NONLINEAR CONTROL OF HYPOTHALAMUS-PITUITARY-ADRENAL AXIS

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
ATILIM UNIVERSITY

AHMED HEFDHI MOHSIN

A MASTER OF SCIENCE THESIS
IN
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Approval of the Graduate School of Natural and Applied Sciences, Atilim University.

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This is to certify that we have read the thesis "NONLINEAR CONTROL OF HYPOTHALAMUS-PITUITARY-ADRENAL AXIS" submitted by "Ahmed Hefdhi Mohsin" and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

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ABSTRACT

NONLINEAR CONTROL OF HYPOTHALAMUS-PITUITARY-ADRENAL AXIS

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In this thesis, an automatic control of the Hypothalamus-Pituitary-Adrenal axis which has main role in circadian rhythms and immune stress responses in humans' organisms and mammalian organisms.

The Hypothalamus-Pituitary-Adrenal axis has nonlinear system equations so that we go to nonlinear approaches which are back-stepping and feedback linearization and the input is adrenocorticotropin hormone which is admit by the nonlinear system and simulate both plasma concentrations changes of cortisol and adrenocorticotropin.

To keep to the daily rhythm of the cortisol, the controllers set the adrenocorticotropin injection and also, we have to mention that we add sinusoidally varying cortisol as reference to the controllers of back-stepping and feedback linearization and the purpose of this addition to keep mechanism of biological clock.

Simulation performed using MATLAB for the controllers, the initial results show negative concentrations which are physically wrong but then we overcome this issue by selecting proper gains and we should mention these gains is different for back-stepping and feedback linearization,

The results showed that, both back-stepping and feedback linearization controllers well performed the synchronization of the cortisol concentration for daily periodic rhythm and results show that the negative concentrations and ability to overcome this problem by selecting proper gains for both controllers.

Keywords: Hypothalamus–Pituitary–Adrenal axis, Homeostasis, Circadian rhythm, Back-stepping control, Feedback linearization control.

ÖZ

HİPOTALAMUS-HİPOFİZ-ADRENAL EKSENİNİN DOĞRUSAL OLMAYAN DENETİMİ

Mohsin, Ahmed Hefdhi

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Danışman: Doç. Dr. Reşat Özgür DORUK

Haziran 2019, # 53 Sayfa

Bu tez çalışmasında canlıların sirkadyen ritm ve immünolojik strese verilen fizyolojik yanıt mekanizmasında önemli rol oynayan hipotalamus-hipofiz-adrenal ekseninin otomatik denetimine ilişkin bir çalışma sunulmaktadır.

Hipotalamus-hipofiz-adrenal ekseninin matematiksel modeli doğrusal olmayan türevsel denklemlerden meydana gelmektedir. Bu nedenle geri adımlamalı ve geri beslemeye dayalı doğrusallaştırma olarak bilinen doğrusal olmayan denetim yöntemleri tercih edilmektedir. Denetim mekanizmasında girdi adrenokortikotropin enjeksiyonu olup, denetimde aynı hormonunun ve kortizolün plazma derişim düzeyleri ölçülerek işlem yapılmaktadır.

Kortizolün günlük ritmini koruyabilmek için yukarıda bahsedilen denetleyiciler adrenokortikotropin hormonunun enjeksiyonunu ayarlamak suretiyle kortizolün belirlenen periyodik sinüzoidal bir ritmi takip etmesini sağlar.

İlk yapılan benzetimlerde negatif değerli derişimler görüldüğünden denetim kazançlarının değiştirilmesi gerekli olmuştur. Bu işlemleri yaparken geri adımlamalı ve geri beslemeye dayalıu doğrusallaştırmaya dayalı denetim süreçlerinde kazançlar ayrı ayrı ayarlanmak durumunda kalınmıştır.

Sonuçlar göstermektedir ki, gerek geri beslemeye dayalı doğrusallaştırma gerekse de ger adımlamalı denetimlerde kazançları uygun şekilde seçmek kaydıyla iyi performans elde edilmiştir. Kazançları seçerken öncelikli olarak negatif değerli derişimlerin

oluşmamasına dikkat edilmiştir. Bunun yanı sıra derişim profilinde titreşim oluşmamasına da özen gösterilmiştir.
Anahtar Kelimeler: Hipotalamus-Hipofiz-Adrenal ekseni, homeostazi, sirkadyen ritmler, geri adımlamalı denetim, geri beslemeye dayalı doğrusallaştırma.

To My Parents

My Father "HEFDHI MOHSIN"

My Mother "KHALIDAH HAJOKE"

And My Sisters

"MARWA and AYA"

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In the Name of Allah, the Most Gracious, the Most Merciful. Praise be to Allah, the Lord of the Worlds; peace and blessings of Allah be upon the noblest of the Prophets and Messengers, our Prophet Mohammed and upon his family, companions and who follows him until the last day. I am truly many people that there is no way to acknowledge them all so I offer my sincerest apologies to anyone who has not been mentioned. I express my sincerest gratitude and appreciation to my respected supervisor, Assoc. Prof. Dr. Resat Ozgur Doruk for the help, instructions, support, and guidance, and what he does offered through my academic journey until I finish this thesis. May Allah reward him with the best reward for this. Also, I'd like to express my gratitude to the head of institute represented by the director Prof. Dr. Ali Kara and I'd like to express my gratitude to the head of electrical and electronic department represented by Assoc. Prof. Dr. Kemal Efe Eseller my dear doctors Dr. Mehmet Efe Ozbek and Dr. Musaria Karim, may Allah bless them for the ethics and knowledge they have offered me. Also, I extend my sincerest gratitude to Dr. Zuhair Abd Al-Ameer and my dear colleagues the engineers Mohammed Shakir, Monther Abid Ali, Ali Hussain, Ali Fadhil, Faisal Bashar, Mohammed Isam, Mustafa, Ahmed Hashim, Zaid, Omar, Yahya Faraj, Hamza Abbas, Abdulqader Adnan My Allah reward them with the best.

Words can't explain how thankful I am to my father and my mother for what you've offered to reach this stage and they encourage me in every step that I made. May Allah reward you with the best. My dear sisters, Dr. Marwa and engineer Aya, I'm grateful for the help you've offered me to finish my study, May Allah reward you with the best. Lastly, I'd like to thank everyone who has offered me help regardless its nature and couldn’t mentioned here, may Allah bless you all and reward you with the best.

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LIST OF ABBREVIATIONS

HPA	-	Hypothalamus–Pituitary–Adrenal
CRH	-	Corticotropin-releasing hormone
ACTH	-	Adrenocorticotropic hormone
REM	-	Rapid eye movement
MR	-	Mineralocorticoid Receptor
GR	-	Glucocorticoid Receptor
AD	-	Alzheimer's disease
SBML	-	Silicomodel

CHAPTER 1

INTRODUCTION

1.1 Physiology in Brief

In human being's stress system, the Hypothalamus–Pituitary–Adrenal (HPA) system connected together and the HPA system is neuroendocrine and one of it is properties it has a quick response to stressful stimuli, and there are complicated feedback mechanisms happens to returning to homeostasis. In the brain there are regions called cortical, for example, amygdala, and hippocampus, and hypothalamus, glutamatergic is connected together with cortical regions [1].

When the hypothalamic neurons are happened by glutamate leads to corticotropin discharge and that will be discharging the (CRH) hormone. In the circulation of hypophyseal portal, the (CRH) hormone is excretion and the hormone will reach the anterior pituitary, afterward in the circulation will be discharged. In the adrenals the cortisol will discharged by ACTH hormone stimulation (see figure 1.1 below). The absorption of serum cortisol should be in regular physiological range.

Osteoporosis, diabetes, visceral obesity or depression caused by hypercortisolism. In the system there is a fundamental element which is cortisol excretion restraint.

