



Permanence and Global Attractivity of a HPA Axis Model Related to Depression

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Abstract : In this paper, a non-autonomous system of the HPA axis, i.e., the hypothalamic-pituitary-adrenal axis. The periodic bell-shaped circadian rhythm function is used in the model. The HPA axis regulates the levels of glucocorticoid hormones in the blood. The axis is an endocrine system which is responsible for coping with stress and depression. Non-negativity of solutions of the model is established. Some sufficient conditions for the permanence of the model are obtained by using the comparison theorem. The global attractivity of the model is proved by constructing a Lyapunov function and using the right upper Dini derivative. Some time series solutions and phase portraits of the model are numerically presented to confirm the analytical results.

Keywords : depression; HPA axis; mathematical modeling.

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1 Introduction

Depression is a disease characterized by an emotional disorder. The patient suffers from the disease because it discourages learning, working and living. By the World Health Organization, 1 in 20 of the world's population is ill with this

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disease and the risk of the disease recurrence is 50-70%. Depression is the leading cause of committing suicide among adolescents. In Thailand, adolescents aged 10-19 years are at risk for depressive disorder by 44% or about 3 million from all adolescents 8 million [1].

In biological and psychosocial factors, depression is a disease, which is caused by abnormal hormonal changes of the three endocrine glands, i.e., malfunctions in the Hypothalamic-Pituitary-Adrenal (HPA) axis. In consequence, the level of cortisol, which is produced and released by the adrenal cortex, is too high (hypercortisolism) or too low (hypocortisolism). These cause depression if maintained over longer periods of time. The secretion of cortisol is controlled by a feedback system. Corticotropin releasing hormone (CRH) is secreted from the hypothalamus and transferred to the anterior pituitary. When CRH stimulates the anterior pituitary which synthesizes and secretes adrenocorticotrophic hormone (ACTH) into the systemic circulation. ACTH is subsequently transported to the adrenal cortex stimulating the synthesis and secretion of cortisol. The level of cortisol hormone has a significant effect on a human body. If it is too high or too low, then it will potentially interfere with the synthesis and secretion of CRH and ACTH. In addition, the hormone cortisol is essential for balancing of body homeostasis as a response to both mental and physical stress. Too high level of the hormone cortisol can cause depression, diabetes, visceral obesity or osteoporosis. On the other hand, if the level of cortisol is lower than a regular level, then it may cause a disturbed memory formations or life-threatening adrenal crisis beyond depression [2].

In 2005, Savic and Jelic [3] presented five versions of a qualitative mathematical model of the HPA axis activity. To observe the changes in each model for the HPA axis, the designed mathematical models are based on fluctuations due to the normal rhythm of the hormones on a daily basis. In 2011, Vinther et al. [4] investigated a model of ordinary differential equations for the Hypothalamic-Pituitary-Adrenal (HPA) axis using analytical and numerical methods and biological knowledge including physiological mechanisms. Later in 2013, Andersen et al. [5] developed HPA models to be more accurate by taking into account saturation concentration. In 2014, Hoeyer et al. [6] studied depression associated with malfunctions in the HPA axis causing abnormal hormone synthesis. So they improved a mathematical model for the HPA axis by adding a differential equation of the regular substance (REG) into the original system consisting of the three differential equations to control the CRH and increase the resolution of hormonal changing in the system. In 2017, Bangsgaard et al. [2] investigated and developed a mathematical model of depression in order to make the model more accurate by adding the circadian rhythm function ($C(t)$) into the HPA axis model. The studied model was classified into three types of hormones: CRH, ACTH and Cortisol denoted by (x_1) , (x_2) and (x_3) , respectively. The diagram demonstrating the relationship among these hormones is shown in Figure 1.

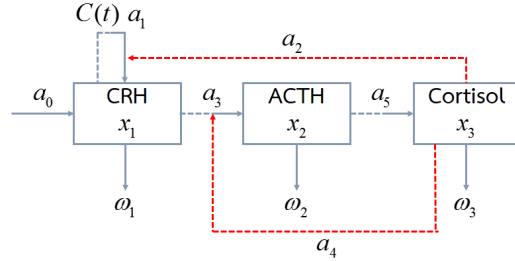


Figure 1: Diagram for the HPA axis model studied by Bangsgaard et al.

The HPA axis model introduced by Bangsgaard et al. can be described by a system of non-autonomous differential equations as follows [2]:

$$\frac{dx_1}{dt} = a_0 + C(t) \frac{a_1}{1 + a_2 x_3^2} \frac{x_1}{\mu + x_1} - \omega_1 x_1, \tag{1.1}$$

$$\frac{dx_2}{dt} = \frac{a_3 x_1}{1 + a_4 x_3} - \omega_2 x_2, \tag{1.2}$$

$$\frac{dx_3}{dt} = a_5 x_2^2 - \omega_3 x_3, \tag{1.3}$$

where $C(t)$ is a circadian rhythm and the interpretation of parameters [2] in Eqs. (1.1)-(1.4) can be found in Table 1 in which all of them are positive.

Table 1: The description of the parameters of the HPA axis model (1.1)-(1.3).

| | Meaning | Unit |
|------------|---|---|
| a_0 | Basic level of secretion of CRH | pg/(mL · min) |
| a_1 | Maximal synthesis of CRH | pg/(mL · min) |
| a_2 | The inhibition of the synthesis of CRH through cortisol | (dL/μg) ² |
| a_3 | Stimulation of ACTH by CRH | min ⁻¹ |
| a_4 | Inhibition of the synthesis of ACTH by cortisol | dL/μg |
| a_5 | Stimulation of cortisol by ACTH | $\frac{\mu\text{g/dL}}{\text{min}(\text{pg/mL})^2}$ |
| ω_1 | The elimination rates of CRH | min ⁻¹ |
| ω_2 | The elimination rates of ACTH | min ⁻¹ |
| ω_3 | The elimination rates of Cortisol | min ⁻¹ |
| δ | Time shifting of the circadian rhythm | min |
| k | Steepness of the increasing function at point $(t - \delta) = \alpha$ | – |
| l | Steepness of the decreasing function at point $(t - \delta) = \beta$ | – |
| μ | Half-saturation constant | pg/mL |
| α | Half saturation point of k | min |
| β | Half saturation point of l | min |
| ϵ | Basic contribution from circadian clock during the night | – |
| N_c | Normalization constant | – |

The proposed circadian rhythm $C(t)$ used in the model is given by

$$C(t) = N_c \left(\frac{t_m^k}{t_m^k + \alpha^k} \cdot \frac{(T - t_m)^l}{(T - t_m)^l + \beta^l} + \varepsilon \right), \quad t \geq 0, \tag{1.4}$$

where $t_m = (t - \delta)$ modulo T with $T = 1440$ mins corresponding to 24 hours. The function $C(t)$ as shown above is obviously positive, continuous and bounded between ε and 1. The function $C(t)$ in Eq. (1.4) is a periodic bell-shaped curve as shown in Figure 2.

