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SENSITIVITY ANALYSIS AND GLOBAL ATTRACTIVITY OF THE HPA AXIS IN A DEPRESSION MODEL

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Abstract: In this paper, we present mathematical model of depression that related hypothalamic-pituitary-adrenal (HPA) axis. HPA axis is an endocrine responsible for stress management that effects from changing level of hormones in HPA axis. Stress management affects the function of the HPA axis causing abnormal hormone secretion, which results in a tendency to depression. Dynamic of depression model is proposed by analysing positive and bounded solutions, existence of equilibria, local stability and sensitivity analysis of equilibrium point. Results of sensitivity analysis can determine which parameters have the most effect on the behaviour of the system. We also analyse global attractivity for impulsive behaviour of the HPA axis model. Moreover, some numerical results of these models may be more inspiring to treat patients more thoroughly and help to diagnose specific patients for low level of risk for depression.

Keywords: Depression; HPA axis; Mathematical modelling; Sensitivity analysis; Global attractivity;

I. INTRODUCTION

Feeling down from time to time is a normal part of life, but when emotions such as hopelessness and despair take hold and just won't go away, you may have depression. More than just sadness in response to life's struggles and setbacks, depression changes how you think, feel, and function in daily activities [1]. Depression is a mental disorder characterized fundamentally by depressive mood, loss of interest, and enjoyment of the positive aspects of life and fatigue, which impoverish the quality of life and generate difficulties in the family, work, and social environment of those who suffer it. Depression can manifest itself regardless of age, gender or socio-economic status.

More than 350 million people in the world suffer from depression, and this can become a serious health problem, especially when it is of long duration and moderate to severe intensity, and can cause great suffering and disrupt work, school, family, economic, and emotional activities, among others. However, you experience depression, left untreated it can become a serious health condition. In the worst case, it can lead to suicide, which is the cause of approximately 1 million deaths annually [2].According to

the World Health Organization (WHO) 1 in 20 of the world's population are currently suffering from the disease and patients' chance to become ill with repeated depression 50-70%, the cause is that the teenage suicide is higher. Some illnesses have a specific medical cause, making treatment straightforward, depression is far more complicated. In addition, severely different biological, psychological and social factors also contribute to the risk of depression [1]. Depression is a mental disease diagnosed by psychiatrists. Such diagnoses are based on patient interviews and symptoms with uncertainties as high as 30% as a consequence. In 2011, Vinther et al. [3] studied the modeling of the Hypothalamic-Pituitary-Adrenal (HPA) axis using an analytical and numerical approach, combined with biological knowledge regarding physiological mechanisms and parameters. In 2013, Andersen et al. [4] developed new HPA models resulting in more accurate by taking into account saturation concentration. In 2014, Hoeyer et al. [5] have been studying depression which is associated with malfunctions in HPA axis, the endocrine system of glands and their synthesized hormones. Later in 2017, Bangsgaard et al. [6] have developed a model of the HPA axis by mainly three hormones are CRH, ACTH and Cortisol. CRH is secreted in the hypothalamus where it is transported to the anterior pituitary then stimulates the synthesis of ACTH from the pituitary gland and ACTH stimulates the synthesis of the stress hormone cortisol. Cortisol has an impact on the whole body and especially feeds back by inhibit the secretion of CRH and ACTH from the respective glands. In this work, we develop the HPA axis model [6] with/without impulse and analyse dynamics and behaviors of three hormones as the following diagram.

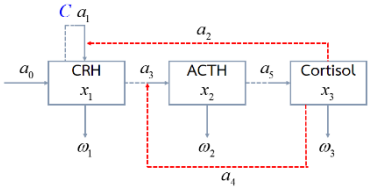


Fig. 1. The diagram of depression model

The HPA axis can be classify three hormones of CRH (x_1), ACTH (x_2) and cortisol (x_3) as the following:

$$\frac{dx_1}{dt} = a_0 + C\frac{a_1}{(1+a_2x_3^2)}\frac{x_1}{(\mu+x_1)} - \omega_1 x_1, \quad (1)$$

$$\frac{dx_2}{dt} = \frac{a_3x_1}{1+a_4x_3} - \omega_2 x_2, \quad (2)$$

$$\frac{dx_3}{dt} = a_5x_2^2 - \omega_3 x_3, \quad (3)$$

where initial conditions $x_1(0) = c_1 > 0, x_2(0) = c_2 > 0,$ $x_3(0) = c_3 > 0$ and all parameters are positive.The interpretation of parameter meanings for the model is shown in the following Table 1.

Table-I:The meaning of parameters for depression model [6]

Parameters	Meaning	Unit
m	Half saturation constant	pg/mL
a_0	Basic level of secretion of CRH	pg/(mL×min)
a_1	Maximal synthesis of CRH	pg/(mL×min)
a_2	Controls the inhibition of the synthesis of CRH through cortisol	$(\mathrm{dL}/mg)^2$
a_3	Stimulation of ACTH by CRH	min^{-1}
a_4	Inhibition of the synthesis of ACTH by cortisol	dL/mg
a_5	Stimulation of cortisol by ACTH	$\frac{mg/\mathrm{dL}}{\mathrm{min(pg/mL)}^2}$
w_1	The elimination rates of CRH	min^{-1}
w_2	The elimination rates of ACTH	min^{-1}
w_3	The elimination rates of cortisol	min^{-1}
C	Circadian rhythm	-

II. POSITIVE AND BOUNDED SOLUTIONS OF THE MODEL

First, we show that the levels of three hormones in the HPA axis model are non-negative as following lemma.

Lemma 1*All levels of three hormones of Eqs.(1)-(3)with any positive initial conditions are non-negative for all* $t..0$.