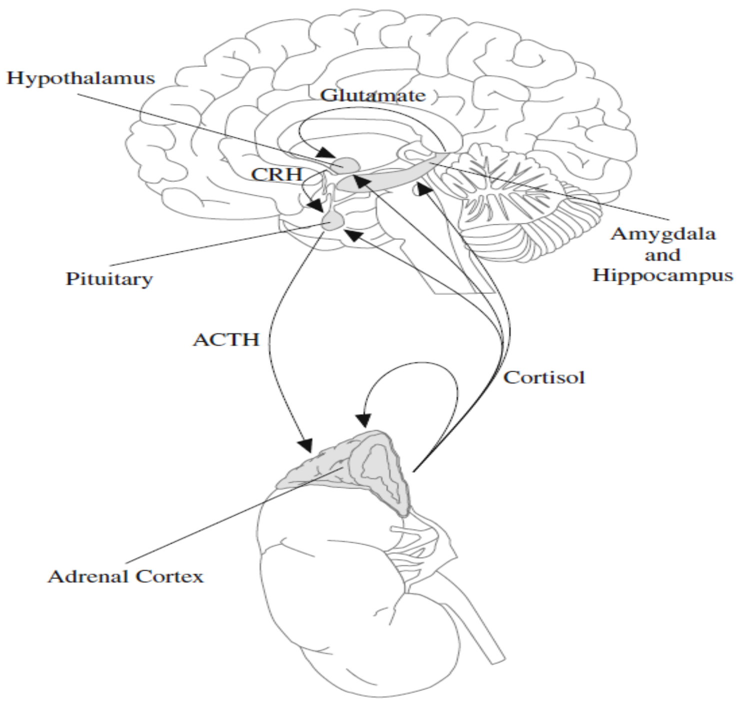


Figure 1.1 In the HPA system the cortisol will supply feedback signal in arranged inorder of rank all levels through MR or GR and as follows, the Glutamate spur theCRH discharge and that lead to ACTH excretion and this also will make cortisolexcreted. [28]

The cortisol bounding to the glucocorticoid receptors in the hypothalamus, adrenals, amygdala, pituitary and hippocampus and this suppression is partially done. Keeping cortisol levels up the critical level is substantial because the low levels may cause adrenal crisis which is life threatening and may damage the memory [2, 3]. According to functional and biochemical characteristics, two kinds of corticoid receptors has been portrayed [4]. In the brain, the mineralocorticoid receptor (MR) has certain cortisol bounding level and in the septal neurons and hippocampal the (MR) main intensity. The 11 β hydroxysteroid dehydrogenase 2 limits the MR intensity for cortisol in lower and circumference of brain, the 11 β hydroxysteroid dehydrogenase 2, make the active cortisol to inactive intracellularly. The glucocorticoid receptor (GR) is vastly hand out and founded in circumference of tissues and organs and also vastly hand out in pituitary, adrenals and hypothalamus and this clearly appears the dominant bounding for cortisol. The MR binds cortisol with a higher affinity if it is compared to GR. The HPA system response is modified by GR and MR and for setting MR and GR, the receptors are complementing each other. When the concentrations of cortisol are high the MR show saturation and sensitives for low level. While GR behavior for high concentrations of cortisol is to make dynamics while in low level show inactive behavior. The cortisol excretion is restrained effect and this returned to cortisol bounding to GR [5]. While the binding of cortisol to MR is unknow how effect on HPA system [16].

When we describe the HPA system properties we can tell that is dynamic, closed loop system, keeping the internal stability in organism in the daily rhythm. The HPA system is spur during rapid eye movement (REM) in the second half of night [6].

In the first morning hours maximum of both ACTH and cortisol will be reached. During daytime the hormones will be subjected to constant decrease. Physical or psychological stress or after a meal will make ACTH and cortisol decreasing again.

Cortisol and ACTH will be in homeostatic level in the first half of the night (see figure 1.2)

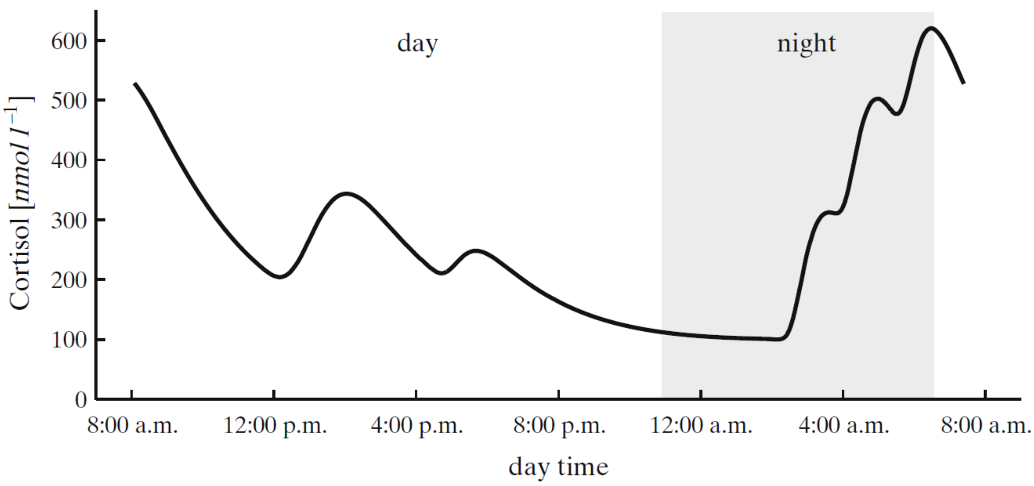


Figure 1.2 Daily cortisol in human [28]

The HPA system is adjustment and arrive to its homeostatic level due to treatment of many kind of diseases such as physiology illnesses for example Cushing's disease and energy and weight problems and diseases such as diabetes and obesity and metabolic instability and mental (psychological) illnesses such as depression and depression will be deep motivation to examine the mechanisms of HPA regulation [7].

For homeostatic regulated system basis, it is needed to robust mechanism, homeostatic state of cortisol due to robust mechanism and principle of homeostasis for the HPA system [8]. See the table 1.1 below

Table 1.1 Principles of homeostasis

Rule	Details
Rule 1	Cortisol is high to the GR and low to MR
Rule 2	Working of GR and MR in reverse to each other
Rule 3	When MR activated, cortisol will rise its own plasma while GR activated will decrease it

1.2 Back-stepping

In my thesis work we will implement the system and compare between them to find the best stability and the two methods is the first one is back-stepping and other is feedback linearization.

In beginning of 1990s the main concept of back-stepping was developed and beginning with ideas of Isidori and Byrnes [10], Tsinias [9], Sussmann and Kokotov [12], Sussmann and Sontag [11], Kokotovic, Sussmann and Saberi [13] and this method used for designing stable control systems for certain and special rank of nonlinear dynamical systems and sometimes nonlinear differential equations which most of time cannot be linear.

In 1995, the book nonlinear and adaptive Control design was published by the previous authors with Kanellakopoulos and Kstic together which is deal with the theory for nonlinear system in certain rank [15].

In chapter three we will explain the method with derivation.

1.3 Feedback linearization

Feedback linearization is an approach to transform nonlinear system equations

into (fully or partly) linear ones to get stable system and it is applying when the system in following form [16]:

$$x^{\bullet} = f(x) + g(x)u \quad (1)$$

$$y = h(x) \quad (2)$$

where x is negative real numbers and vector state, u is positive real numbers and it is input vector, y is also real numbers and output vector and the desired output is:

$$u = a(x) + b(x)v$$

And as we mention before in chapter three, we will completely discuss the method.

1.4 Objective of study

The objectives of thesis can be described as followings:

The thesis attempts to implement the Hypothalamus–Pituitary–Adrenal (HPA) system in back-stepping and feedback linearization.

To check if the two implementation is true theoretically and practically and not conflicts with basic laws of physics.

To compare the results of two implementation of two methods to get an asymptotically stable system.

1.5 Research Questions

In this section there is a research questions are presented and these questions as follow:

Can we make the nonlinear differential equation that describe the HPA into linear equations and then implement it?

How we can sure that the implementations of the two methods are correct?

Which is more stable the back-stepping implementation or feedback linearization?

What is the accuracy of the results?

1.6 Organization of thesis

Chapter 1

In chapter one we explain the introduction of the thesis including background of model and it is Physiology and two method back-stepping and feedback linearization that will implement model using it.

Chapter 2

In chapter two we explain the related works according to their characteristics like in age, season, specific time period, delay, stability of system, dysregulation, predicate axis response, memory or structure from linear or nonlinear models using negative feedback method or mixed of negative feedback method or dynamics.

Chapter 3

In chapter three we explain extensively the formulas derivation, the parameters estimation of differential equations, back-stepping method, feedback linearization method.

Chapter 4

In chapter four we explain the results from each method (back-stepping and feedback linearization) and how controller gains effect on correctness of plots and how we maintain it to get plots without negative values and then make plot comparison between old and new correct values and make final comparison between back-stepping and feedback linearization methods.

Chapter 5

In chapter five we make the discussion, conclusion, limitation of study, future works related to thesis.