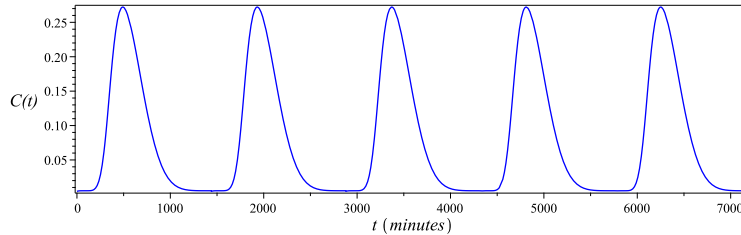


Figure 2: Graph of the circadian rhythm $C(t)$ in Eq. (1.4) for four days (7200 minutes).

2 Preliminaries

In this section, we will give some definitions, notations and some relevant theorems which will be useful for our main results.

Lemma 2.1 ([7, 8]). *Consider the non-autonomous linear equation*

$$\frac{dx}{dt} = A(t) - B(t)x, \tag{2.1}$$

where the functions $A(t)$ and $B(t)$ are bounded and continuous on $\mathbb{R}_+ = [0, \infty)$ and $A(t) \geq 0$ for all $t \geq 0$. Suppose that there are constants $\eta_i > 0$ ($i = 1, 2$) such that

$$\liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} A(\theta)d\theta > 0 \quad \text{and} \quad \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} B(\theta)d\theta > 0. \tag{2.2}$$

Then there exists constants $m > 0$ and $M > 0$ such that for any solution $x(t)$ of Eq. (2.1)

$$m < \liminf_{t \rightarrow \infty} x(t) \leq \limsup_{t \rightarrow \infty} x(t) < M. \tag{2.3}$$

Theorem 2.2. (Comparison theorem [9]) *Suppose $f(t, u)$ is continuous in t and u and Lipschitz continuous in u . Suppose $u(t), v(t)$ are C^1 for $t \geq t_0$ and satisfy*

$$u'(t) \leq f(t, u(t)), \quad v'(t) = f(t, v(t)), \tag{2.4}$$

and $u(t_0) \leq v(t_0)$. Then $u(t) \leq v(t)$ for $t \geq t_0$.

Definition 2.3. (Dini derivative [10]) The right upper Dini derivative $D^+f(t)$ of a continuous function $f : \mathbb{R} \rightarrow \mathbb{R}$ at t is

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

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

Definition 2.4 ([11]). Let $f : D \rightarrow \mathbb{R}$ be a function. We say that f is uniformly continuous on the domain D if for every $\epsilon > 0$ there exists $\delta > 0$ such that for every $x, y \in D$ with $|x - y| < \delta$, we have that

$$|f(x) - f(y)| < \epsilon.$$

Lemma 2.5. (Barbalat’s lemma [12]) *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 $\lim_{t \rightarrow \infty} f(t) = 0$.*

3 Main Results

3.1 Non-negative solutions of the HPA axis model

Firstly, we show in the following lemma that all solutions of the HPA axis model in Eqs. (1.1)-(1.3) are non-negative.

Lemma 3.1. *All solutions of Eqs. (1.1)-(1.3) with non-negative initial conditions are non-negative for all $t \geq 0$.*

Proof. Let $(x_1(t), x_2(t), x_3(t))^T$ be a solution of the initial value problem consisting of system (1.1)-(1.3) and the non-negative initial condition $(x_1(0), x_2(0), x_3(0))^T$. Assuming there exists a time $t_1 > 0$ such that $x_1(t_1) = 0$ and $dx_1(t_1)/dt \leq 0$. Substituting $x_1(t_1) = 0$ into Eq. (1.1), we obtain

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

which contradicts to $dx_1(t_1)/dt \leq 0$. Thus, $x_1(t)$ is non-negative for all $t \geq 0$.

Next, it is not difficult to see that Eq. (1.3) is linear in $x_3(t)$ and its solution is of the form

$$\begin{aligned} x_3(t) &= x_3(0)\exp(-\omega_3 t) + a_5 \exp(-\omega_3 t) \int_0^t x_2^2(s)\exp(\omega_3 s) ds, \\ &\geq x_3(0)\exp(-\omega_3 t) > 0. \end{aligned}$$

The solution $x_3(t)$ in the above equation is obviously non-negative for all $t \geq 0$.

Finally, the same process for $x_3(t)$ is applied to Eq. (1.2) for obtaining the solution $x_2(t)$, which is expressed as

$$\begin{aligned} x_2(t) &= x_2(0)\exp(-\omega_2 t) + a_3 \exp(-\omega_2 t) \int_0^t \left(\frac{x_1(s)}{1 + a_4 x_3(s)} \right) \exp(\omega_2 s) ds, \\ &\geq x_2(0)\exp(-\omega_2 t) > 0. \end{aligned}$$

The solution $x_2(t)$ as shown above is non-negative for all $t \geq 0$ since $x_1(t)$ and $x_3(t)$ are non-negative as shown before. Therefore, all solutions of the HPA axis model are non-negative for $t \geq 0$. \square

3.2 Permanence of all hormones for the HPA axis model

On the permanence of hormones x_1, x_2 and x_3 , we investigate levels of these three hormones are bounded as follows.

Theorem 3.2. *All solutions of the HPA axis model in Eqs. (1.1)-(1.3) with any non-negative initial conditions are permanent, if $\liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} C(\theta)d\theta < (\omega_1 \eta_2 (1 + a_2 M_3^2)(\mu + M_1))/a_1$ where $\eta_2 > 0$ and M_1, M_3 are the positive constants which are determined later.*

Proof. From Eq. (1.1), we have that for all $t \geq 0$,

$$\begin{aligned} \frac{dx_1(t)}{dt} &= a_0 + C(t) \frac{a_1}{1 + a_2 x_3^2(t)} \frac{x_1(t)}{\mu + x_1(t)} - \omega_1 x_1(t), \\ &\leq \mathcal{A}(t) - \mathcal{B}(t)x_1(t), \end{aligned} \tag{3.1}$$

where $\mathcal{A}(t) = (a_0 + C(t)a_1)$ and $\mathcal{B}(t) = \omega_1$. Since $C(t) > 0$, then for $\eta_1 > 0$ we obtain

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} \mathcal{A}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} (a_0 + C(\theta)a_1)d\theta, \\ &= a_0 \eta_1 + a_1 \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} C(\theta)d\theta, \\ &> a_1 \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} C(\theta)d\theta > 0. \end{aligned} \tag{3.2}$$

In addition, for $\eta_2 > 0$ we have

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \mathcal{B}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} (\omega_1)d\theta, \\ &= \omega_1 \eta_2 > 0. \end{aligned} \tag{3.3}$$

