2bl \quad (7)$$

For Small Delays ($\tau_1 << 1$, $\tau_2 << 1$)

The stability condition:

$$\lambda = (a_1 + a_3 l) + (a_2 + a_3 l) - 2bl < 0 \quad (8)$$
$$a_1 + a_2 - 2(b - a_3)l < 0$$
$$a_1 + a_2 - 2(b - a_3)\frac{a_1 + a_2}{b - a_3} < 0$$
$$a_1 + a_2 > 0$$

For Large Delays ($\tau_1 > 1, \tau_2 > 1$)

$a_1 + a_3 l < 1$, $a_2 + a_3 l < 1$ and $l < 1, a_3 < 1$, $\lambda = -2bl < 0$

So, the condition of the stability system:

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

For more stability, since $a_3 < 1$ one gets:

$$a_1 + a_2 + 2l < 2\,,\ a_1 + a_2 + 2\frac{a_1 + a_2}{b - a_3} < 2 \quad (9)$$

Example3. Let $\tau_1 = 0.1, \tau_2 = 0.2$, $a_1 = 0.1, a_2 = 0.2, a_3 = 0.3, b = 0.8, \text{and}\ h = 1$, equilibrium point $l = 0.6$, see Fig. 3.

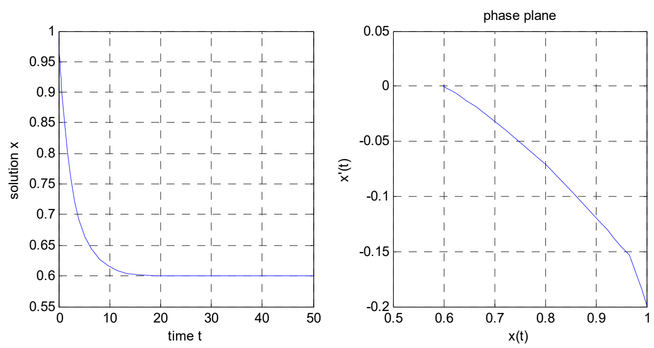

Fig. 3 The stability condition $a_1 + a_2 > 0$ satisfied

Example4. Let $\tau_1 = 0.1, \tau_2 = 0.2$ $a_1 = 0.1, a_2 = 0.2, a_3 = 8, b = 10, \text{and}\ h = 1$, fixed point $l = 0.15$, see Fig. 4.

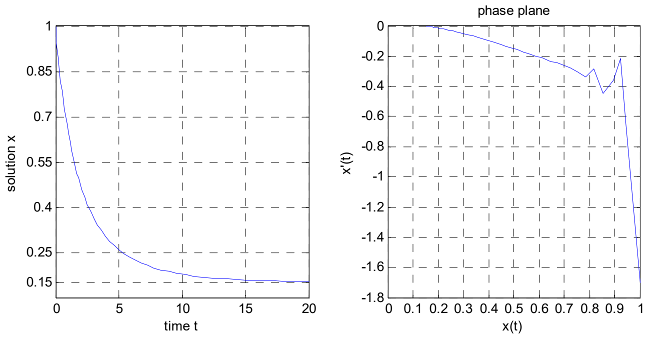

Fig. 4 The stability conditions $a_3 > 1$ and $a_1 + a_2 > 0$ different from the stability conditions for [5]

Example5. Let $\tau_1 = 50$, $\tau_2 = 300$ $a_1 = 0.1$, $a_2 = 0.2$, $a_3 = 0.4$, $b = 0.8$, $and\ s = 1$, fixed point $l = 0.75$, see Fig. 5.