1.7 Flowchart of the study

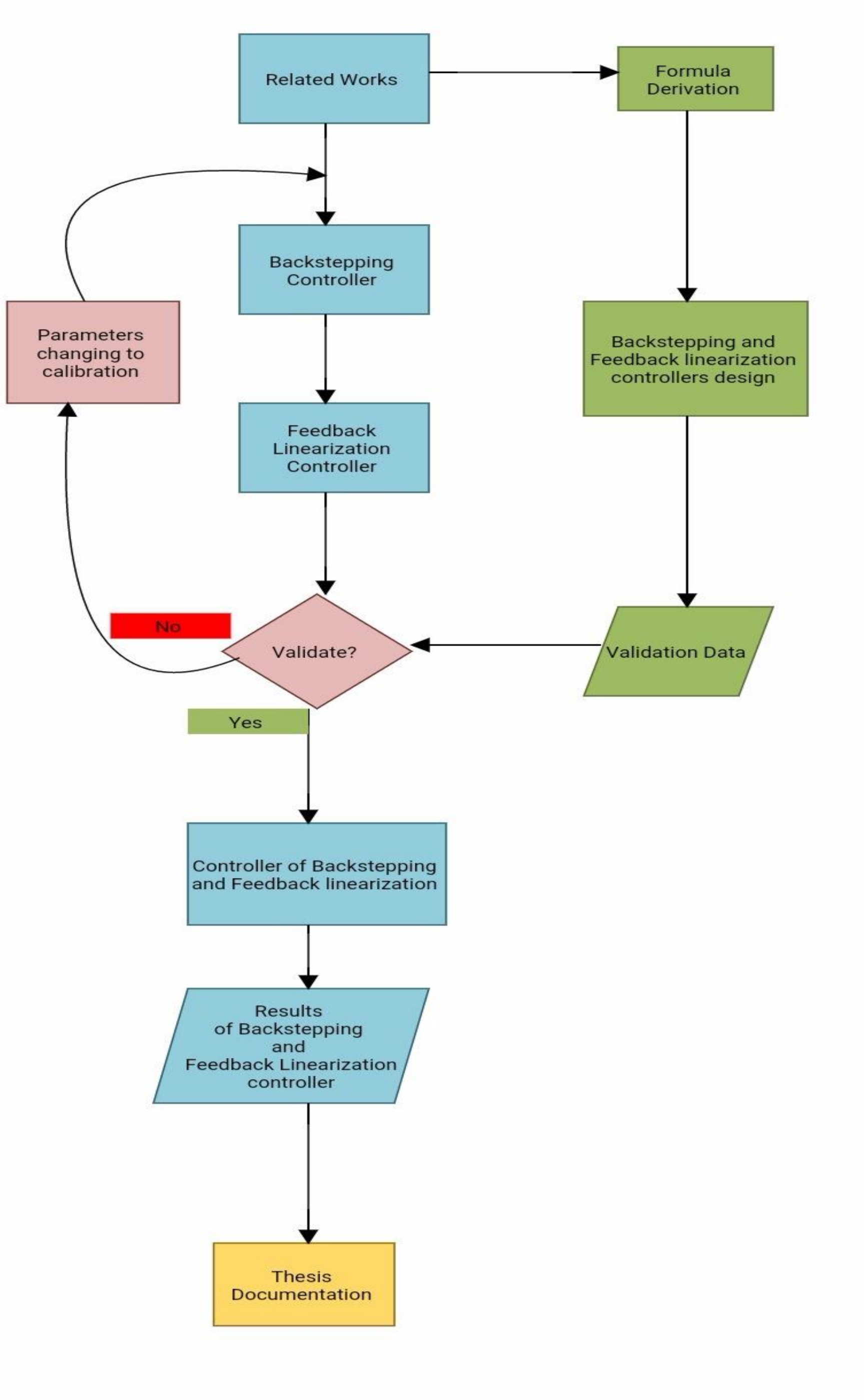


Figure 1.3 Flowchart of the study

CHAPTER 2

RELATED WORKS

In [17], Bingzheng, Zhenye and Liansong proposed a mathematical model for glucocorticoids and they calculate the factors of the ordinary differential equations in excretion system and the system implementation show that is some way is right because some calculated results match the experimental results.

In [18], Bing and Min implement an improved mathematical model for excretion hypothalamus–pituitary–adrenal system axis system and they think it is more real implementation system than any other previous implementation, for example, Smith in 1980 mathematical model and Cartwright & Husain (1986) mathematical model. They make the mathematical model in wide differential equations and they solved it in fourth order of Runge-kutta method.

In [19], Rohatagi, Bye, Mackie, and Derendorf make a linear discharge model for cortisol inhibition and cortisol baseline properties better than other model which made before and the model suppose that there is decrease in cortisol production from 4-5 a.m. in day till midnight and there is shorter linear increase of excretion from the midnight till 4-5 a.m. in next day. When they make a comparison between the experimental measured cortisol levels for 3 days (72 hours) and results from the model they give good match which make the model real and reasonable. Also, they make five models cosine, exponential, biexponential self-inhibition, monoexponentially self-inhibition, and linear discharge model and see the figure below of the models over three days (72 h). and the main purpose of this study is to model circadian variation of cortisol excretion and this excretion inhibition made by negative feedback mechanism so that they want to make a fixed PK/PD model to estimate the impact of administered exogenous corticosteroids through rhythm.

In [20], Wilkinson, Peskind, and Raskind show that there is bit decrease of sensitive of HPA axis in cortisol feedback suppression due to human getting old and in that time the behavior was unclear. They make the study with three group samples 16, 26, and

70 years people and factor 11β hydroxylase and 0.03 mg/kg/h or 0.06 mg/kg/h cortisol for 150 min in intravenous and they see the response of decreased cortisol and ACTH and the response.

In [21], Liu, Hu, Ping and Zheng proposed a dynamical model for excretion of hypothalamus–pituitary–adrenal axis and their model contains the bounding of hormone with protein in tissues and plasma, as well compound interactions of hormone. The results from model is show good match with experimental results and more reasonable and real system and they represent the HPA system through fifth order differential equations, they neglect the interactions of hormone in different axes due to small values that enable them to decide to neglect it.

In [22], Lenbury and Pornsawad proposed mathematical model to describe delay in hypothalamus–pituitary–adrenal axis of feedback controller in humans. They suppose that the excretion is ruled by time delayed and nonlinear differential equations and the time delayed has the properties of both feedforward and feedback signal reciprocity. Also, they explain the role of coefficients β 1 and β2, their model is seeming reasonable and real.

In [23], Jelic, Cupic and Anic proposed a mathematical model for hypothalamus–pituitary–adrenal system, their system contains four-dimensional nonlinear differential equation that represents the excretion hormones and the analysis will describe the work of plasma cortisol in humans and the model is simple and this due to sight of researchers to make their study first step to more complex studies in this field and objectives of the study is to explore the working of system in normal, homeostatic and working condition because until the study the HPA system working and behavior are not fully clear.

In [24], Kyrylov, Severyanova, and Vieira proposed a mathematical model of the hypothalamic-pituitary adrenal (HPA) axis system in humans, this time this model came as development of the previous mathematical models and the model with two nonlinear coefficients and the model get used from fact that negative hormone condensations that rejected normally physiology of limited size of gland. Their model show robustness remarks and this due to that model can bear -50 to 100% disturbances, the model new features contain of circadian rhythm , the model is more simple and this related to decreasing of parameters number to half, ability to add model to endocrinology text book for medicine teaching institutes, other important application of model is studying hypothalamic-pituitary adrenal disturbances of dynamics size of gland, abnormal of hormones level and model enable to see response to hormone injections. Other feature of this model that take into considerations critical parameters that neglected in previous studies. The results of model show robust system.

In [25], Svic, Jelic and Buric proposed a mathematical model of hypothalamic-pituitary adrenal (HPA) axis system to check it is delay stability and HPA role is to stress response but may be transmit rhythmic signals from the pacemaker, suprachiasmatic nucleus (SCN), to the circumference.

The stability of Hypothalamic-Pituitary Adrenal (HPA) axis system by Roushe's theorem. And linear stability analysis. The results demonstrate that hypothalamic-pituitary adrenal (HPA) axis system is not responsible of circadian oscillations generation and it is only duty to response to external pacemaker and the most important check from this study it was the delay stability system is asymptotically stable.

In [26], Gupta, Aslakson, Gurbaxani and Vernon proposed mathematical model of the Hypothalamic Pituitary Adrenal (HPA) axis that contains the glucocorticoid receptor (GR) Which is nonlinear dynamic and this due to background of the Hypothalamic Pituitary Adrenal (HPA) axis that main stress system of body and through controlling cortisol in body enable the HPA axis to react to mental changes in body to keep the homeostasis condition.

The model can be used to examine the Hypothalamic Pituitary Adrenal disturbances mechanisms and diseases.

When the cortisol activates, a nonlinear behavior will appear on glucocorticoid receptor (GR) and will GR homodimerizes.

The homodimerization in glucocorticoid receptor (GR) have three states, in unstable state of the glucocorticoid receptor (GR), the Hypothalamic Pituitary Adrenal (HPA) axis is bi-stable the other stable states are low and high.

dysregulated steady state will appear as high GR intensity while low GR will appear as normal steady state. Low GR intensity can quickly return to it is level by short stress while high GR does not have this characteristic even if high GR intensity is continuous iterate for long time.