Using (3.1), (3.2) and (3.3), then we obtain the resulting inequality as shown in the result of Lemma 2.1. Applying the comparison theorem to the obtained result,

consequently there exist positive constants M_1 and T_1 , where M_1 is independent of any positive solution of system (1.1)-(1.3), such that

$$x_1(t) \leq M_1 \quad \text{for all } t \geq T_1. \tag{3.4}$$

Next, Eq. (1.2) it is obvious that $a_3x_1(t)/(1+a_4x_3(t)) < a_3x_1(t)$ and $a_3x_1(t) \leq a_3M_1$ for $t \geq T_1$. Hence, we obtain

$$\begin{aligned} \frac{dx_2(t)}{dt} &= \frac{a_3x_1(t)}{1+a_4x_3(t)} - \omega_2x_2(t), \\ &\leq C(t) - D(t)x_2(t), \end{aligned} \tag{3.5}$$

where $C(t) = a_3M_1$ and $D(t) = \omega_2$. For $\eta_1 > 0$, we have

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} C(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} a_3M_1d\theta, \\ &= a_3M_1\eta_1 > 0, \end{aligned} \tag{3.6}$$

and for $\eta_2 > 0$, we get

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} D(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \omega_2d\theta, \\ &= \omega_2\eta_2 > 0. \end{aligned} \tag{3.7}$$

Employing (3.5), (3.6) and (3.7), then we obtain the inequality as shown in the result of Lemma 2.1. Then we similarly apply the comparison theorem to the obtained result so that there exist positive constants M_2 and $T_2 \geq T_1$, where M_2 is independent of any positive solution of the system, such that

$$x_2(t) \leq M_2 \quad \text{for all } t \geq T_2. \tag{3.8}$$

From Eq. (1.3), we get that for $t \geq T_2$

$$\begin{aligned} \frac{dx_3(t)}{dt} &= a_5(x_2(t))^2 - \omega_3x_3(t), \\ &\leq \mathcal{E}(t) - \mathcal{F}(t)x_3(t), \end{aligned} \tag{3.9}$$

where $\mathcal{E}(t) = a_5M_2^2$ and $\mathcal{F}(t) = \omega_3$. Then for $\eta_1 > 0$, we get

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} \mathcal{E}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} a_5M_2^2d\theta, \\ &= a_5M_2^2\eta_1 > 0, \end{aligned} \tag{3.10}$$

and for $\eta_2 > 0$, we have that

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \mathcal{F}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \omega_3d\theta, \\ &= \omega_3\eta_2 > 0. \end{aligned} \tag{3.11}$$

Using (3.9), (3.10) and (3.11), then we get the resulting inequality as shown in the result of Lemma 2.1. Applying the comparison theorem to the obtained result, consequently there exist positive constants M_3 and $T_3 \geq T_2$, where M_3 is independent of any positive solution of the system, such that

$$x_3(t) \leq M_3 \quad \text{for all } t \geq T_3. \tag{3.12}$$

Therefore, any positive solution $(x_1(t), x_2(t), x_3(t))^T$ of system (1.1)-(1.3) is ultimately bounded.

On the other hand, we demonstrate that all solutions of the system are bounded below. From Eq. (1.1), we have that for all $t > T_3$

$$\begin{aligned} \frac{dx_1(t)}{dt} &= a_0 + C(t) \frac{a_1}{(1 + a_2x_3(t)^2)} \frac{x_1(t)}{(\mu + x_1(t))} - \omega_1x_1(t), \\ &\geq a_0 + \left(\frac{C(t)a_1}{(1 + a_2M_3^2)(\mu + M_1)} - \omega_1 \right) x_1(t), \\ &= \mathcal{G}(t) - \mathcal{H}(t)x_1(t), \end{aligned} \tag{3.13}$$

where $\mathcal{G}(t) = a_0$ and $\mathcal{H}(t) = \omega_1 - (C(t)a_1)/((1 + a_2M_3^2)(\mu + M_1))$. Then for $\eta_1 > 0$, we get

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} \mathcal{G}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} (a_0)d\theta, \\ &= a_0\eta_1 > 0. \end{aligned} \tag{3.14}$$

For $\eta_2 > 0$, we have

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \mathcal{H}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \left(\omega_1 - \frac{C(\theta)a_1}{(1 + a_2M_3^2)(\mu + M_1)} \right) d\theta, \\ &= \omega_1\eta_2 - \left(\frac{a_1}{(1 + a_2M_3^2)(\mu + M_1)} \right) \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} C(\theta)d\theta. \end{aligned}$$

From the assumption as stated above,

$$\liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \mathcal{H}(\theta)d\theta > 0. \tag{3.15}$$

Utilizing (3.13), (3.14) and (3.15), we then obtain the resulting inequality as shown in the result of Lemma 2.1. Applying the comparison theorem to the obtained result, consequently there exist positive constants m_1 and $T_4 \geq T_3$, where m_1 is independent of any positive solution of the system, such that

$$x_1(t) \geq m_1 \quad \text{for all } t \geq T_4. \tag{3.16}$$

Next, from Eq. (1.2) of the model and for $t \geq T_4$, we directly have

$$\begin{aligned} \frac{dx_2(t)}{dt} &= \frac{a_3x_1(t)}{1 + a_4x_3(t)} - \omega_2x_2(t), \\ &\geq \mathcal{I}(t) - \mathcal{J}(t)x_2(t), \end{aligned} \tag{3.17}$$

where $\mathcal{I}(t) = (a_3m_1)/(1 + a_4M_3)$ and $\mathcal{J}(t) = \omega_2$. Then for $\eta_1 > 0$, we get

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} \mathcal{I}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} \frac{a_3m_1}{1 + a_4M_3}d\theta, \\ &= \frac{a_3m_1\eta_1}{1 + a_4M_3} > 0, \end{aligned} \tag{3.18}$$

and for $\eta_2 > 0$, we have

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \mathcal{J}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \omega_2d\theta, \\ &= \omega_2\eta_2 > 0. \end{aligned} \tag{3.19}$$

Using (3.17), (3.18) and (3.19), then we obtain the resulting inequality as shown in the result of Lemma 2.1. Applying the comparison theorem to the obtained result, consequently there exist positive constants m_2 and $T_5 \geq T_4$, where m_2 is independent of any positive solution of the system, such that

$$x_2(t) \geq m_2 \quad \text{for all } t \geq T_5. \tag{3.20}$$

From Eq. (1.3) of the HPA axis model, we have for $t \geq T_5$

$$\begin{aligned} \frac{dx_3(t)}{dt} &= a_5(x_2(t))^2 - \omega_3x_3(t), \\ &\geq \mathcal{K}(t) - \mathcal{L}(t)x_3(t), \end{aligned} \tag{3.21}$$

where $\mathcal{K}(t) = a_5m_2^2$ and $\mathcal{L}(t) = \omega_3$. Then for $\eta_1 > 0$, we get

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} \mathcal{K}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_1} a_5m_2^2d\theta, \\ &= a_5m_2^2\eta_1 > 0, \end{aligned} \tag{3.22}$$

and for $\eta_2 > 0$, we get

$$\begin{aligned} \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \mathcal{L}(\theta)d\theta &= \liminf_{t \rightarrow \infty} \int_t^{t+\eta_2} \omega_3d\theta, \\ &= \omega_3\eta_2 > 0. \end{aligned} \tag{3.23}$$

Using (3.21), (3.22) and (3.23), then we obtain the resulting inequality as shown in the result of Lemma 2.1. Applying the comparison theorem to the obtained result, consequently there exist positive constants m_3 and $T_6 \geq T_5$, where m_3 is independent of any positive solution of the system, such that

$$x_3(t) \geq m_3 \quad \text{for all } t \geq T_6. \tag{3.24}$$

From Eqs. (3.4),(3.8),(3.12),(3.16),(3.20) and (3.24), we finally attain the following inequalities

$$m_i \leq \liminf_{t \rightarrow \infty} x_i(t) \leq \limsup_{t \rightarrow \infty} x_i(t) \leq M_i, \quad i = 1, 2, 3.$$

This completes the theorem 3.2. □

3.3 Global attractivity for non-autonomous model

In this section, we next investigate the global attractivity of the HPA axis model based on using the following definition.