Proof: Consider a solution $(x_1(t), x_2(t), x_3(t))$ofEqs.(1)-(3)with the positive initial conditions. Assuming that there exists a $t_1 > 0$ such that $x_1(t_1) = 0$ and $dx_1(t_1)/dt,, 0$.
The equation (1)implies that

$$\frac{dx_1(t_1)}{dt} = a_0 > 0,$$

which contradicts with $dx_1(t_1)/dt,, 0$, so $x_1(t) > 0$ for all $t > 0$.
Next, the solution of Eq.(3)is gives

$$x_3(t) = x_3(0)e^{-w_3t} + a_5e^{-w_3t}\int_0^t x_2^2(s)e^{w_3s}ds > 0,$$

so $x_3(t) > 0$ for all $t > 0$.
Lastly, the solution of Eq.(2), we have

$$x_2(t) = x_2(0)e^{-w_2t} + a_3e^{-w_2t}\int_0^t \left(\frac{x_1(s)}{1+a_4x_3(s)}\right)e^{w_2s}ds$$

So, $x_2(t) > 0$ for all $t > 0$. This proof is complete. W

Lemma 2 *All hormone levels in the HPA axis model (1)-(3) with any positive initial conditions are bounded.*

Proof: From, Eq.(1), we have

$$\frac{dx_1}{dt} = a_0 + C\frac{a_1}{1+a_2x_3^2}\frac{x_1}{m+x_1} - w_1x_1,$$

$$\Rightarrow (a_0 + a_1) - w_1x_1.$$

therefore

$$x_1(t) \Rightarrow \left(\frac{a_0 + a_1}{w_1}\right) - \left(\frac{a_0 + a_1}{w_1}\right) + x_1(0)e^{-w_1t},$$

$$\Rightarrow \frac{a_0 + a_1}{w_1} = M_1, \text{ as } t \to \infty$$

so, $x_1(t) \Rightarrow M_1$. From Eq.(2), we have

$$\frac{dx_2(t)}{dt} = \frac{a_3x_1(t)}{1+a_4x_3(t)} - w_2x_2(t),$$

$$\Rightarrow a_3M_1 - w_2x_2(t),$$

Which gives $x_2(t) \Rightarrow (a_3M_1 / w_2) = M_2$, as $t \to \infty$.

Finally, in Eq.(3), it obtains

$$\frac{dx_3(t)}{dt} = a_5(x_2(t)^2) - w_3x_3(t),$$

$$\Rightarrow a_5M_2^2 - w_3x_3(t).$$

Hence $x_3(t) \Rightarrow (a_5M_2^2 / w_3) = M_3$ as $t \to \infty$.

The proof is complete. W

III. EXISTENCE OF EQUILIBRIUMS

From Eqs. (1)-(3), the system of algebraic equations as

$$a_0 + C\frac{a_1}{(1+a_2(x_3^*)^2)}\frac{x_1^*}{(m+x_1^*)} - w_1x_1^* = 0,$$

$$\frac{a_3x_1^*}{1+a_4x_3^*} - w_2x_2^* = 0, \qquad (4)$$

$$a_5(x_2^*)^2 - w_3x_3^* = 0,$$

can provide the first equilibrium point $E_0(0,0,0)$, $(a_0 = 0)$ and the second equilibrium point $(a_0 \neq 0)$, $E_1(x_1^*, x_2^*, x_3^*)$, where $x_3^* = (a_5(x_2^*)^2 / w_3) > 0$, the values of $x_1^*, x_2^* > 0$ are in the system of equations,

$$A_1x_1^* + (B_1 + C_1(x_2^*)^2)x_2^* = 0,$$

$$A_2x_1^* + (B_2x_1^* + C_2x_1^* + D_2)(x_2^*)^4 = E_2, \qquad (5)$$

where the constants are

$$A_1 = a_3w_3, \qquad B_1 = w_2w_3,$$

$$C_1 = a_4a_5w_2(x_2^*)^2,$$

$$A_2 = Ca_1w_3^2 - mw_1w_3^2 - w_1w_3^2x_1^* + a_0w_3^2,$$

$$B_2 = -a_2a_5^2w_1, \quad C_2 = a_0a_2a_5^2 - ma_2a_5^2w_1,$$

$$D_2 = ma_0a_2a_5^2, \quad E_2 = -ma_0w_3^2.$$

The Newton-Raphson method [7] can be applied to solve x_2^*, x_3^*.

IV. THE BASIC REPRODUCTION NUMBER

A basic reproductive number (R_0) is the average ratio number for the current levels of hormones as the first stage and the level of the hormone at the next time as second stage, which is widely used to analyse whether increasing or decreasing levels of hormones [8]. We apply the next-generation method [9] to compute a basic reproductive number (R_0) by compartment the HPA axis model as

$$\mathrm{F} = \begin{bmatrix} \frac{Ca_1x_1}{(a_2x_3^2+1)(m+x_1)} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \mathrm{V} = \begin{bmatrix} w_1x_1 - a_0 \\ \frac{a_3x_1}{a_4x_3+1} + w_2x_2 \\ -a_5x_2^2 + w_3x_3 \end{bmatrix}$$

Two Jacobian matrices of F and V at $E_0(0,0,0)$ can provide the next generation matrix as

$$FV^{-1} = \begin{bmatrix} Ca_1/mw_1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

where all eigenvalues of FV^{-1} are $l_1 = Ca_1/mw_1$, $l_{2,3} = 0$. Consequently, the basic reproduction number (R_0) is

$$R_0 = \frac{Ca_1}{mw_1}, \text{ where } a_0 = 0. \qquad (6)$$

If $R_0 < 1$, i.e. $Ca_1 < mw_1$ then the hormone cortisol will gradually decrease to 0, which means that the depression is slowing down. On the other hand, if $R_0 > 1$ cause more depression which affects to a patient.

V. THE LOCAL STABILITY OF THE HPA AXIS MODEL

The stability is a way of determining behaviour for three hormones and some sufficient conditions of local stability.

Lemma 3 *The hormone-free equilibrium* $E_0(0,0,0)$ *of HPA axis model Eqs. (1)-(3) is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$.