It is noticed from some stress disturbances like Chronic Fatigue Syndrome (CFS) that increasing steady state GR will reduce cortisol regular state.

Addition of GR expression in HPA axis lead to more reasonable model of the Hypothalamic Pituitary Adrenal (HPA) axis that this time take into consideration hypercortisolism and bi-stable states.

In [27], McAuley, Kenny, Kirkwood, Wilkinson, Jones and Miller (2009) proposed mathematical model of the Hypothalamic Pituitary Adrenal (HPA) axis about hippocampal dysfunction that related to cortisol levels and aging in humans.

The model is directly related to Alzheimer's disease (AD) which is the common nowadays for old and make them dementing in ages is not quite long.

Relapsing amnesia related to quite increase of plasma cortisol and transient hippocampal suppression, to avoid Alzheimer's disease (AD) type hippocampal dysfunction by constant monitoring the cortisol level because the chronic increased of cortisol level connected with hippocampal atrophy.

In the model we use the systems biology mark-up language (SBML) for creating silicomodel that related to quite increase of plasma cortisol.

We put a number of biological interferences to model to ensure that may cortisol linked to hippocampal be revoked.

The results from applying the silicoSBML model show increasing of both negative feedback and cortisol level for the HPA.

We found that aging reduces the hippocampus activity by 12% and noticed 30% raise in acute and 40% raise in chronic of cortisol level.

Also, we have to mention that adding a number of biological interferences to model make a significant reduction of cortisol linked hippocampal dysfunction in the hippocampus activity by 8% in chronic simulation of model and 2% in acute cortisol of model simulation.

As we see the hippocampus activity loss related to increasing of chronic and acute in cortisol excretion and this will increase aging linked hippocampal atrophy.

The using of SMBL model with vivo studies (means in Latin within the living) and vitro together may help to make system for predicting changes in brains and this will decrease the chances of early Alzheimer's disease (AD) type hippocampal dysfunction or avoid it.

In [28], Conrad, Hubold, Fischer, and Peters proposed mathematical model of the Hypothalamic Pituitary Adrenal (HPA) axis to achieve homeostasis in the axis using positive

and negative feedback. The model is created to deal with day and night that in day the activity of system reduced and homeostatic happens late evening, the model work on the rules which is Cortisol is high to the GR and low to MR working of GR and MR in reverse to each other when MR activated, cortisol will rise its own plasma while GR activated will decrease it. In other models there is just negative feedback while in this model both positive and negative.

We make parameter estimation to prove that model is work correctly and to adjust the model for variety of clinical status.

The model prove it can be applying for long time model and enable it to apply the model to make it for predicating disease like diabetes, depression.

In [29], Vinther, Andersen and Ottesen proposed mathematical model of the Hypothalamic Pituitary Adrenal (HPA) axis and this time they try to make minimum model as can as possible, their model based on combine the three hormones, CRH, ACTH, and cortisol, which connected in the HPA axis together with biological knowledge, physiological mechanisms and parameters. Of course, the model based on nonlinear differential equations as usual (from previous models).

Oscillating solutions is mathematical expression used to ultradian rhythm which paper work on it and the oscillating solutions have eigenvalues with real part and imaginary (complex) and unstable and negative feedback from cortisol on is ACTH and CRH and their mechanism and dynamics theory is scientifically accepted in this model. And we called it minimal model because we use few factors with HPA axis.

Simulation of the model show that intensity of hormones cortisol, ACTH and CRH show that go to region called trapping and the intensity of hormones will not be negative or go to infinity.

In the model there is unparalleled fixed point and it is local stability criteria go from stable to unstable status and indicates Hopf bifurcation.

The conclusion from first part of paper is ultradian rhythm cannot be resulted from the model,

The second part discuss the reasonable values of stability cases for fixed point from physiological view and when apply the parameters it was unstable of fixed point then when changes values it be stable in all fixed points also examine the worst-case parameters in the simulation of model.

In [30], Markovic, Cupic, Vukojevic and Kolar-Anic proposed model of the Hypothalamic Pituitary Adrenal (HPA) axis to predict the chronic and acute response.

The HPA axis in regular have many parameters like ultradian phase, healthy, circadian phase in night and day and ill so that it is complex work to compare the HPA axis on every individual case, so that we use first know the parameters and then we use four-dimensional model to examine axis in self-regulation mechanisms.

A suddenly change made to cortisol level to simulate acute stress to model, while we make a change in constant level of CRH intensity levels to simulate chronic stress.

We take into consideration and study the following parameters time, duration, effect of acute concentrations, circadian phase, ultradian phase and its amplitude.

chronic stress response predication using bifurcation and we make comparison between experimental results and simulation of models.

In [31], Vinther, Andersen and Ottesen proposed mathematical model of the Hypothalamic Pituitary Adrenal (HPA) axis but this time with three hormones cortisol, CRH and ACTH with hippocampal mechanisms., the model based on nonlinear differential equations as usual, the model contains the hippocampus influence and its relation to CRH.

Oscillating solutions is mathematical expression used to ultradian rhythm which is found in simulation data and there are also many fixed points related to illnesses such as hypocortisolemic and hypercortisolemic depression.

Simulation figures does not have non-negative and infinity data curves due to trapping region, and this led us to homeostasis mathematical expression.

When we use physiologically parameter there will be oscillating solutions and that many kinds of mechanism are the origin of ultradian rhythm.

Case with globally stable and unique fixed point can be achieve by using physiologically parameter, after ending the duration of mild stress the cortisol levels will return to its normal status.

Bifurcation case happens when applying perturbing parameters and this case have three fixed points instead of one unique fixed point, in this case one unstable and two points is stable, initial conditions play role to decide which is from two fixed point is convergence characteristic.

From this we can conclude the reason of two group of sick people first is hypocortisolemic

depressive and hypercortisolemic depressive.

In [32], Kaslik and Neamtu proposed mathematical model of the Hypothalamic Pituitary Adrenal (HPA) axis and this time they make model with more factual by adding memory and first part fractional-order derivatives and second part is time delay.

To achieve general distributed delays, we have to find a unique equilibrium point prove it then make suitable analysis of stability for it.

For the distributed delays models many analysis methods make for example bifurcation, delay kernels, and discrete delays for fractional-order.

Experimental results with result from model prove that the model can handle smoothly pivotal of the HPA system functions.

In [33], D’Orsogna and Chou proposed mathematical dynamical model of the Hypothalamic Pituitary Adrenal (HPA) axis about ACTH and dexamethasone (DEX) and to see what behavior of adrenal glands and pituitary response.

They show the following:

Disturbances time is close to oscillation and this may explain as response to this confuse in HPA axis, dynamic responses may emerge to model instead of physiological disturbances may form as responses to permeant parameters.

We make two-stage DEX/external stressor and the reason from make it to have recognize between hypothalamus dynamics bi-stable and classical pituitary excretion of hypothesis.

Also, we notice that no need for PTSD for cortisol repression in the model.

In [34], Pierre, Schlesinger, Androulakis and Chou proposed mathematical dynamical model of the Hypothalamic Pituitary Adrenal (HPA) axis about production of cortisol and metabolism and what changes happen in each season for them.

the suprachiasmatic nucleus (SCN) is control of cortisol dynamics, the 11β–hydroxysteroid dehydrogenase (HSD) type enzymes is an example of the hypothalamic-pituitary-adrenal (HPA)

axis, and metabolic enzymes and this enzyme is much existing in renal and hepatic tissue.

Different pathophysiological conditions are play main role in keeping cortisol circadian rhythms for both normal and abnormal cortisol dynamics state.

The proposed model focused on predicating of domination of proinflammatory and genetic changes that happen in winter season and any changes may happen to 11β-HSD enzyme functions in this season and HPA axis dysregulation for example happens by recalling subgroups that over sensitives to illnesses.

The symptom exacerbation, peak inflammatory and rising of cortisol levels is connected with photoperiod (the light-dark cycle period) in winter season and effect on SCN activity and the photoperiod in winter is short.

It supposes the activity of 11β-HSD1 protein happens in winter and it is also connected to inflammatory conditions.

In the work related to HPA axis they use semi-mechanistic mathematical model; disease and its development may understand and may treat if overall understanding of the connection between cortisol mechanism and it is activity alterations.

CHAPTER 3

MODELS AND METHODS

3.1 Model Formula Derivation

Mathematical models of the Hypothalamic Pituitary Adrenal (HPA) axis until now being examined and investigated and proposed different models of purpose and structure with different controller approach, while many models of glucose metabolism proposed [17] [35-37].

And as we see from related works there is wide number of Hypothalamic Pituitary Adrenal (HPA) axis in their purpose like in age, season, specific time period, delay, stability of system, dysregulation, predicate axis response, memory or structure from linear or nonlinear models using negative feedback method or mixed of negative feedback method or dynamics.