Definition 3.3 ([7]). The HPA axis model in Eqs. (1.1)-(1.3) is said to be globally attractive, if for any two solutions $(x_1^{(1)}(t), x_2^{(1)}(t), x_3^{(1)}(t))^T$ and $(x_1^{(2)}(t), x_2^{(2)}(t), x_3^{(2)}(t))^T$ of model Eqs. (1.1)-(1.3), we have

$$\lim_{t \rightarrow \infty} |x_i^{(1)}(t) - x_i^{(2)}(t)| = 0, \quad i = 1, 2, 3. \tag{3.25}$$

Theorem 3.4. Suppose that there exist constants $\mu_i > 0$ ($i = 1, 2, 3$) such that $\liminf_{t \rightarrow \infty} A_i(t) > 0$, $i = 0, 1$ and $A_2 > 0$, where

$$A_0(t) = \mu_1 \text{sign}(x_1^{(1)}(t) - x_1^{(2)}(t)) \left\{ a_1 C(t) M_1 \left(\frac{1}{(1 + a_2 M_3^2)(\mu + M_1)} - \frac{1}{(\mu + m_1)} \right) \right\} + \mu_2 \text{sign}(x_2^{(1)}(t) - x_2^{(2)}(t)) \left\{ a_3 M_1 \left(\frac{1}{1 + a_4 M_3} - \frac{1}{1 + a_4 m_3} \right) \right\}, \tag{3.26}$$

$$A_1(t) = \mu_1 \omega_1 - \frac{\mu_1 a_1 C(t)}{(1 + a_2 m_3^2)(\mu + m_1)} - \frac{\mu_2 a_3}{1 + a_4 m_3}, \tag{3.27}$$

$$A_2 = \mu_2 \omega_2 - 2\mu_3 a_5 M_2, \tag{3.28}$$

where m_1, m_3, M_1, M_2 and M_3 are given in the proof of Theorem 3.2. Then the solution of model (1.1)-(1.3) is globally attractive.

Proof. Let $\mathbf{x}_1 = (x_1^{(1)}(t), x_2^{(1)}(t), x_3^{(1)}(t))^T$ and $\mathbf{x}_2 = (x_1^{(2)}(t), x_2^{(2)}(t), x_3^{(2)}(t))^T$ be any two positive solutions of the model in Eqs. (1.1)-(1.3). From Theorem 3.2, we have, for all $t \geq T_6$ and for $j = 1, 2$,

$$m_1 \leq x_1^{(j)}(t) \leq M_1, \quad m_2 \leq x_2^{(j)}(t) \leq M_2, \quad m_3 \leq x_3^{(j)}(t) \leq M_3, \tag{3.29}$$

where $m_i, M_i, i = 1, 2, 3$ are defined in Theorem 3.2.

Choosing the Lyapunov function $(V(t))$ as follows:

$$V(t) = \mu_1 V_1(t) + \mu_2 V_2(t) + \mu_3 V_3(t), \tag{3.30}$$

where $V_i = |x_i^{(1)}(t) - x_i^{(2)}(t)|$, for $i = 1, 2, 3$. The function $V(t)$ defined above is positive definite if $\mathbf{x}_1 \neq \mathbf{x}_2$. Taking the right upper Dini derivative on both sides of Eq. (3.30), we then have

$$D^+V(t) = \mu_1 D^+V_1(t) + \mu_2 D^+V_2(t) + \mu_3 D^+V_3(t). \tag{3.31}$$

From Eq. (3.29), we first obtain the following inequality for $D^+V_1(t)$:

$$\begin{aligned}
 D^+V_1(t) &= D^+\mu_1|x_1^{(1)}(t) - x_1^{(2)}(t)|, \\
 &= \mu_1\text{sign}(x_1^{(1)}(t) - x_1^{(2)}(t)) \left\{ D^+x_1^{(1)}(t) - D^+x_1^{(2)}(t) \right\}, \\
 &= \mu_1\text{sign}(x_1^{(1)}(t) - x_1^{(2)}(t)) \left\{ a_1C(t) \left(\frac{x_1^{(1)}(t)}{\left(1 + a_2(x_3^{(1)}(t))^2\right)(\mu + x_1^{(1)}(t))} \right. \right. \\
 &\quad \left. \left. - \frac{x_1^{(2)}(t)}{\left(1 + a_2(x_3^{(2)}(t))^2\right)(\mu + x_1^{(2)}(t))} \right) - \omega_1(x_1^{(1)}(t) - x_1^{(2)}(t)) \right\}, \\
 &\leq \mu_1\text{sign}(x_1^{(1)}(t) - x_1^{(2)}(t)) \left\{ a_1C(t) \left(\frac{x_1^{(1)}(t)}{(\mu + m_1)} - \frac{x_1^{(2)}(t)}{(1 + a_2M_3^2)(\mu + M_1)} \right) \right. \\
 &\quad \left. - \omega_1(x_1^{(1)}(t) - x_1^{(2)}(t)) \right\}, \\
 &= \mu_1\text{sign}(x_1^{(1)}(t) - x_1^{(2)}(t)) \left\{ a_1C(t) \left(\frac{x_1^{(1)}(t)}{(\mu + m_1)} - \frac{x_1^{(2)}(t)}{(\mu + m_1)} \right. \right. \\
 &\quad \left. \left. + \frac{x_1^{(2)}(t)}{(\mu + m_1)} - \frac{x_1^{(2)}(t)}{(1 + a_2M_3^2)(\mu + M_1)} \right) - \omega_1(x_1^{(1)}(t) - x_1^{(2)}(t)) \right\}, \\
 &\leq \mu_1\text{sign}(x_1^{(1)}(t) - x_1^{(2)}(t)) \left\{ \frac{a_1C(t)}{(\mu + m_1)} (x_1^{(1)}(t) - x_1^{(2)}(t)) \right. \\
 &\quad \left. + a_1C(t)M_1 \left(\frac{1}{(\mu + m_1)} - \frac{1}{(1 + a_2M_3^2)(\mu + M_1)} \right) - \omega_1(x_1^{(1)}(t) - x_1^{(2)}(t)) \right\}, \\
 &= \mu_1\text{sign}(x_1^{(1)}(t) - x_1^{(2)}(t)) \left\{ a_1C(t)M_1 \left(\frac{1}{(\mu + m_1)} - \frac{1}{(1 + a_2M_3^2)(\mu + M_1)} \right) \right\} \\
 &\quad + \mu_1 \left\{ \left(\frac{a_1C(t)}{(\mu + m_1)} - \omega_1 \right) |x_1^{(1)}(t) - x_1^{(2)}(t)| \right\}. \tag{3.32}
 \end{aligned}$$