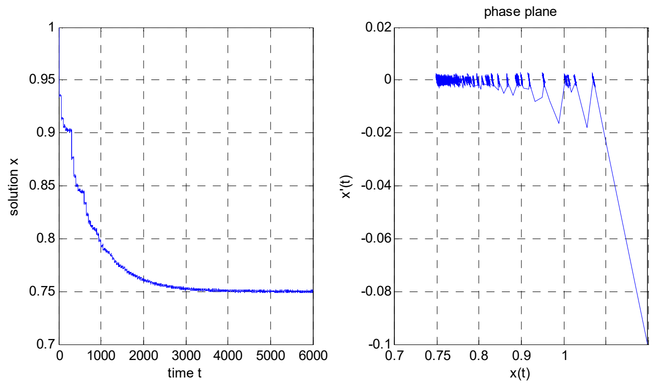

Fig. 5 In the case of large delays and after a long period of time, the solution stability

Example6. Let $\tau_1 = 50$, $\tau_2 = 300$ $a_1 = 0.1$, $a_2 = 0.2$, $a_3 = 0.7$, $b = 0.8$, $and\ s = 1$, see Fig. 6.

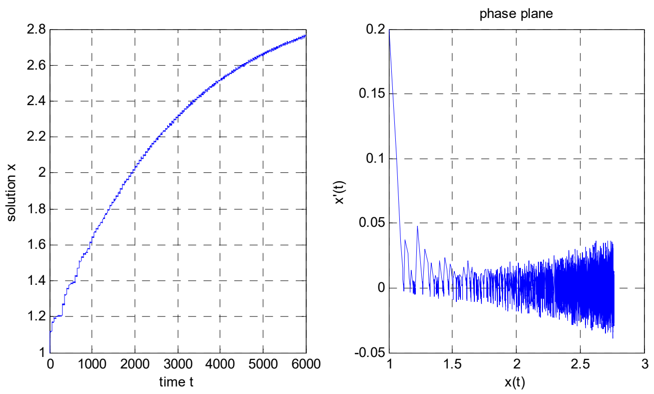

Fig. 6 The stability condition $a_1 + a_2 + a_3 < b$ not satisfied

IV. The QX-Modification Model

In this section, we will study another amendment to the original model in (1) under the same conditions, and the amendment will be as follows:

$$\frac{dx(t)}{dt} = a_1\, x(t-\tau_1) + a_2\, x(t-\tau_2) + a_3\, x(t-\tau_1)x(t-\tau_2) + qx$$
$$x(t) = h,\ t > 0\ \ and\ \ -\tau_2 < -\tau_1 < t < 0 \qquad (10)$$

Stability Analysis

Let,

$$f(x,x(t-\tau_1),x(t-\tau_2)) = a_1\, x(t-\tau_1) + a_2\, x(t-\tau_2) + a_3\, x(t-\tau_1)x(t-\tau_2) + qx$$

The system has critical points $x^* = 0$ and $x^* = -\dfrac{a_1 + a_2 + q}{a_3}$

$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_1)} = a_1 + a_3 x^*$$
$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t-\tau_2)} = a_2 + a_3 x^*$$
$$\frac{\partial f(x,x(t-\tau_1),x(t-\tau_2))}{\partial x(t)} = q$$

Stability for Zero Fixed Point ($x^* = 0$)

The equivalence linear system will be for $x^* = 0$:

$$\frac{dx(t)}{dt} = a_1\, x(t-\tau_1) + a_2\, x(t-\tau_2) + qx(t) \qquad (11)$$
$$x(t) = h,\ t > 0\ \ and\ \ -\tau_2 < -\tau_1 < t < 0$$

The characteristic equation is:

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

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

$$\lambda = a_1 + a_2 + q$$

The system will be stable if

$$a_1 + a_2 < -q \qquad (12)$$

- For large delays ($\tau_1 > 1$, $\tau_2 > 1$) the condition of stability system:

$$a_1 << 1, a_2 << 1 \text{ and } q < 0$$

Stability for Non-Zero Fixed Point ($x^* = -\dfrac{a_1 + a_2 + q}{a_3}$)

$$\frac{dx(t)}{dt} = -(a_2 + q)\,x(t-\tau_1) - (a_1 + q)\,x(t-\tau_2) + qx(t) \quad (13)$$