The Hypothalamic Pituitary Adrenal (HPA) axis models only in negative feedback elements [41-43].

The Hypothalamic Pituitary Adrenal (HPA) axis models only in positive feedback elements [44].

And the Hypothalamic Pituitary Adrenal (HPA) axis models contain two negative and positive feedback elements together [28].

The model will contain the elements GR, MR, CRH and ACTH.

The models follow the three main rules, the first rule Cortisol (Z) is high to the GR (R_2) and low to MR (R_1), C_1 represent MR and cortisol from receptor while C_2 represent GR from the receptor. K_1, K_{-1}, K_2, K_{-2} denoted to the equation reactions.

$$Z + R_1 \underset{K_{-1},}{\overset{K_1,}{\rightleftharpoons}} C_1, \qquad (3)$$

$$Z + R_2 \underset{K_{-2,}}{\overset{K_{2,}}{\rightleftarrows}} C_2. \quad (4)$$

The following response relations derive it according to bound mass action law and biochemical kinetics law [20].

$$c_1 = \frac{e_1\, z}{z + K_1} \quad (5)\ and$$

$$c_2 = \frac{e_2\, z}{z + K_2} \quad (6)$$

In the model the chemical equilibrium, the Z concentration symbolize to z (C_1 and C_2)

While we symbolize to maximum efficiencies of MR and GR in different location of brain regions such as pituitary, amygdala, hippocampus and hypothalamus by e_1 and e_2 respectively.

$$K_1 = \frac{K_{-1}}{K_1} \quad (7)$$

$$K_2 = \frac{K_{-2}}{K_2} \quad (8)$$

Represent affinity of MR and GR, consequently and according to second rule of homeostasis that affinity of GR is lower than affinity of MR

Which verify the inequality as $K_1 < K_2$

$$h(z) = \frac{e_1\, z}{z + K_1} - \frac{e_2\, z}{z + K_2} = c_1(z) - c_2(z) \quad (9)$$

h represents cortisol feedback in the Hypothalamic Pituitary Adrenal axis.

Y represents gathering of ACTH, integrated influences of glutamate, CRH and as we know this related to various sections of brain and make it into one variable while positive stimulus supposed given from y on z.

Strong and fast synchrony between ACTH and CRH hormones can be explained due to gathering of ACTH and CRH hormones behavior [45].

Drolet notice that ACTH intensity has directly relate and impact on CRH [46].

There is mathematical model of the Hypothalamic Pituitary Adrenal axis (HPA) consider ACTH as transfer hormone [41] [47] [48] while Heydrich in their model they neglect the CRH [40].

See Figure 3.1 and 3.2 below.

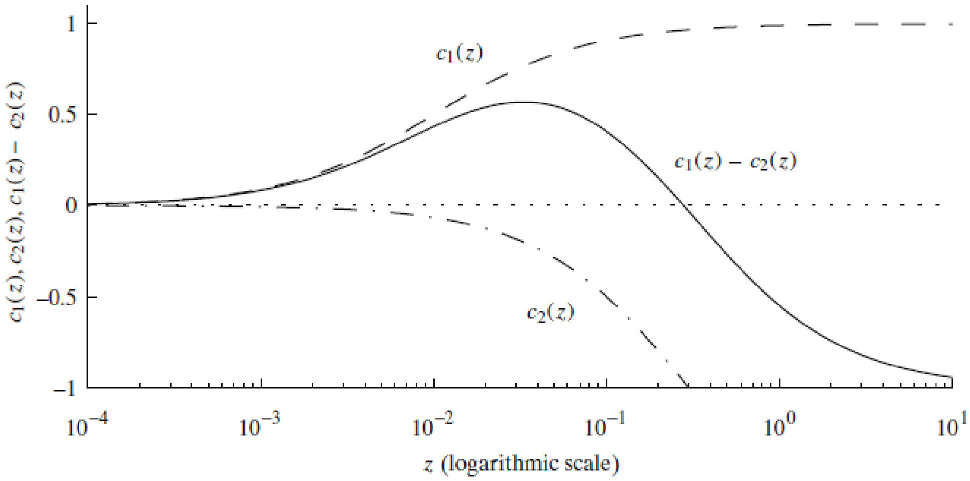


Figure 3.1 The HPA axis system with factors
e_1=1, e_2=2, K_1=0.01, K_2=0.3, z ∈ [10^{-4},10] [28]

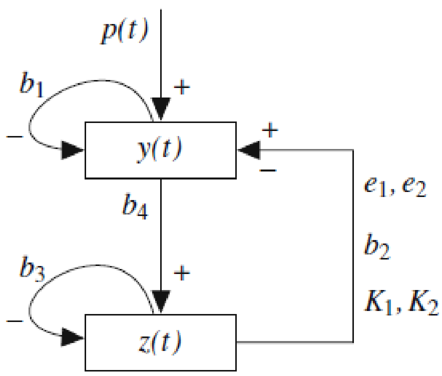


Figure 3.2 Flowchart of differential equations
versus time [28]

b_2 represents the adrenal cortex compartment transition in the pituitary and it is constant and $b_2 \in R^+$.

The differential equation become:

$$\frac{dy}{dt} = -b_1 y + \frac{e_1 Z(t)}{Z(t)+b_2 K_1} - \frac{e_2 Z(t)}{Z(t)+b_2 K_2} + p(t) \tag{10}$$

Y supposed to be linear decay rate at $b_1 \in R^+$ and p: $R \rightarrow R^+$ and the external input of models combine with ACTH.

There is another linear decay rate which is $b_3 \in R^+$ of Z and $b_4 \in R^+$ of Y on Z.

And the following differential equations of model as follow:

$$\frac{dy}{dt} = -b_1 y + \frac{e_1 Z(t)}{Z(t)+b_2 K_1} - \frac{e_2 Z(t)}{Z(t)+b_2 K_2} + p(t) \tag{11}$$

$$\frac{dz}{dt} = -b_3 z + b_4 y \tag{12}$$

And the parameters as following [62]:

$e_1 = 0.1290, e_2 = 0.1633, b_3 = 0.0336, \; b_4 = 2.2234$

Add to that we already know $K_1 = 0.5$, $K_2 = 5$, $b_1 = \frac{\log(2)}{20}$, $b_2 = 28$ from [5],[49].

And initial conditions of $y_0 = 2.5345$, $z_0 = 148.0701$.

3.2 Back-Stepping Method

In beginning of 1990s the main concept of back-stepping was developed and beginning with ideas of Isidori and Byrnes [10], Tsinias [9], Sussmann and Kokotov [12], Sussmann and Sontag [11], Kokotovic, Sussmann and Saberi [13] and this method used for designing stable control systems for certain and special rank of nonlinear dynamical systems and sometimes nonlinear differential equations which most of time cannot be linear.

In 1995, the book nonlinear and adaptive Control design was published by the previous authors with Kanellakopoulos and Kstic together which is deal with the theory for nonlinear system in certain rank [15].

The back-stepping controller has a recursive nature so that the name back-stepping derives from this property.

The design of back-stepping controller begins from the inner scalar function and steps back control across external control input.

In the design of back-stepping procedure a subsystem and must be controlled and this subsystem came from suppose of each nonlinear differential equation in the system [55],[56].

The subsystem is controlled in cascade sequence by external control input and from the inner subsystem to outer subsystem [57].

In the design procedure of back-stepping there is a virtual control input that represent the status of differential equation but in higher order and virtual control input make each subsystem stabile about the origin.

$$x^{\bullet} = f(x) + \delta \qquad (13)$$

$$\delta = u \qquad (14)$$

$$V = \frac{1}{2}x^2 \qquad (15)$$

$$\delta_{des} = \alpha(x), V \leq 0 \qquad (16)$$

$$z = \delta - \delta_{des} \qquad (17)$$

$$V_a = \frac{1}{2}x^2 + \frac{1}{2}z^2 \qquad (18)$$

$$u = \alpha_c(x), V_a \leq 0 \qquad (19)$$

$V, V_a = Lyapunov\ Functions$

x, δ = State Variables

z = Virtual State

α(x) = Virtual Control

u = system input

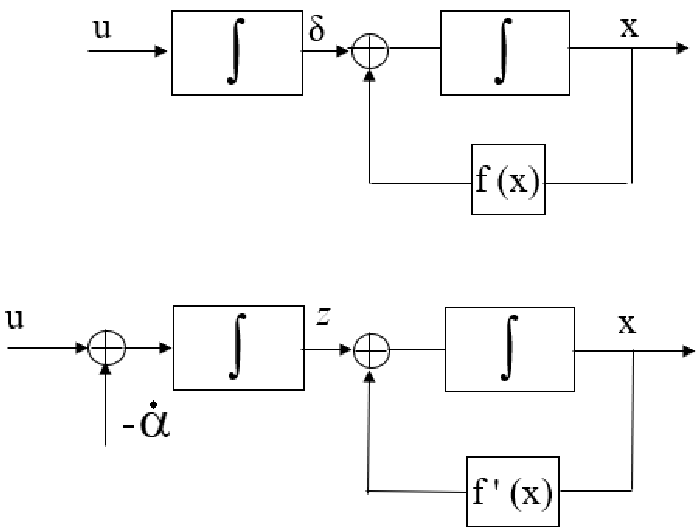


Figure 3.4 Block diagram of Back-stepping

3.2.1 Advantages of Back-Stepping Method

Making the controlled system simpler by cascade subsystem.