Using Eq. (3.29), we secondly obtain the following inequality:

$$\begin{aligned}
 D^+V_2(t) &= D^+\mu_2|x_2^{(1)}(t) - x_2^{(2)}(t)|, \\
 &= \mu_2\text{sign}(x_2^{(1)}(t) - x_2^{(2)}(t)) \left\{ D^+x_2^{(1)}(t) - D^+x_2^{(2)}(t) \right\}, \\
 &= \mu_2\text{sign}(x_2^{(1)}(t) - x_2^{(2)}(t)) \left\{ a_3 \left(\frac{x_1^{(1)}(t)}{1 + a_4x_3^{(1)}(t)} - \frac{x_1^{(2)}(t)}{1 + a_4x_3^{(2)}(t)} \right) \right. \\
 &\quad \left. - \omega_2(x_2^{(1)}(t) - x_2^{(2)}(t)) \right\}, \\
 &\leq \mu_2\text{sign}(x_2^{(1)}(t) - x_2^{(2)}(t)) \left\{ a_3 \left(\frac{x_1^{(1)}(t)}{1 + a_4m_3} - \frac{x_1^{(2)}(t)}{1 + a_4M_3} \right) \right. \\
 &\quad \left. - \omega_2(x_2^{(1)}(t) - x_2^{(2)}(t)) \right\},
 \end{aligned}$$

$$\begin{aligned}
D^+V_2(t) &= \mu_2 \text{sign}(x_2^{(1)}(t) - x_2^{(2)}(t)) \left\{ a_3 \left(\frac{x_1^{(1)}(t)}{1 + a_4 m_3} - \frac{x_1^{(2)}(t)}{1 + a_4 m_3} \right. \right. \\
&\quad \left. \left. + \frac{x_1^{(2)}(t)}{1 + a_4 m_3} - \frac{x_1^{(2)}(t)}{1 + a_4 M_3} \right) - \omega_2 (x_2^{(1)}(t) - x_2^{(2)}(t)) \right\}, \\
&\leq \mu_2 \text{sign}(x_2^{(1)}(t) - x_2^{(2)}(t)) \left\{ \frac{a_3}{1 + a_4 m_3} (x_1^{(1)}(t) - x_1^{(2)}(t)) \right. \\
&\quad \left. + a_3 M_1 \left(\frac{1}{1 + a_4 m_3} - \frac{1}{1 + a_4 M_3} \right) - \omega_2 (x_2^{(1)}(t) - x_2^{(2)}(t)) \right\}, \\
&\leq \mu_2 \text{sign}(x_2^{(1)}(t) - x_2^{(2)}(t)) \left\{ a_3 M_1 \left(\frac{1}{1 + a_4 m_3} - \frac{1}{1 + a_4 M_3} \right) \right\} \\
&\quad + \mu_2 \left\{ \frac{a_3}{1 + a_4 m_3} |x_1^{(1)}(t) - x_1^{(2)}(t)| - \omega_2 |x_2^{(1)}(t) - x_2^{(2)}(t)| \right\}. \quad (3.33)
\end{aligned}$$

Similarly, using Eq. (3.29), we finally have the inequality for $D^+V_3(t)$ as follows:

$$\begin{aligned}
D^+V_3(t) &= D^+ \mu_3 |x_3^{(1)}(t) - x_3^{(2)}(t)|, \\
&= \mu_3 \text{sign}(x_3^{(1)}(t) - x_3^{(2)}(t)) \left\{ D^+ x_3^{(1)}(t) - D^+ x_3^{(2)}(t) \right\}, \\
&= \mu_3 \text{sign}(x_3^{(1)}(t) - x_3^{(2)}(t)) \left\{ a_5 \left((x_2^{(1)}(t))^2 - (x_2^{(2)}(t))^2 \right) \right. \\
&\quad \left. - \omega_3 (x_3^{(1)}(t) - x_3^{(2)}(t)) \right\}, \\
&= \mu_3 \text{sign}(x_3^{(1)}(t) - x_3^{(2)}(t)) \left\{ a_5 (x_2^{(1)}(t) - x_2^{(2)}(t)) (x_2^{(1)}(t) + x_2^{(2)}(t)) \right. \\
&\quad \left. - \omega_3 (x_3^{(1)}(t) - x_3^{(2)}(t)) \right\}, \\
&\leq \mu_3 \text{sign}(x_3^{(1)}(t) - x_3^{(2)}(t)) \left\{ 2a_5 M_2 (x_2^{(1)}(t) - x_2^{(2)}(t)) \right. \\
&\quad \left. - \omega_3 (x_3^{(1)}(t) - x_3^{(2)}(t)) \right\}, \\
&\leq \mu_3 \left\{ 2a_5 M_2 |x_2^{(1)}(t) - x_2^{(2)}(t)| - \omega_3 |x_3^{(1)}(t) - x_3^{(2)}(t)| \right\}. \quad (3.34)
\end{aligned}$$

From Eqs. (3.31)-(3.34), we have

$$\begin{aligned}
D^+V(t) &\leq - \left[\mu_1 \text{sign}(x_1^{(1)}(t) - x_1^{(2)}(t)) \left\{ a_1 C(t) M_1 \left(\frac{1}{(1 + a_2 M_3^2)(\mu + M_1)} - \frac{1}{(\mu + m_1)} \right) \right\} \right. \\
&\quad \left. + \mu_2 \text{sign}(x_2^{(1)}(t) - x_2^{(2)}(t)) \left\{ a_3 M_1 \left(\frac{1}{1 + a_4 M_3} - \frac{1}{1 + a_4 m_3} \right) \right\} \right] \\
&\quad - \left(\mu_1 \omega_1 - \frac{\mu_1 a_1 C(t)}{(\mu + m_1)} - \frac{\mu_2 a_3}{1 + a_4 m_3} \right) |x_1^{(1)}(t) - x_1^{(2)}(t)| \\
&\quad - (\mu_2 \omega_2 - 2\mu_3 a_5 M_2) |x_2^{(1)}(t) - x_2^{(2)}(t)| \\
&\quad - (\mu_3 \omega_3) |x_3^{(1)}(t) - x_3^{(2)}(t)|,
\end{aligned}$$

$$\begin{aligned}
 &= -\left(A_0(t) + A_1(t)|x_1^{(1)}(t) - x_1^{(2)}(t)| + A_2|x_2^{(1)}(t) - x_2^{(2)}(t)| \right. \\
 &\quad \left. + A_3|x_3^{(1)}(t) - x_3^{(2)}(t)| \right), \tag{3.35}
 \end{aligned}$$