Proof: The Jacobian matrix of Eqs. (1)-(3) at $E_0(0,0,0)$ is obtained by

$$J(E_0) = \begin{bmatrix} (Ca_1/mw_1) - w_1 & 0 & 0 \\ a_3 & -w_2 & 0 \\ 0 & 0 & -w_3 \end{bmatrix}$$

where the characteristic equation is

$$(l + w_3)(l + w_2)(l - \frac{a_1C}{m} + w_1) = 0.$$

The necessary condition for local stability is the real parts of all eigenvalues must be negative. It is obvious that $l_1 = -w_3 < 0, l_2 = -w_2 < 0$ and

$$l_3 = \frac{Ca_1 - mw_1}{m} = w_1(R_0 - 1) < 0,\ R_0 < 1.$$

So, the hormone-free equilibrium $E_0(0,0,0)$ is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. W

Lemma 4 *The equilibrium* $E_1(x_1^*, x_2^*, x_3^*)$, $x_i^* \neq 0$, $i = 1,2,3$ *in (1)-(3) is locally asymptotically stable, when* $d_1 d_2 > d_3$ *which is sufficient conditions of the Routh-Hurwitz criterion [10].*

Proof: The Jacobian matrix of the model at E_1 is

$$J(E_1) = \begin{bmatrix} D & 0 & -2Aa_2 x_1^* x_3^* (m + x_1^*) \\ B(a_4 x_3^* + 1) & -w_2 & -Ba_4 x_1^* \\ 0 & 2a_5 x_2^* & -w_3 \end{bmatrix}$$

where $D = A(a_2(x_3^*)^2 + 1)(m + x_1^*) - Ax_1^*(a_2(x_3^*)^2 + 1) - w_1$, $A = a_1 C / (a_2(x_3^*)^2 + 1)^2 (m + x_1^*)^2$ and $B = a_3 / (a_4 x_3^* + 1)^2$, so the characteristic equation becomes

$$l^3 + d_1 l^2 + d_2 l + d_3 = 0,$$

and all coefficients are

$$d_1 = w_1 + w_2 + w_3 - \frac{a_1 Cm}{(a_2(x_3^*)2 + 1)(m + x_1^*)^2} > 0,$$

$$d_2 = \frac{2a_3 a_4 a_5 x_1^* x_2^*}{(a_4 x_3^* + 1)^2} + w_1(w_2 + w_3) + w_2 w_3 - \frac{a_1 Cm(w_2 + w_3)}{(a_2 x_3^{*2} + 1)(m + x_1^*)^2} > 0,$$

$$d_3 = \frac{2Ca_1 a_2 a_3 a_5 x_1^* x_2^* x_3^* (ma_4 x_3^* + 2a_4 x_1^* x_3^* + 2m)}{(a_4 x_3^* + 1)^2 (a_2 x_3^{*2} + 1)^2 (m + x_1^*)^2} + \frac{2Ca_1 a_3 a_5 x_1^* x_2^* (2a_2 x_1^* x_3^* - ma_4)}{(a_4 x_3^* + 1)^2 (a_2(x_3^*)^2 + 1)^2 (m + x_1^*)^2} + w_1 w_2 w_3 + \frac{2a_3 a_4 a_5 w_1 x_1^* x_2^*}{(a_4 x_3^* + 1)^2} - \frac{Cma_1 w_2 w_3}{(a_2 x_3^{*2} + 1)(m + x_1^*)^2} > 0$$

$$d_1 d_2 - d_3 = w_1^2(w_2 + w_3) + w_2^2(w_1 + w_3) + w_3^2(w_1 + w_2) + 2w_1 w_2 w_3 + \frac{2a_3 a_4 a_4 x_1^* x_2^* (w_1 + w_2 + w_3)}{(a_4 x_3^* + 1)^2} + \frac{C^2 m^2 a_1^2 (w_2 + w_3)}{(a_2(x_3^*)^2 + 1)^2 (m + x_1^*)^4} + \frac{Cma_1 w_2 w_3}{(a_2(x_3^*)^2 + 1)(m + x_1^*)^2} - \frac{Cma_1(2w_1 w_2 + 2w_1 w_3 + 3w_2 w_3 + w_2^2 + w_3^2)}{(a_2 x_3^{*2} + 1)(m + x_1^*)^2} - \frac{4Ca_1 a_2 a_3 a_5 x_1^* x_2^* x_3^*}{(a_2(x_3^*)^2 + 1)^2 (a_4 x_3^* + 1)(m + x_1^*)} - \frac{2a_3 a_4 a_5 w_1 x_1^* x_2^*}{(a_4 x_3^* + 1)^2}.$$

Since $d_1 > 0, d_3 > 0$, if $d_1 d_2 - d_3 > 0$ which satisfies the Routh-Hurwitz criterion, then $E_1(x_1^*, x_2^*, x_3^*)$ is asymptotically stable. W

In numerical simulation for the HPA axis model, the parameter values are given in Table 2.

Table-II:The parameter values of depression model [6]

Parameters	Meaning	Unit
m	5.8300×10^2	pg/mL
a_0	3.9031×10^{-4}	pg/(mL×min)
a_1	6.8390×10^{12}	pg/(mL×min)
a_2	1.7809×10^9	$(\mathrm{dL}/mg)^2$
a_3	2.2803×10^4	min^{-1}
a_4	1.7745×10^5	dL/mg
a_5	4.6170×10^{-4}	$\frac{mg/\mathrm{dL}}{\mathrm{min}(\mathrm{pg/mL})^2}$
w_1	0.0337	min^{-1}
w_2	0.0205	min^{-1}
w_3	0.0238	min^{-1}
C	0.07978	-

The numerical results and all parameters in Table 2, the equilibrium $E_1(8.895, 14.218, 3.922)$ is local stability by Lemma 4 where the values of $d_1 = 0.045 > 0$, $d_2 = 0.001 > 0$ and $d_1 d_2 - d_3 = 2.507 \times 10^{-7} > 0$. The graphs of solutions are depicted for determining the local stability for $0 \leq t \leq 14400$ (mins) as shown in the following graphs.

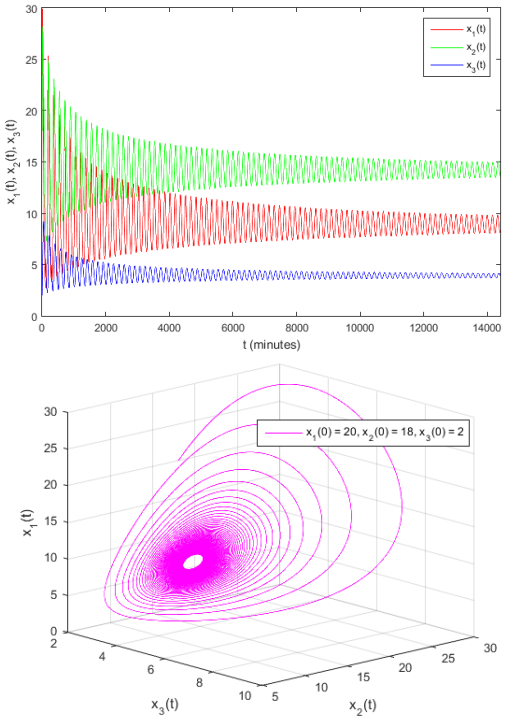


Fig. 2: Graph of local stability for the depression model.