We can be sure that stability and control law.

3.2.2 Application of Back-Stepping Method

High-performance aircraft, industrial robots, biomedical devices and systems, vehicle control and helicopters.

Now we are giving the derivation of Back-stepping method for HPA model [62]

$$y^{\bullet} = -b_1 y + \frac{E_1 Z}{Z+b_2 K_1} - \frac{E_2 Z}{Z+b_2 K_2} + p(t)$$

$$z^{\bullet} = -b_3 z + b_4 y$$

We have to define a variable reference that we want to control and should time varying signal and may be periodic and define error variable

$E_1 = z - z_r$ (20) z_r : *is the desired value of z* and suppose it is constant

$$E_1^{\bullet} - z^{\bullet} = -b_3 z + b_4 y \qquad (21)$$

Then define the control error caused by the virtual control input

$$E_2 = y - y_r \qquad (22)$$

y_r : *a virtual variable which is generated by the controller*

$$y = E_2 + y_r \qquad (23)$$

$$E_1^{\bullet} = -b_3 z + b_4 E_2 + b_4 y_r \qquad (24)$$

Then define a Lyapunov function according to given specification.

$$V_1 = \frac{1}{2} E_1^2 \qquad (25)$$

The rate of change for the above function is:

$$V_1^{\bullet} = E_1 E_1^{\bullet} = E_1 [-b_3 z + b_4 E_2 + b_4 y_r]$$
$$= b_4 E_1 E_2 + [-b_3 z + b_4 y_r] E_1 \qquad (26)$$

$Where \quad -b_3 z + b_4 y_r = -K_1 E_1 \quad , K_1 > 0$

$$y_r = \frac{-K_1 E_1 + b_3 z}{b_4} \qquad (27)$$

Then (27) reaches final form as follow:

$$V_1^{\bullet} = b_4 E_1 E_2 - K_1 E_1^2 \qquad (28)$$

Now we complete procedure for the stabilization of cortisol and the next step will be stabilized the dynamics of the plasma ACTH

The dynamics of (20) can be found as follows:

$$E_2^{\bullet} = y^{\bullet} - y_r^{\bullet} = -b_1\, y + \frac{E_1\, Z}{Z+b_2\ K_1} - \frac{E_2\, Z}{Z+b_2\ K_2} + p(t) - \frac{1}{b_4}\,[-K_1\, E_1^{\bullet} + b_3\, z^{\bullet}] \quad (29)$$

Where $y_r^{\bullet} \neq 0$

Now we define a control Lyapunov function

$$V_2 = V_1 + \frac{1}{2}\ E_2^2 \quad (30)$$

The rate of change of the above function is:

$$V_2^{\bullet} = V_1^{\bullet} + E_2\ E_2^{\bullet} = b_4\, E_1\, E_2 - K_1\, E_1^2 \quad (31)$$

$$+ E_2\left[-b_1\, y + \frac{E_1\, Z}{Z+b_2\ K_1} - \frac{E_2\, Z}{Z+b_2\ K_2} + p(t) - \frac{1}{b_4}\,[-K_1\, E_1^{\bullet} + b_3\, z^{\bullet}]\right] \quad (32)$$

$$V_2^{\bullet} = -K_1\, E_1^2 + E_2\,[b_4\, E_1$$

$$-b_1\, y + \frac{E_1\, Z}{Z+b_2\ K_1} - \frac{E_2\, Z}{Z+b_2\ K_2} + p(t) - \frac{1}{b_4}\,[-K_1\, E_1^{\bullet} + b_3\, z^{\bullet}]\,] \quad (33)$$

$$p(t) = -K_2\, E_2 - b_4\, E_1 + b_1\, y - \frac{E_1\, Z}{Z+b_2\ K_1} + \frac{E_2\, Z}{Z+b_2\ K_2} + \frac{1}{b_4}\,[-K_1\, E_1^{\bullet} + b_3\, z^{\bullet}] \quad (34)$$

And we can obtain Lyapunov function as follow:

$$V_2^{\bullet} = -K_1\, E_1^2 - K_2\, E_2^{\bullet} < 0 \quad (35)$$

$$K_1\,, K_2 > 0 \quad (36)$$

The above is connected with the closed loop dynamics of the control law (35) and will be negative definite, we have to mention if the control gains K1 and K2 are positive (36). If satisfied, the closed loop will be asymptotically stable.

3.3 Feedback Linearization Method

Feedback linearization is an approach to transform nonlinear system equations

into partly or fully linear to get stable system and it is applying when the system in following form [16]:

$$x^{\bullet} = f(x) + g(x)u \quad (1)$$

$$y = h(x) \quad (2)$$

where x is negative real numbers and vector state, u is positive real numbers and it is input vector, y is also real numbers and output vector and the desired output is:

$$u = a(x) + b(x)v \quad (37)$$

And the procedure is:

We keep differentiate y until u appears in one of the equations for the derivatives of y.

$y^{\bullet}$
$y^{\bullet\bullet}$

•••

$$y^{(r)} = \alpha(x) + \beta(x)u \quad (38)$$

u appears as soon as r steps completed

y (r) = v, where v is input and choose u

$u = \alpha(x) + \beta(x)v$

The system will form $y^{(r)} = v$

Begin designing r-integrator system according to linear control laws.

Check it stability and dynamics [58],[59],[60],[61].

3.3.1 Advantages of Feedback Linearization

Transfer nonlinear system equation to exactly linear equation.

The stability of the results system is global asymptotically.

3.3.2 Disadvantages of Feedback Linearization

We cannot apply the method on every system.

There are faults and limitations of it and especially with critical applications like aircrafts.

3.3.3 Application of Feedback Linearization

Industrial robots, high-performance aircraft, biomedical devices and systems, vehicle control and helicopters.

Now we will show the of Feedback Linearization method for HPA model and we have to mention that the HPA dynamics is of full relative degree so that the input P must appear when the output z is differentiated twice [62].

$$y^{\bullet} = -b_1\, y + \frac{E_1\, Z}{Z+b_2\ K_1} - \frac{E_2\, Z}{Z+b_2\ K_2} + p(t)$$

$$z^{\bullet} = -b_3\, z + b_4\, y$$

$$E = Z - r_z \qquad (39)$$

Output = z

$$\frac{d}{dt} output = z^{\bullet} = -b_3\, z + b_4\, y \qquad (40)$$

$$\frac{d^2}{dt^2} output = z^{\bullet\bullet} = -b_3 z^{\bullet} + b_4\, y^{\bullet} = -b_3\,[-b_3\, z + b_4\, y] + b_4\,[-b_1\, y + \frac{E_1\, Z}{Z+b_2\ K_1} - \frac{E_2\, Z}{Z+b_2\ K_2} + p(t)] \qquad (41)$$

$$v = z^{\bullet\bullet} = -b_3 z^{\bullet} + b_4\, y^{\bullet} = -b_3\,[-b_3\, z + b_4\, y] + b_4\,[-b_1\, y + \frac{E_1\, Z}{Z+b_2\ K_1} - \frac{E_2\, Z}{Z+b_2\ K_2} + p(t)] \qquad (42)$$

$${b_3}^2\, z - b_3\, b_4\, y - b_1\, b_4\, y + \frac{b_4\, E_1\, Z}{Z+b_2\ K_1} - \frac{b_4\, E_2\, Z}{Z+b_2\ K_2} + b_4\, p(t) = v \qquad (43)$$

$$\frac{d}{dt}\begin{bmatrix} X_1 \\ X_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix}\begin{bmatrix} X_1 \\ X_2 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} v \qquad (44)$$

The above equation is a linearizing control law that can be subjected to a complete state controllable and observable second order linear system [62]

Where $X_1 = z$ (45)

$X_2 = z^{\bullet}$ (46)

$${X_1}^{\bullet} = X_2 \qquad (47)$$

The design procedure as follow:

$$E_1 = X_1 - r_1 \qquad (48)$$

and the rate of above error is:

$$E_1^{\bullet} = X_1^{\bullet} - r_1^{\bullet} \quad (49)$$

Then define the tracking error

$$E_2 = X_2 - r_2 \quad (50)$$

$$X_2 = E_2 + r_2 \quad (51)$$

define a Lyapunov function for E_1

$$V_1 = \frac{1}{2} E_1^2 \quad (52)$$

$$V_1^{\bullet} = E_1 \; E_1^{\bullet} = E_1[E_2 + r_2] = E_1 \, E_2 + E_1 \, r_2 = E_1 \, E_2 - K_1 E_1^2 \quad (53)$$