where $A_i(t)$, $i = 0, 1$ and A_2 are defined in Eqs. (3.26), (3.27) and (3.28), respectively and $A_3 = \mu_3\omega_3 > 0$. Because $\liminf_{t \rightarrow \infty} A_i(t) > 0$, $i = 0, 1$, then there exist constants $\tilde{\xi} > 0$ and $T_0 \geq T_6$ such that $A_i(t) \geq \tilde{\xi}$, $i = 0, 1$ for all $t \geq T_0$. Then we select $\xi > 0$ such that $\xi = \min\{\tilde{\xi}, A_2, A_3\}$. In consequence, we obtain for all $t \geq T_0$

$$\begin{aligned}
 D^+V(t) &\leq -\xi \left(1 + |x_1^{(1)}(t) - x_1^{(2)}(t)| + |x_2^{(1)}(t) - x_2^{(2)}(t)| + |x_3^{(1)}(t) - x_3^{(2)}(t)| \right), \\
 &\leq -\xi \left(|x_1^{(1)}(t) - x_1^{(2)}(t)| + |x_2^{(1)}(t) - x_2^{(2)}(t)| + |x_3^{(1)}(t) - x_3^{(2)}(t)| \right), \\
 &= -\xi z(t), \tag{3.36}
 \end{aligned}$$

where $z(t) = |x_1^{(1)}(t) - x_1^{(2)}(t)| + |x_2^{(1)}(t) - x_2^{(2)}(t)| + |x_3^{(1)}(t) - x_3^{(2)}(t)|$.

Integrating Eq. (3.36) from T_0 to t , then we have

$$\begin{aligned}
 V(t) - V(T_0) &\leq -\xi \int_{T_0}^t z(s)ds, \\
 V(t) + \xi \int_{T_0}^t z(s)ds &\leq V(T_0).
 \end{aligned}$$

Since $V(t)$ is positive, we get

$$\xi \int_{T_0}^t z(s)ds \leq V(T_0) < \infty.$$

Thus, $z(t)$ is integrable on $[T_0, \infty)$. By Eq. (3.29), we have $|x_i^{(1)}(t) - x_i^{(2)}(t)|$, $i = 1, 2, 3$ are bounded on $[T_0, \infty)$ and then $\frac{d}{dt} \left(|x_i^{(1)}(t) - x_i^{(2)}(t)| \right)$, $i = 1, 2, 3$ are bounded for $t \geq T_0$. Therefore, $|x_i^{(1)}(t) - x_i^{(2)}(t)|$, $i = 1, 2, 3$ are uniformly continuous on $[T_0, \infty)$. Using Lemma 2.5, we can conclude that $\lim_{t \rightarrow \infty} z(t) = 0$. Then we finally have

$$\lim_{t \rightarrow \infty} |x_i^{(1)}(t) - x_i^{(2)}(t)| = 0, \quad i = 1, 2, 3.$$

This shows that Eqs. (1.1)-(1.3) are globally attractive. □

4 Numerical Results

In this section we investigate the numerical results for the HPA axis model in Eqs. (1.1)-(1.3) using two sets of the parameter values. The first parameter set is for healthy population consisting of normal healthy people or depressive patients who are under medical supervision. This group is called the treated depressed patients. The second parameter set is for hypercortisolemic depressed patients whose levels of cortisol hormone are higher than normal levels. With the high level of cortisol, it may cause depression and put patients at risk to hurt themselves or the people around them. The two parameter sets used in our numerical experiments are shown in Table 2 in which their values are referred from [2].

Table 2: Two sets of the parameter values used in the simulations for system (1.1)-(1.3).

| | Treated patient | Hypercortisolemic patient |
|------------|-------------------------|---------------------------|
| a_0 | 3.9031×10^{-4} | 1.3110×10^{-1} |
| a_1 | 6.8390×10^{12} | 1.2921×10^{13} |
| a_2 | 1.7809×10^9 | 1.7809×10^9 |
| a_3 | 2.2803×10^4 | 2.2803×10^4 |
| a_4 | 1.7745×10^5 | 1.7745×10^5 |
| a_5 | 4.6170×10^{-4} | 3.0311×10^{-4} |
| ω_1 | 0.0337 | 0.0457 |
| ω_2 | 0.0205 | 0.0146 |
| ω_3 | 0.0238 | 0.0210 |
| δ | 83.8 | 20.1 |
| k | 5 | 5 |
| l | 6 | 6 |
| μ | 583 | 583 |
| α | 300 | 300 |
| β | 950 | 950 |
| ϵ | 0.01 | 0.01 |
| N_c | 0.5217 | 0.5217 |

To better understand the permanence behaviors of the hormones $x_1(t), x_2(t)$ and $x_3(t)$ in the model, we simulate the numerical solutions for a long period of time using the following two initial conditions $(x_1(0), x_2(0), x_3(0))^T = (2, 5, 10)^T, (60, 50, 18)^T$. Figure 3 does not only represent the phase portraits of the levels of the hormones for treated and hypercortisolemic depressed patients but also shows that all of the hormones are bounded, which is the solution curves finally converge into closed curves in 3-D space. All graphs in this figure are plotted for $t \in [0, 7200]$ using the parameter values in Table 2 and the above initial conditions.

Next, we study behaviors of each hormone between the two groups. This can be done by comparing each time series hormone level for a treated patient

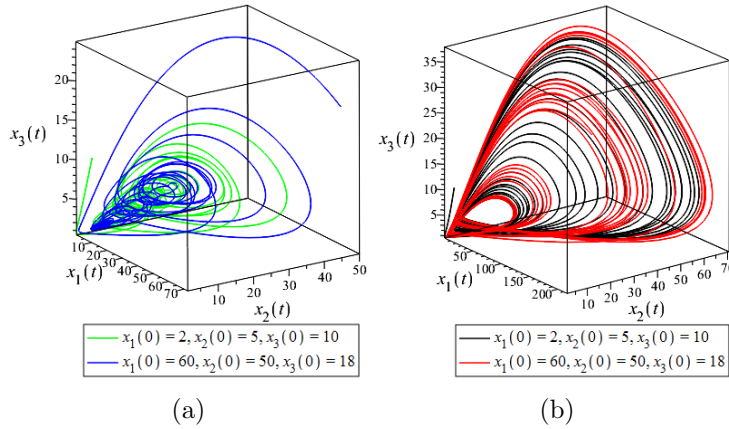
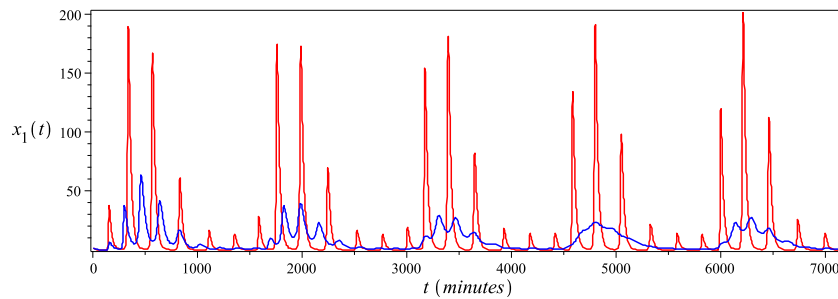


Figure 3: Phase portraits of the model (1.1)-(1.3) for $t \in [0, 7200]$ using the different initial conditions: (a) a treated patient (b) a hypercortisolemic patient.