VI. SENSITIVITY ANALYSIS OF THE EQUILIBRIUM POINT

A sensitivity analysis is the study of how changing values of parameter that effect to some levels of hormones in the HPA axis model. The sensitivity index can determine the most effective parameters for changing levels of a hormone. Define $x_i^* \in \{x_1^*, x_2^*, x_3^*\}$ and $k_j \in \{a_0, a_1, a_2, a_3, a_4, a_5, m, w_1, w_2, w_3\}, j = 1,2,\ldots,10.$

The sensitivity index [6] of x_i^* with respect to parameters k_j is defined by

$$SI(x_i^*, k_j) = \frac{k_j}{x_i^*}\left(\frac{\partial x_i^*}{\partial k_j}\right), \quad i = 1,2,3, \quad j = 1,2,3,\ldots,10.$$

Taking partial derivative for each $x_i^*, i = 1,2,3$ in the system (4)with respect to the parameter a_0, it obtains

$$\frac{\partial}{\partial a_0}\left(a_0 + C\frac{a_1}{(1+a_2(x_3^*)^2)}\frac{x_1^*}{(m+x_1^*)} - w_1 x_1^*\right) = -1,$$

$$\frac{a_3}{1+a_4 x_1^*}\left(\frac{\partial x_1^*}{\partial a_0}\right) - w_2\left(\frac{\partial x_2^*}{\partial a_0}\right) - \frac{a_3 a_4 x_1^*}{(1+a_4 x_1^*)^2}\left(\frac{\partial x_3^*}{\partial a_0}\right) = 0,$$

$$2a_5 x_2^*\left(\frac{\partial x_2^*}{\partial a_0}\right) - w_3\left(\frac{\partial x_3^*}{\partial a_0}\right) = 0,$$

it obtains the matrix equation

$$\begin{bmatrix} D - w_1 & 0 & E \\ B(a_4 x_3^* + 1) & -w_2 & -Ba_4 x_1^* \\ 0 & 2a_5 x_2^* & -w_3 \end{bmatrix} \begin{bmatrix} \frac{\partial x_1^*}{\partial a_0} \\ \frac{\partial x_2^*}{\partial a_0} \\ \frac{\partial x_3^*}{\partial a_0} \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}$$

where

$$A = \frac{a_1 C}{\left(a_2(x_3^*)^2 + 1\right)^2 (m + x_1^*)^2}, \quad B = \frac{a_3}{(a_4 x_3^* + 1)^2},$$

$$D = A\left(a_2(x_3^*)^2 + 1\right)(m + x_1^*) - Ax_1^*\left(a_2(x_3^*)^2 + 1\right),$$

$$E = -2Aa_2 x_1^* x_3^* (m + x_1^*).$$

The partial derivatives $\partial x_i^* / \partial a_0, i = 1,2,3$ can be solve, $i = 3$, for exaple the sensitivity index is

$$SI(x_3^*, a_0) = \frac{a_0}{x_3^*}\left(\frac{\partial x_3^*}{\partial a_0}\right) = \frac{2Ba_0 w_3^2\left(a_4 a_5 (x_2^*)^2 + w_3\right)}{M},$$

where

$$M = \left(2ABa_2 a_4 a_5^3 x_1^* (x_2^*)^5 (m + 2x_1^*) - Aa_2 a_5^2 w_3 (x_2^*)^3 \left(mw_2 x_2^* - 4Bx_1^*(m + x_1^*)\right) - w_3^2 (Am - w_1)(2Ba_4 a_5 x_1^* x_2^* + w_2 w_3)\right) x_2^*.$$

The sensitivity index of x_1^*, x_2^* and x_3^* for each parameter can be shown in Table 2 with the parameters in Table 3.

Table-III:Sensitivity indices for the equilibrium point

Parameters	x_1^*	x_2^*	x_3^*
m	0.00097	0.00032	0.00064
a_0	0.74092 (3)	0.24697	0.49395 (2)
a_1	-0.74092 (3)	-0.24697	-0.49395 (2)
a_2	-0.98790 (1)	0.00403	0.00807
a_3	0.98790 (1)	-0.00403	-0.00807
a_4	-0.49395	-0.49798	0.00403
a_5	-0.72979 (4)	-0.24326	-0.48653 (3)
w_1	-0.74189 (2)	-0.24730	-0.49459 (1)
w_2	0.98790 (1)	-0.00403	-0.00807
w_3	0.49395	0.49798	-0.00403

Table 3 shows that the parameters $a_3, a_4,$ and w_2 are the most effective parameters to hormone x_1. For example, if a_4 and w_2 decrease or a_3 increases, then the hormone levels of x_1 decreases rapidly.In the other hand, decreasing hormone cortisol x_3 we have to increasing w_1, a_2 and deceasing a_1 for reducing hormone cortisol.

VII. GLOBAL ATTRACTIVITY OF THE HPA AXIS MODEL

Too much stress that affects from high levels of hormone cortisol may cause abnormally high levels of risk for depression. In this section, we extend the HPA axis model by including impulsive condition in order to controlling high levels of risk for depression as

$$\begin{cases} \dfrac{dx_1}{dt} = a_0 + C\dfrac{a_1}{(1+a_2 x_3^2)}\dfrac{x_1}{(m+x_1)} - w_1 x_1, \\ \dfrac{dx_2}{dt} = \dfrac{a_3 x_1}{1+a_4 x_3} - w_2 x_2, \\ \dfrac{dx_3}{dt} = a_5 x_2^2 - w_3 x_3, \end{cases} \quad t \neq nT, \tag{7}$$

$$\begin{cases} x_1(t^+) = x_1(t), \\ x_2(t^+) = x_2(t), \\ x_3(t^+) = (1-q)x_3(t), \end{cases} \quad t = nT.$$

In addition, $x_1(t^+), x_2(t^+)$ and $x_3(t^+)$ represent the levels of hormones CRH, ACTH and cortisol after the n^{th} pulse. We determine the amount of medication dispensed to

patients $q \in [0,1)$ at each moment of pulsing time nT, where $n = 1, 2, \ldots$, and T is the period of impulsive effect, into the HPA axis model. Here, some definitions, notations are useful for our main results.