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

The characteristic equation is:

$$\lambda = -(a_2 + q)\,e^{-\lambda\tau_1} - (a_1 + q)\,e^{-\lambda\tau_2} + q$$

❖ For small delays ($\tau_1 << 1, \tau_2 << 1$)

$$\lambda = -(a_1 + a_2 + q)$$

The stability condition:

$$a_1 + a_2 + q > 0$$

and for positive fixed point $a_3 < 0$

❖ For large delays ($\tau_1 > 1, \tau_2 > 1$) the stability condition:

$$-a_2 - q << 1,\ -a_1 - q << 1,\ q < 0$$

and for positive fixed point: $a_3 < 0$

Example7. Let $\tau_1 = 0.1, \tau_2 = 0.2, a_1 = 0.1, a_2 = 0.2, a_3 = 0.7, q = -0.8,$ *and* $h = 0.5$, see Fig. 7.

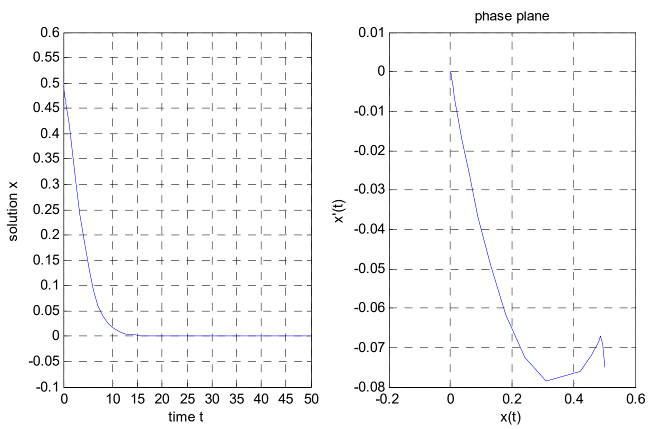

Fig. 7 The stability condition $a_1 + a_2 < -q$ satisfied

Example8. Let $\tau_1 = 0.1, \tau_2 = 0.2, a_1 = 0.1, a_2 = 0.2, a_3 = 0.7, q = -0.8,$ *and* $h = 0.5$, see Fig. 8.

Example9. Let $\tau_1 = 100, \tau_2 = 150, a_1 = 0.1, a_2 = 0.2, a_3 = -0.1, q = -0.5,$ *and* $h = 0.5$, see Fig. 9.

Example10. Let $\tau_1 = 100, \tau_2 = 150, a_1 = 0.3, a_2 = 0.4, a_3 = -0.1, q = -0.5,$ *and* $h = 0.5$, see Fig. 10.