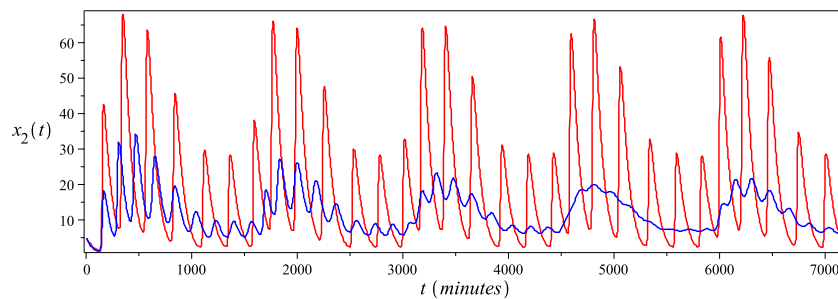
and a hypercortisolemic depressed patient. Figure 4 shows the comparison of the time series solutions of each hormone for treated and hypercortisolemic depressed patients. These graphs are depicted on $t \in [0, 7200]$ with the initial condition $(2, 5, 10)^T$. It is found from Figure 4 that the hormone levels of a hypercortisolemic depressed patient are much significantly higher than the hormone levels of a treated patient. In Table 3, the difference values of the hormone levels for these two types of people are numerically computed at some specific times for two days such as 6 a.m., noon, 6 p.m., and midnight of each day. Moreover, the normal levels of each hormone at such specific times are shown in Table 3 as well. We can observe from Table 3 that the biggest differences of each hormone level mainly occur around 6 a.m. of each day.

Table 3: The normal level of the hormones and the differences of the hormone levels of a hypercortisolemic patient deviated from the normal levels at some specific times.

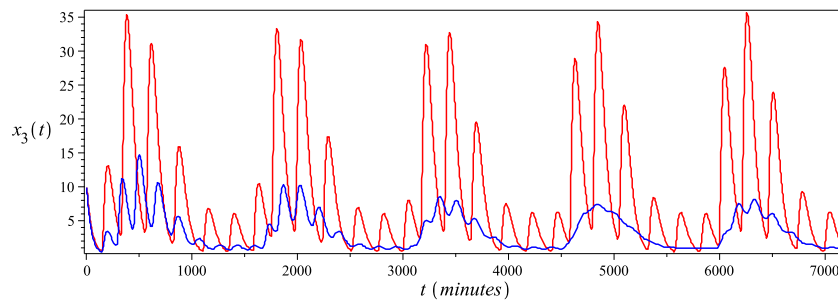
| Time | x_1^T | x_2^T | x_3^T | $ x_1^T - x_1^H $ | $ x_2^T - x_2^H $ | $ x_3^T - x_3^H $ |
|------|---------|---------|---------|-------------------|-------------------|-------------------|
| 60 | 0.273 | 5.697 | 3.801 | 0.132 | 2.217 | 0.392 |
| 360 | 19.802 | 26.162 | 13.075 | 119.064 | 11.14 | 9.276 |
| 720 | 13.757 | 19.784 | 9.645 | 12.497 | 2.294 | 5.557 |
| 1080 | 3.010 | 11.598 | 2.027 | 2.460 | 8.521 | 0.600 |
| 1440 | 1.515 | 9.265 | 1.399 | 0.105 | 9.724 | 4.692 |
| 1800 | 10.760 | 12.782 | 3.938 | 157.921 | 54.210 | 8.046 |
| 2160 | 17.004 | 15.605 | 4.218 | 16.272 | 0.958 | 8.382 |
| 2520 | 1.593 | 6.685 | 1.247 | 1.552 | 3.984 | 0.370 |
| 2880 | 1.367 | 6.875 | 0.826 | 0.482 | 9.118 | 4.816 |



(a)



(b)

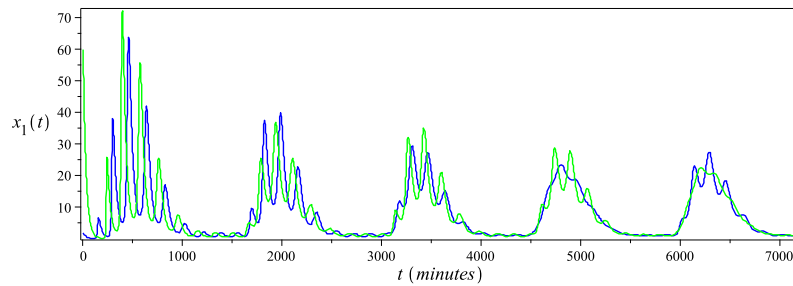


(c)

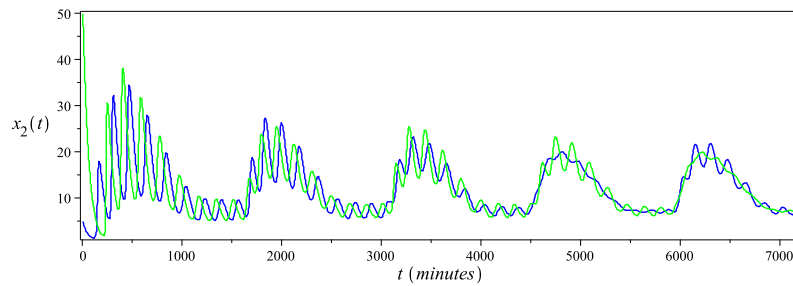
Figure 4: Comparison of the time series hormone levels between a treated patient (blue curve) and a hypercortisolemic depressed patient (red curve). All graphs are generated from the initial condition $(2, 5, 10)^T$ and plotted for 5 days : (a) $x_1(t)$, (b) $x_2(t)$, (c) $x_3(t)$.

In this part, the investigation of the global attractivity of model (1.1)-(1.3) is considered. We separate this study for the two types of patients: treated and hypercortisolemic depressed patients. The experimental simulations for such two types of patients are obtained using the parameter values in Table 2 and the initial conditions: $(2, 5, 10)^T$ and $(60, 50, 18)^T$. Using the above initial conditions, we first

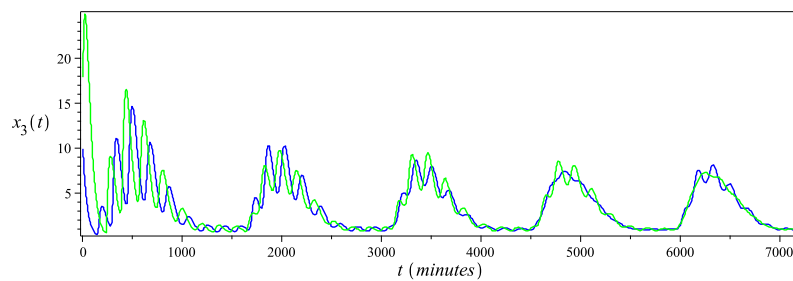
plot the hormone levels $x_1(t)$, $x_2(t)$, and $x_3(t)$ of a treated patient for 5 days in Figure 5. It can be observed from Figure 5 (a) that the curves of $x_1(t)$ generated using the distinct initial conditions have the greatest difference for the first day and the difference between these two curves are then gradually decreasing for the second and third days. Eventually, these two graphs are very close to each other for the last two days. In a remarkably similar fashion, the hormones $x_2(t)$ and $x_3(t)$ of a treated patient are considered to have the same globally attractive behaviors as the behavior of $x_1(t)$ when the specified initial conditions employed.