Definition 1*(Dini derivative [11])*

The right upper Dini derivative $D^+ f(t)$ *of a continuous function* $f : \square \to \square$ *at* t *is*

$$D^+ f(t) = \limsup_{h \to 0^+} \frac{f(t+h) - f(t)}{h}.$$

If f *is differentiable at* t*, then* $D^+ f(t) = df(t)/dt$*, where* $df(t)/dt$ *is the usual derivative at* t*.*

Definition 2*A model is said to be globally attractive [12], if for any two solutions* $x_1(t)$ *and* $x_2(t)$*, then*

$$\lim_{t \to \infty} |x_1(t) - x_2(t)| = 0.$$

Lemma 5*(Barbalat's lemma [13]) Let* f *be a non-negative function defined on* $[0, \infty)$ *such that* f *is integrable on* $[0, \infty)$ *and uniformly continuous on* $[0, \infty)$*, then* $\lim_{t \to \infty} f(t) = 0.$

Theorem 1*Suppose that there exist constants* $\mu_i > 0, i = 1, 2, 3$ *such that* $A_j > 0, j = 0, 1, 2$ *where*

$$\begin{aligned} A_0 &= \mu_1 \operatorname{sign}\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right)\Big\{a_1 C M_1 \\ &\quad \cdot \left(\frac{1}{(1 + a_2 M_3^2)(\mu + M_1)} - \frac{1}{(\mu + m_1)}\right)\Big\} \\ &\quad + \mu_2 \operatorname{sign}\left(x_2^{(1)}(t) - x_2^{(2)}(t)\right)\Big\{a_3 M_1 n \\ &\quad \cdot \left(\frac{1}{1 + a_4 M_3} - \frac{1}{1 + a_4 m_3}\right)\Big\}, \end{aligned} \tag{8}$$

$$A_1 = \mu_1 \omega_1 - \frac{\mu_1 a_1 C}{\left(1 + a_2 m_3^2\right)(\mu + m_1)} - \frac{\mu_2 a_3}{1 + a_4 m_3},$$

$$A_2 = \mu_2 \omega_2 - 2\mu_3 a_5 M_2,$$

where M_1, M_2 *and* M_3 *are given in Lemma 2. Then solution of Eqs. (1)-(3)is globally attractive.*

Proof: Let $\left(x_1^{(1)}(t), x_2^{(1)}(t), x_3^{(1)}(t)\right)$ and $\left(x_1^{(2)}(t), x_2^{(2)}(t), x_3^{(2)}(t)\right)$ be any solutions of the HPA axis model in Eqs. (1)-(3). From Lemma 2, without loss of generality, we may assume that

$$m_1 \le x_1^{(k)}(t) \le M_1,\ m_2 \le x_2^{(k)}(t) \le M_2,\ m_3 \le x_3^{(k)}(t) \le M_3,$$

for all $t \ge 0$ and $k = 1, 2$. We define a function is $V_1(t) = \mu_1 \left|x_1^{(1)}(t) - x_1^{(2)}(t)\right|$ then the right upper Dini derivative of $V_1(t)$ along Eq. (1) is given by

$$\begin{aligned} D^+ V_1(t) &= D^+ \mu_1 \left|x_1^{(1)}(t) - x_1^{(2)}(t)\right|, \\ &= \mu_1 \operatorname{sign}\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right)\left\{D^+ x_1^{(1)}(t) - D^+ x_1^{(2)}(t)\right\}, \\ &= \mu_1 \operatorname{sign}\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right) \\ &\quad \Bigg\{a_1 C \cdot \Bigg[\frac{x_1^{(1)}(t)}{\left(1 + a_2\left(x_3^{(1)}(t)\right)^2\right)\left(\mu + x_1^{(1)}(t)\right)} \\ &\quad - \frac{x_1^{(2)}(t)}{\left(1 + a_2\left(x_3^{(2)}(t)\right)^2\right)\left(\mu + x_1^{(2)}(t)\right)}\Bigg] \\ &\quad - \omega_1\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right)\Bigg)\Bigg\}, \\ &\le \mu_1 \operatorname{sign}\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right) \\ &\quad \Bigg\{a_1 C \cdot \left(\frac{x_1^{(1)}(t)}{(\mu + m_1)} - \frac{x_1^{(2)}(t)}{(1 + a_2 M_3^2)(\mu + M_1)}\right) \\ &\quad - \omega_1 (x_1^{(1)}(t) - x_1^{(2)}(t))\Big\}, \\ &= \mu_1 \operatorname{sign}\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right)\Bigg\{a_1 C\Bigg(\frac{x_1^{(1)}(t)}{(\mu + m_1)} - \frac{x_1^{(2)}(t)}{(\mu + m_1)} \\ &\quad + \frac{x_1^{(2)}(t)}{(\mu + m_1)} - \frac{x_1^{(2)}(t)}{(1 + a_2 M_3^2)(\mu + M_1)}\Bigg) \\ &\quad - \omega_1 (x_1^{(1)}(t) - x_1^{(2)}(t))\Big\}, \\ &\le \mu_1 \operatorname{sign}\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right)\Bigg\{\frac{a_1 C}{(\mu + m_1)}\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right) \\ &\quad + a_1 C M_1\left(\frac{1}{(\mu + m_1)} - \frac{1}{(1 + a_2 M_3^2)(\mu + M_1)}\right) \\ &\quad - \omega_1 (x_1^{(1)}(t) - x_1^{(2)}(t))\Big\}, \\ &= \mu_1 \operatorname{sign}\left(x_1^{(1)}(t) - x_1^{(2)}(t)\right)\Bigg\{a_1 C M_1\Bigg(\frac{1}{(\mu + m_1)} \\ &\quad - \frac{1}{(1 + a_2 M_3^2)(\mu + M_1)}\Bigg\}\Bigg) \\ &\quad + \mu_1 \left\{\left(\frac{a_1 C}{(\mu + m_1)} - \omega_1\right)\left|x_1^{(1)}(t) - x_1^{(2)}(t)\right|\right\}. \end{aligned}$$