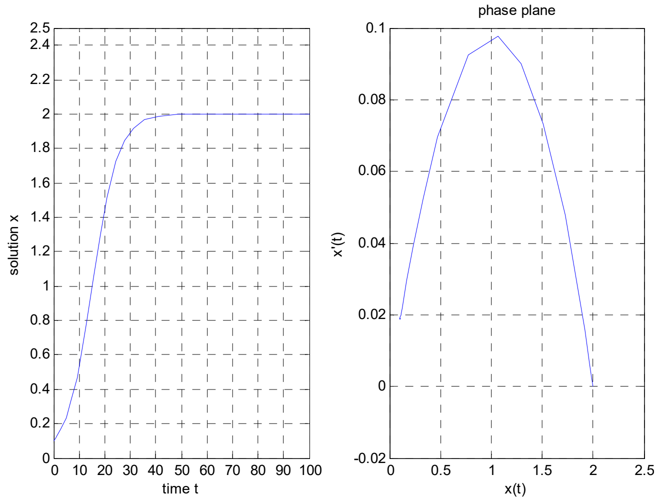

Fig. 8 Stability conditions $a_1 + a_2 + q > 0$ and $a_3 < 0$ satisfied

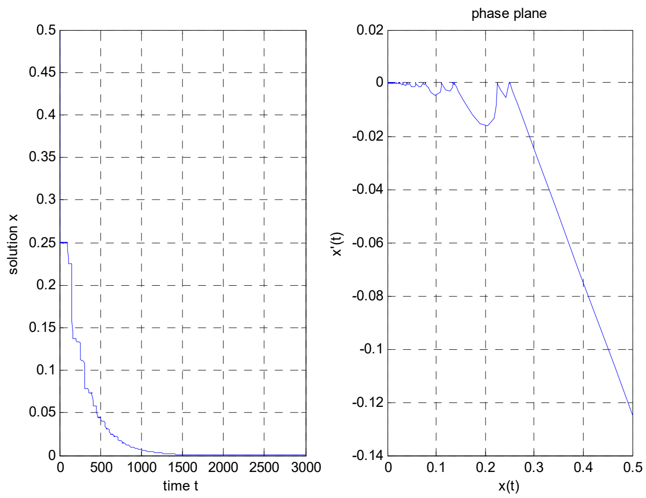

Fig. 9 Stability conditions $a_1 << 1, a_2 << 1$ *and* $q < 0$ satisfied

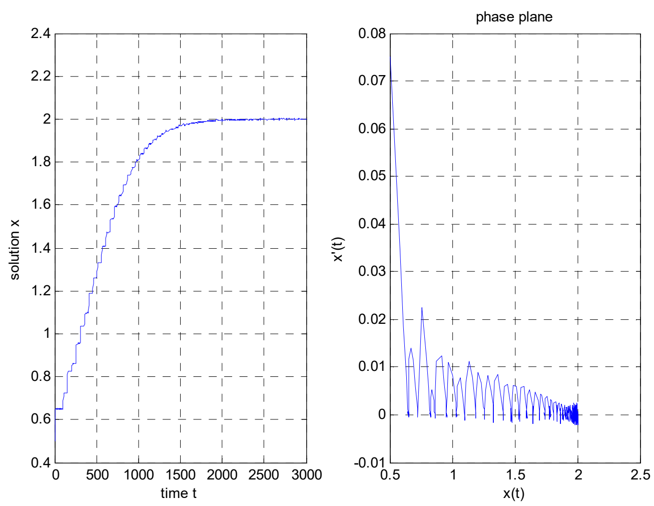

Fig. 10 Stability conditions $-a_2 - q << 1,\ -a_1 - q << 1,\ q < 0$ and $a_3 < 0$ satisfied

V. Conclusion

Model (1) was generalized. Kinematic defects have been expressed in general terms and the use of delay differential equations. A numerical example is given to illustrate stability conditions and not connected to any clinical data. It is explained that the value of negative and positive feedback determines the behavior of the model and the stability of the zero or non-zero stability point shown in Figs. 1 and 2.

When estimating the constants in Model (1), some positive values of the constants appeared, and this makes the model unstable, but far from the process of estimating the constants.

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 [7].

This paper focused on the mathematical aspect and determining the stability of these models without addressing any clinical data, which should be discussed in the future, and the extent to which these various modifications are compatible with the patients' clinical data.

The proposed suggestion has a more fitting parameter b and is compatible with biological systems. Stability conditions for the proposed modification are calculated and simulated with some figures. The effect of the two delays and stability conditions are discussed and shown in Figs. 3-10.

The proposed model in (1) is unbounded, as well as it is unstable in the case under study; it is stable if the negative feedback (control on) is greater than the positive (control off), but in the case of estimating the constants with positive values, it is unbounded and unstable and this is not consistent with any biological dynamic system. The model in (4) is proposed to solve this problem, but adding $-x^2$ is a restriction to the system, so we generalized this addition in our modification and generalized the conditions of equilibrium more and the system was stable even though the sum of the constants was greater than 1.

We presented another proposed modification in model in (1), which is to add the (qx) term to the model in (1), and we studied stability and determined its conditions under the same imposed conditions, which are the positive values of the constants, and the system had stability under specific conditions for the zero fixed point and the non-zero fixed point.

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