(a)



(b)



(c)

Figure 5: Globally attractive behaviors of the hormones for a treated patient using the initial conditions: $(2, 5, 10)^T$ (blue curves) and $(60, 50, 18)^T$ (green curves): (a) $x_1(t)$, (b) $x_2(t)$, (c) $x_3(t)$.

Next, the globally attractive study of the hormone levels $x_1(t)$, $x_2(t)$, and $x_3(t)$ of the model for a hypercortisolemic depressed patient can be attained using the same procedure as for a treated patient. The numerical results in Figure 6 reveal that the two curves of each hormone level have a very different phase and structure for the first three days and they comes closer to each other for the last two days. Of course, the hormone levels for a hypercortisolemic depressed patient are much higher than the levels for a treated people.

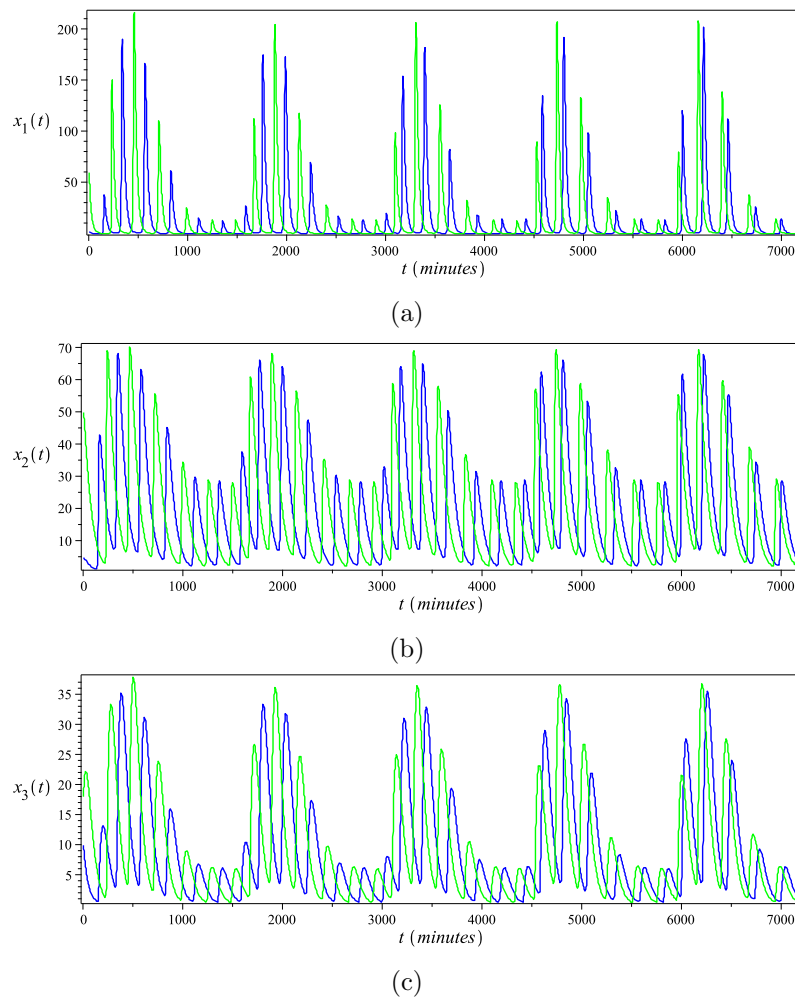


Figure 6: Globally attractive behaviors of the hormones for a hypercortisolemic depressed patient using the initial conditions: $(2, 5, 10)^T$ (blue curves) and $(60, 50, 18)^T$ (green curves): (a) $x_1(t)$, (b) $x_2(t)$, (c) $x_3(t)$.

In the final part, we combine the phase portraits of the model for treated and hypercortisolemic depressed patients to compare the permanence areas of them. In Figure 7, the phase portraits of the hormone levels for treated and hypercortisolemic depressed patients are portrayed using the parameter values as described in Table 2 and starting with the same initial condition $(2, 5, 10)^T$. It is noticed that the permanence of the hormone levels for a treated patient is limited in a smaller region than the region of the permanence for a hypercortisolemic depressed patient.

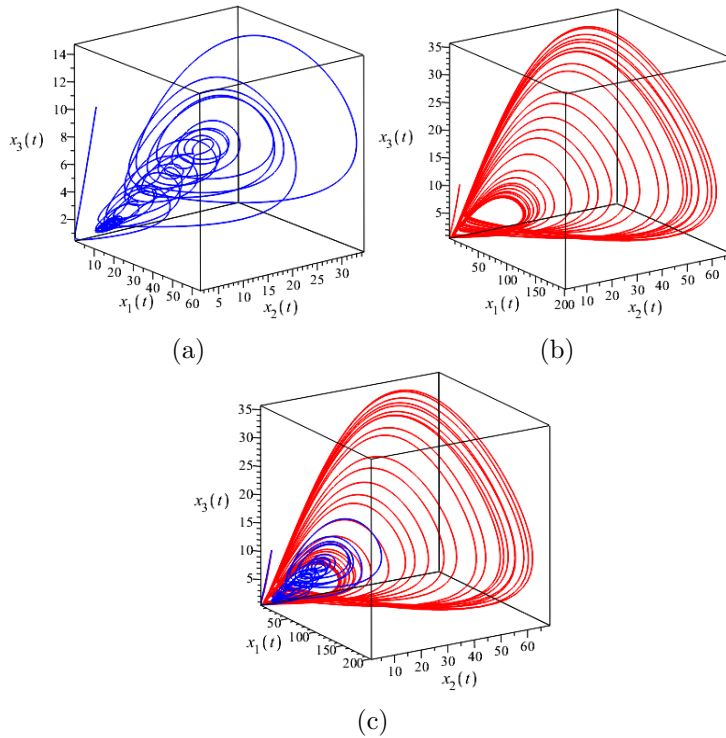


Figure 7: Permanence regions of the model for (a) a treated patient, (b) a hypercortisolemic depressed patient, (c) combined between the two types of patients.

5 Conclusions

Different from previous work [2], in this article we have investigated the non-autonomous HPA axis model (1.1)-(1.3) in many aspects. For example, the non-negativity of solutions of the model has been proved. We have established the sufficient conditions for the permanence of the model. In other words, the bound-

edness of the hormone levels is shown. Furthermore, the sufficient conditions for the global asymptotic stability of the model have been provided. Some interesting numerical results have been demonstrated to verify the obtained theoretical results. The numerical results, which are shown in section 4, help us better understand the changes of levels of the studied three hormones between treated and hypercortisolemic depressed patients at the monitored different times. These could be some benefits for clinical diagnosis of depression.

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