Define $V_2(t) = \mu_2 \,|\, x_2^{(1)}(t) - x_2^{(2)}(t) \,|$. The right upper Dini derivative along Eq. (2), we have

$$D^+V_2(t)=\mu_2\text{sign}\left(x_2^{(1)}(t)-x_2^{(2)}(t)\right)$$
$$\left\{a_3\left(\frac{x_1^{(1)}(t)}{1+a_4m_3}-\frac{x_1^{(2)}(t)}{1+a_4m_3}+\frac{x_1^{(2)}(t)}{1+a_4m_3}-\frac{x_1^{(2)}(t)}{1+a_4M_3}\right)\right.$$
$$\left.-\omega_2\left(x_2^{(1)}(t)-x_2^{(2)}(t)\right)\right\},$$
$$,, \mu_2\text{sign}\left(x_2^{(1)}(t)-x_2^{(2)}(t)\right)$$
$$\left\{\frac{a_3}{1+a_4m_3}\left(x_1^{(1)}(t)-x_1^{(2)}(t)\right)\right.$$
$$+a_3M_1\left(\frac{1}{1+a_4m_3}-\frac{1}{1+a_4M_3}\right)$$
$$\left.-\omega_2\left(x_2^{(1)}(t)-x_2^{(2)}(t)\right)\right\},$$
$$,, \mu_2\text{sign}\left(x_2^{(1)}(t)-x_2^{(2)}(t)\right)\left\{a_3M_1\left(\frac{1}{1+a_4m_3}\right.\right.$$
$$\left.\left.-\frac{1}{1+a_4M_3}\right)\right\}+\mu_2\left\{\frac{a_3}{1+a_4m_3}\left|x_1^{(1)}(t)-x_1^{(2)}(t)\right|\right.$$
$$\left.-\omega_2\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|\right\}.$$

Finally define $V_3(t)=\mu_3\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|$. Then the Dini derivative of V_3 is

$$D^+V_3(t)=\mu_3\text{sign}\left(x_3^{(1)}(t)-x_3^{(2)}(t)\right)\left\{a_5\left(x_2^{(1)}(t)\right)^2-\left(x_2^{(2)}(t)\right)^2\right.$$
$$\left.-\omega_3\left(x_3^{(1)}(t)-x_3^{(2)}(t)\right)\right\},$$
$$=\mu_3\text{sign}(x_3^{(1)}(t)-x_3^{(2)}(t))\left\{a_5\left(x_2^{(1)}(t)-x_2^{(2)}(t)\right)\right.$$
$$\left.\cdot\left(x_2^{(1)}(t)+x_2^{(2)}(t)\right)-\omega_3\left(x_3^{(1)}(t)-x_3^{(2)}(t)\right)\right\},$$
$$,, \mu_3\text{sign}\left(x_3^{(1)}(t)-x_3^{(2)}(t)\right)\left\{2a_5M_2\left(x_2^{(1)}(t)+x_2^{(2)}(t)\right)\right.$$
$$\left.-\omega_3\left(x_3^{(1)}(t)-x_3^{(2)}(t)\right)\right\},$$
$$,, \mu_3\left\{2a_5M_2\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|-\omega_3\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|\right\}.$$

Define the Lyapunov function $V(t)=V_1(t)+V_2(t)+V_3(t),$ it obtains

$$D^+V(t),, -\left[\mu_1\text{sign}\left(x_1^{(1)}(t)-x_1^{(2)}(t)\right)\left\{a_1CM_1\right.\right.$$
$$\left.\cdot\left(\frac{1}{(1+a_2M_3^2)(\mu+M_1)}-\frac{1}{(\mu+m_1)}\right)\right\}$$
$$+\mu_2\text{sign}\left(x_2^{(1)}(t)-x_2^{(2)}(t)\right)\left\{a_3M_1\right.$$
$$\left.\left.\cdot\left(\frac{1}{1+a_4M_3}-\frac{1}{1+a_4m_3}\right)\right\}\right]$$
$$-\left(\mu_1\omega_1-\frac{\mu_1a_1C}{(\mu+m_1)}-\frac{\mu_2a_3}{1+a_4m_3}\right)\left|x_1^{(1)}(t)-x_1^{(2)}(t)\right|$$
$$-\left(\mu_2\omega_2-2\mu_3a_5M_2\right)\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|$$
$$-\left(\mu_3\omega_3\right)\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|,$$
$$=-\left(A_0+A_1\left|x_1^{(1)}(t)-x_1^{(2)}(t)\right|\right.$$
$$\left.+A_2\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|+A_3\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|\right).$$

For $t=nT, n=1, 2, \ldots,$ we can obtain that

$$V(t^+)=V_1(t^+)+V_2(t^+)+V_3(t^+)$$
$$=\mu_1\left|x_1^{(1)}(t^+)-x_1^{(2)}(t^+)\right|+\mu_2\left|x_2^{(1)}(t^+)-x_2^{(2)}(t^+)\right|$$
$$+\mu_3\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|,$$
$$=\mu_1\left|x_1^{(1)}(t^+)-x_1^{(2)}(t^+)\right|+\mu_2\left|x_2^{(1)}(t^+)-x_2^{(2)}(t^+)\right|$$
$$+\mu_3\left|(1-q)x_3^{(1)}(t)-(1-q)x_3^{(2)}(t)\right|,$$
$$=\mu_1\left|x_1^{(1)}(t^+)-x_1^{(2)}(t^+)\right|+\mu_2\left|x_2^{(1)}(t^+)-x_2^{(2)}(t^+)\right|$$
$$+(1-q)\mu_3\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|,$$
$$=V_1(t)+V_2(t)+(1-q)V_3(t)=V(t).$$