For stability should $K_1 > 0$

$$r_2 = -K_1 \, E_1 \quad (54)$$

The rate of the error $E_2^{\bullet}$

$$E_2^{\bullet} = X_2^{\bullet} - r_2^{\bullet} = v + K_1 E_1^{\bullet} = v + K_1 X_2 \quad (55)$$

define a Lyapunov function for E_2

$$V_2 = \frac{1}{2} E_2^2 \quad (56)$$

And rate of change

$$V_2^{\bullet} = E_2 \; E_2^{\bullet} = -K_1 E_1^2 + E_1 \, E_2 + E_2[v + K_1 X_2] \quad (57)$$

And the final control law form

$$V_2^{\bullet} = -K_1 E_1 z + E_1 \, E_2 + E_2[E_1 + v + K_1 X_2] \quad (58)$$

$$V_2^{\bullet} = -K_1 E_1 z + E_2[-K_2 E_2^2] \quad (59)$$

For stability $K_1 \, , K_2 > 0$ (60)

CHAPTER 4

RESULTS

In chapter three we explain the formula derivation then we explain extensively the back-stepping method and feedback linearization, now time to show results of two methods.

4.1 Back-Stepping Method Results

For controller gains L1 =5 and L2=0.5

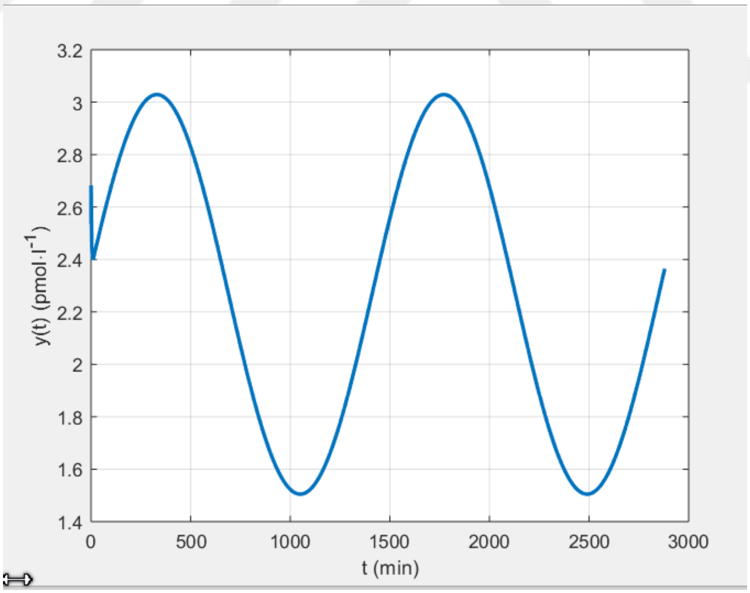


Figure 4.1 Variation of the plasma ACTH levels of back-stepping method of controller gains L1 =5 and L2=0.5

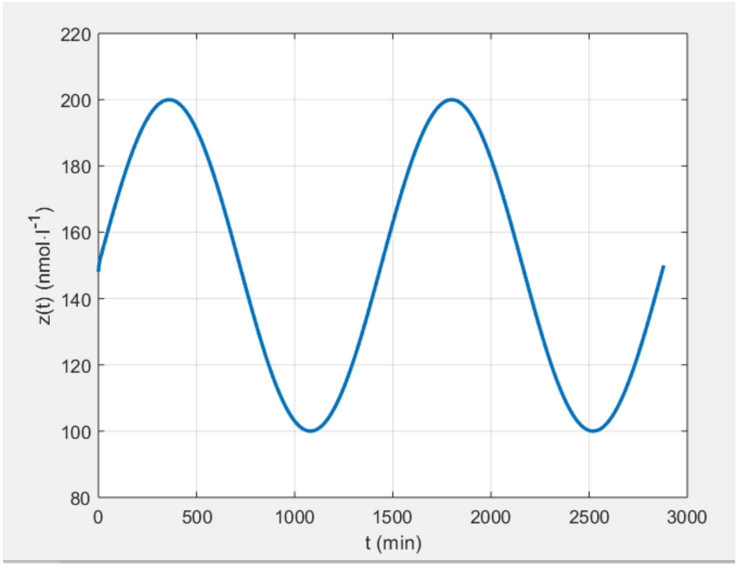


Figure 4.2 Variation of the plasma cortisol levels of back-stepping method of controller gains L1 =5 and L2=0.5

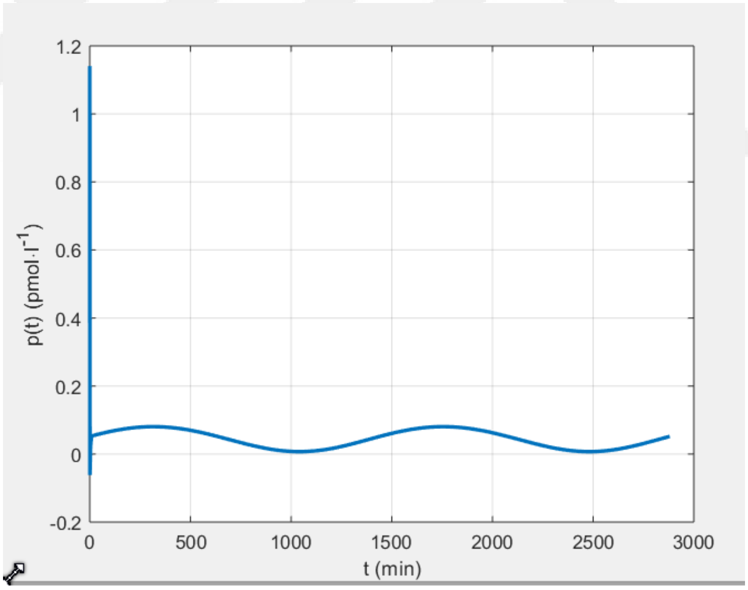


Figure 4.3 Variation of the tracking error between the reference plasma cortisol level of back-stepping method of controller gains L1 =5 and L2=0.5

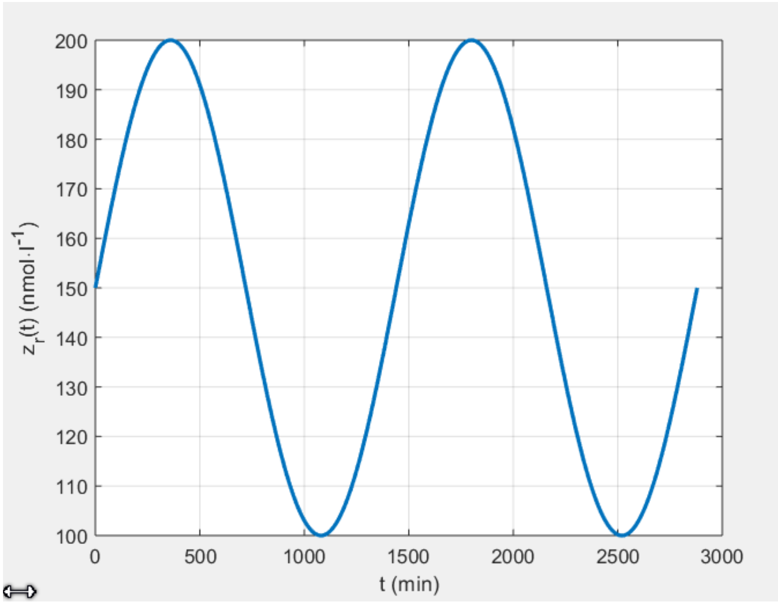


Figure 4.4 Variation of the tracking error between the reference plasma cortisol level of back-stepping method of controller gains L1 =5 and L2=0.5

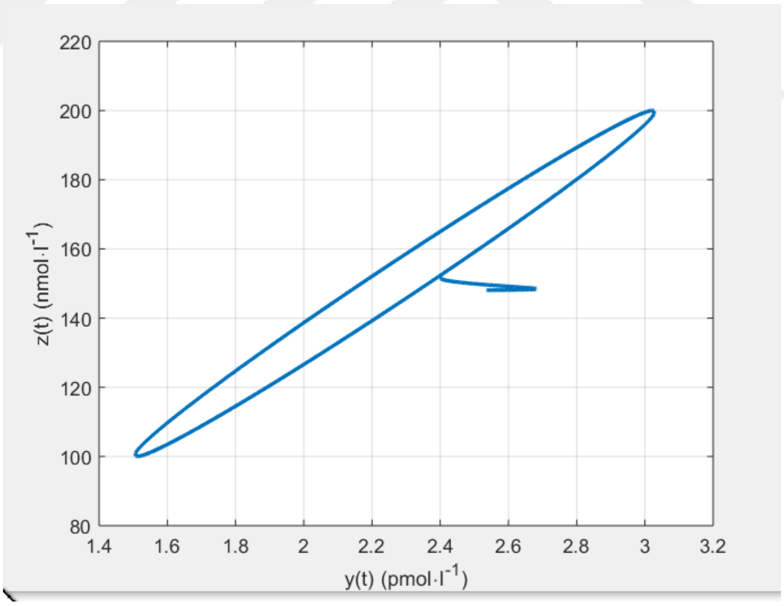


Figure 4.5 The closed trajectory of cortisol and plasma ACTH levels of back-stepping method of controller gains L1 =5 and L2=0.5

But when we check it for negative values then it had negative concentrations and this is physically wrong and lead that controller gains L1 and L2 values not suitable and after changing controller gains L1 and L2 values lead to threshold with L1=0.1 and L2=0.05

we merge two plots together.