Since $A_j,\ j=0,1,2$ are defined in Eq.(8) and $A_3=\mu_3\omega_3>0$. Then we select $\xi>0$ such that $\xi=\min\{A_0,A_1,A_2\}$. In consequence, we obtain for all $t..T_0$

$$D^+V(t),, -\xi\left(1+\left|x_1^{(1)}(t)-x_1^{(2)}(t)\right|+\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|\right.$$
$$\left.+\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|\right), \quad (9)$$
$$,, -\xi z(t),$$

where

$$z(t)=\left|x_1^{(1)}(t)-x_1^{(2)}(t)\right|+\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|+\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|,$$

so $D^+V(t),, -\xi z(t),, N,\ N>0.$

Consider $\mu=\min\{\mu_1,\mu_2,\mu_3\}$ in Eq. (9), then

$$\mu z(t),, \mu_1\left|x_1^{(1)}(t)-x_1^{(2)}(t)\right|+\mu_2\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|$$
$$+\mu_3\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|, \quad (10)$$
$$=V(t),$$

taking the right upper Dini derivative along Eq.(10), we have $\mu D^+z(t),, D^+V(t),, N,$ thus $D^+z(t),, (N/\mu)=M,$

and $D^{+}z(t)$ is bounded. Integrating Eq. (9)from T_0 to t, then we have

$$V(t)+\xi\int_{T_0}^{t} z(s)ds \;,,\; V(T_0),$$

which gives

$$\xi\int_{T_0}^{t} z(s)ds,,\; V(t)+\xi\int_{T_0}^{t} z(s)ds,,\; V(T_0),\; V(t)>0.$$

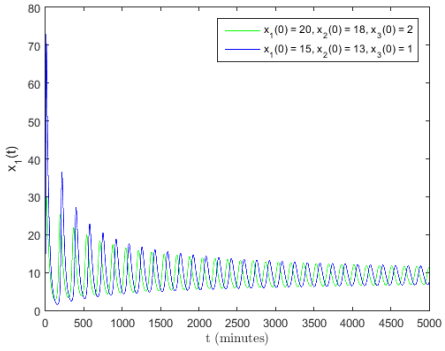
Hence,

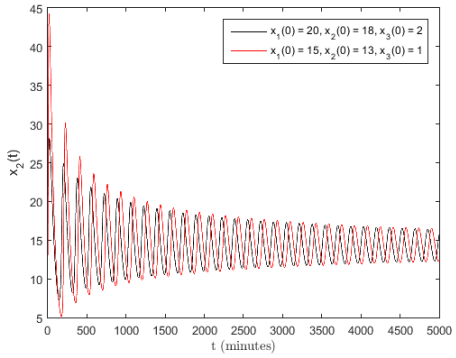
$$\xi\int_{T_0}^{t} z(s)ds<\infty \text{ or } \int_{T_0}^{t} z(s)ds<\infty. \qquad (11)$$

So, $z(t)$ is integrableon $[0,\infty)$. Since $A_j>0,\ j=0,1,2,3$ and the solutions $\left(x_1^{(1)}(t),\ x_2^{(1)}(t),\ x_3^{(1)}(t)\right)$ and $\left(x_1^{(2)}(t),\ x_2^{(2)}(t),\ x_3^{(2)}(t)\right)$ on $[0,\infty)$ are bounded by Lemma 2. So, $\left|x_1^{(1)}(t)-x_1^{(2)}(t)\right|,\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|$ and $\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|$ are bounded and uniformly continuous [14]on $[0,\infty)$. By Lemma 5, then

$$\lim_{t\to\infty}\left|x_1^{(1)}(t)-x_1^{(2)}(t)\right|=0,$$
$$\lim_{t\to\infty}\left|x_2^{(1)}(t)-x_2^{(2)}(t)\right|=0,$$
$$\lim_{t\to\infty}\left|x_3^{(1)}(t)-x_3^{(2)}(t)\right|=0.$$

Therefore, all solution are globally attractive. W
The following graphs show the levels of three hormones (x_1,x_2,x_3) with two initial conditions $(2,18,10)$, $(60,30,18)$ respectively in 5000 minutes.





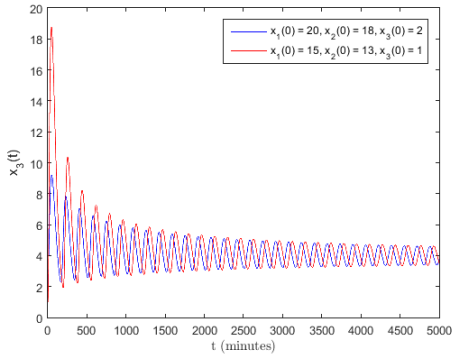
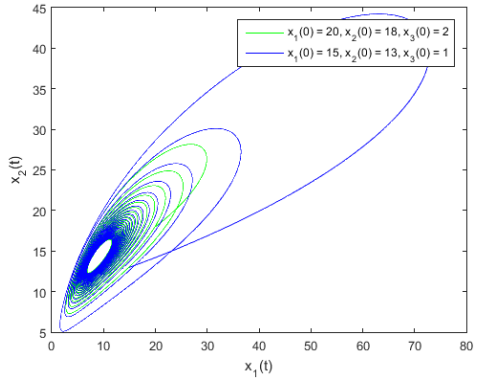
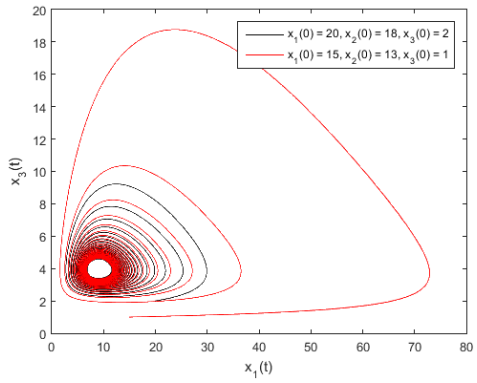


Fig. 3. Graphs of hormones x_1, x_2 and x_3 respectively





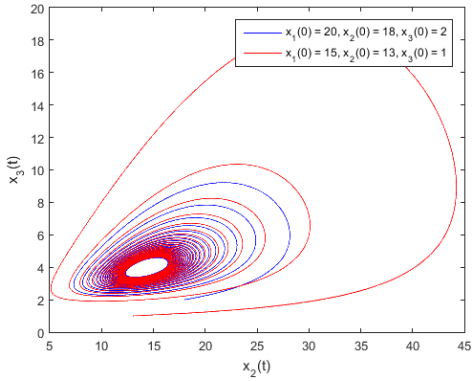


Fig. 4. Phase planes of hormones (x_1, x_2), (x_1, x_3) and (x_2, x_3)

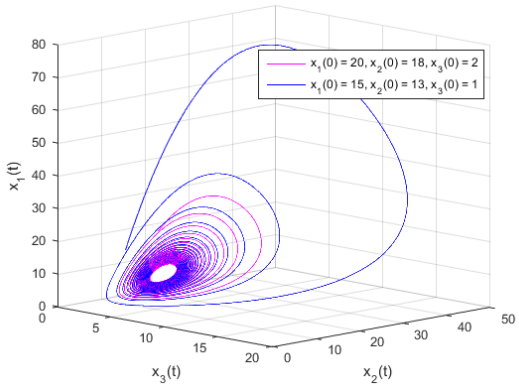
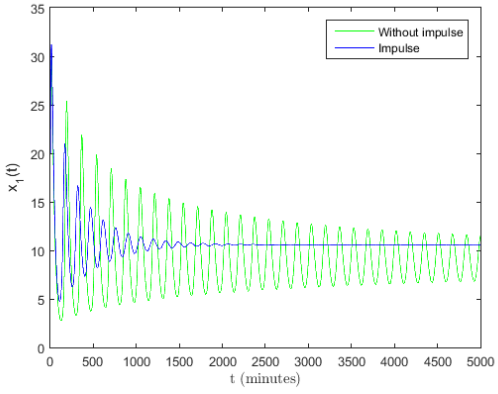
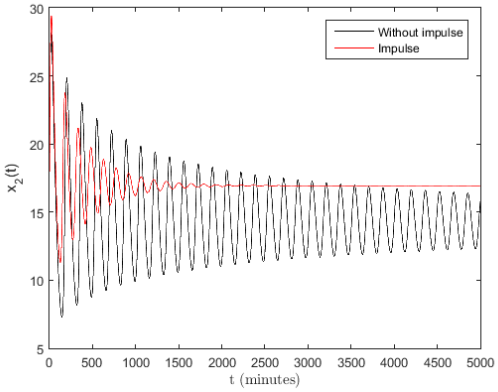


Fig. 5. Graph 3-D of all three hormones

Finally, we compare numerical results of the model between without impulse and impulse behavior, where $q = 0.01$ and $T = 1$ for $t \in [0, 5000]$ with the initial condition $(20, 18, 2)$ by using the parameter values in Table 2.





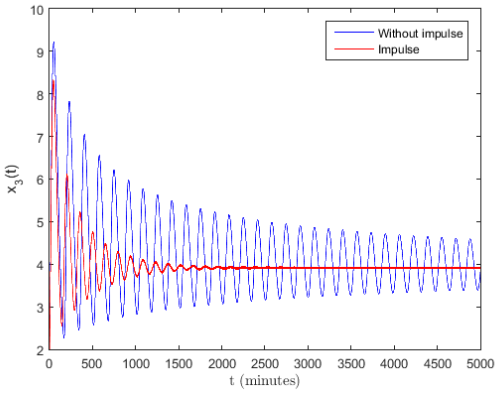
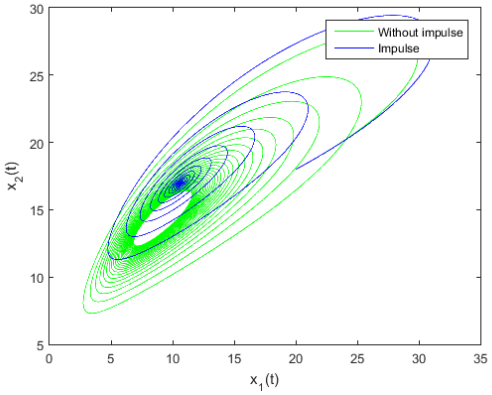
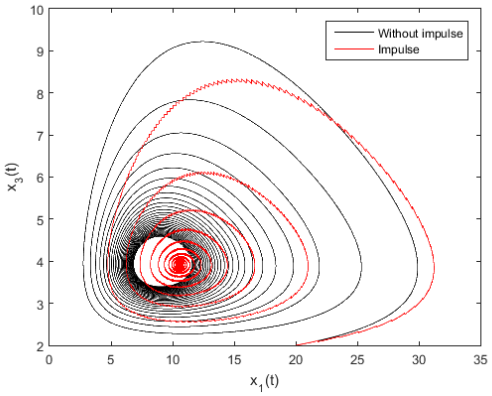


Fig. 6. Graphs of hormones x_1, x_2 and x_3 respectively





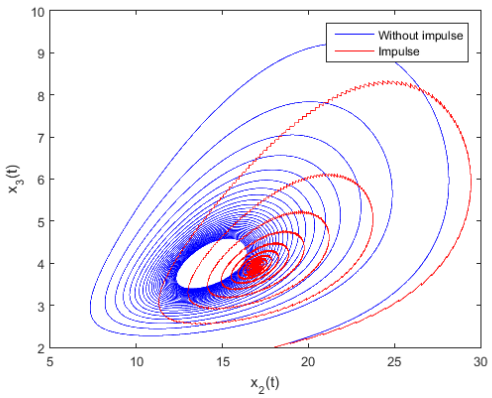


Fig. 7. Phase planes of hormones (x_1, x_2), (x_1, x_3) and (x_2, x_3)

VIII. Conclusion

In this work, we studied the mathematical HPA axis model with/without impulse condition and further analyzed it in the case of the HPA axis model in order to be able to interpret system behavior over a longer period of time. For sensitivity analysis of the equilibrium point, we are able to determine which parameters are the most affect to hormonal changes in the system. Finally, we investigate conditions for global attractivity for impulsive behavior of the HPA axis model. The results of sensitivity analysis and global attractivity in the HPA axis model can be used for treatment and medication to patients precisely.

IX. Acknowledgment

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