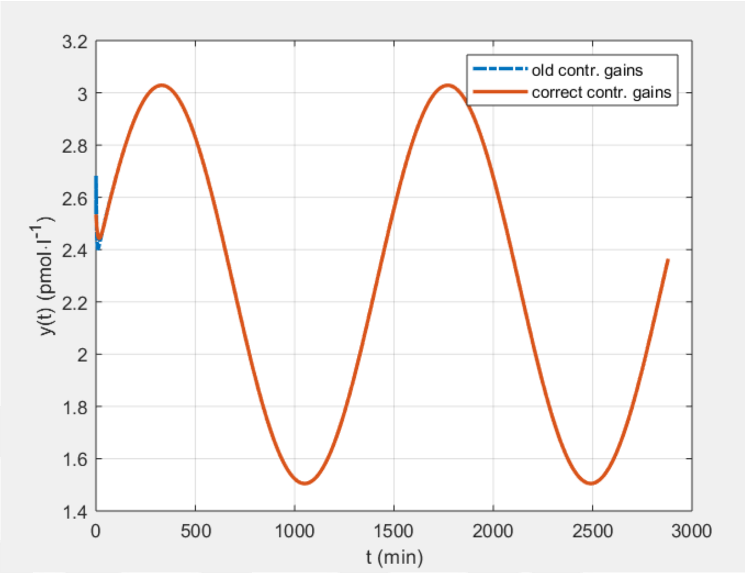


Figure 4.6 Variation of the plasma ACTH levels of back-stepping method and comparison between old values of contr. gains L and correct values of L1 =0.1 and L2=0.05

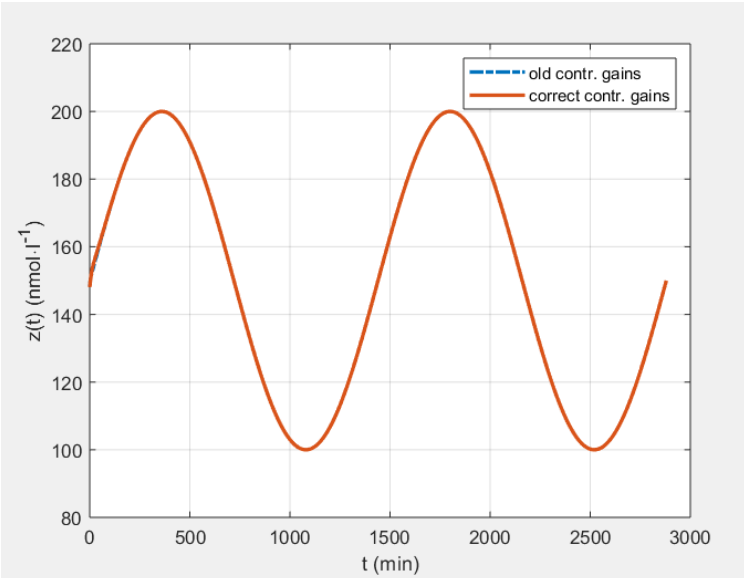


Figure 4.7 Variation of the plasma cortisol levels of back-stepping method and comparison between old values of contr. gains L and correct values of L1 =0.1 and L2=0.05

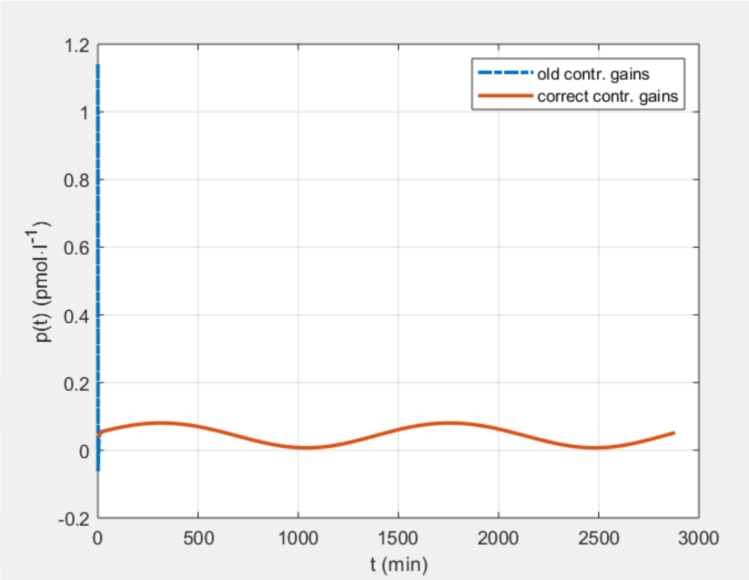


Figure 4.8 Variation of the tracking error between the reference plasma cortisol level of back-stepping method and comparison between old values of contr. gains L and correct values of L1 =0.1 and L2=0.05

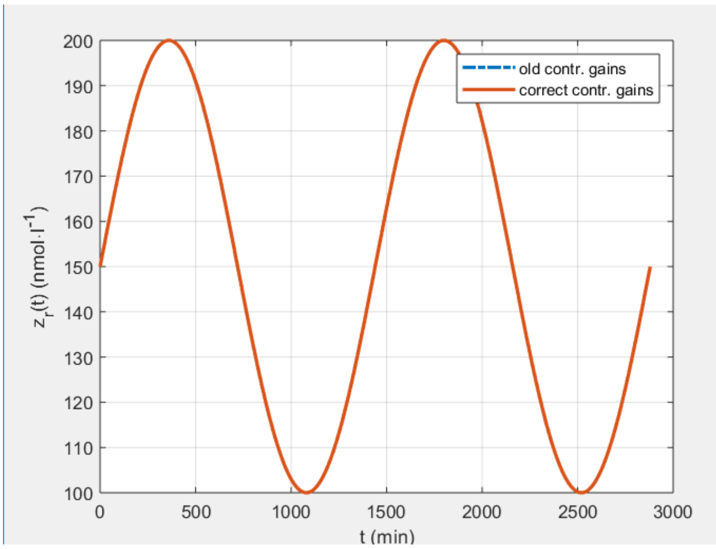
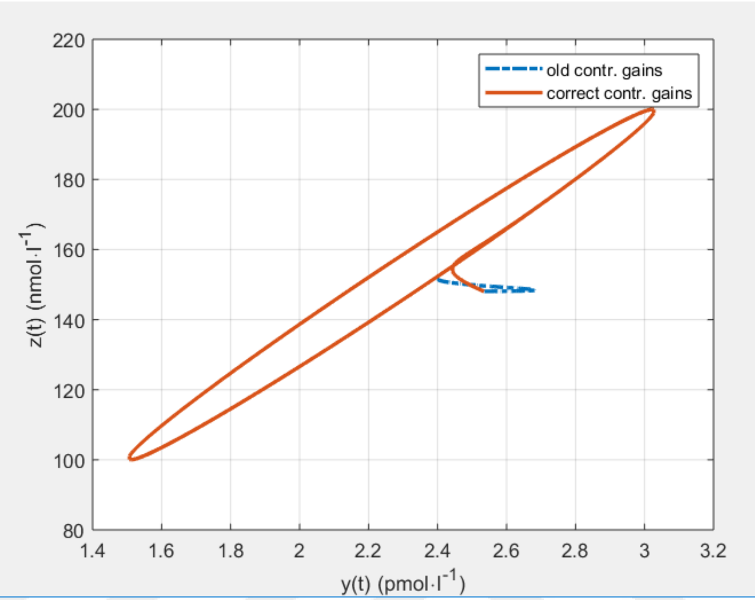


Figure 4.9 Variation of the tracking error between the reference plasma cortisol level of back-stepping method and comparison between old values of contr. gains L and correct values of L1 =0.1 and L2=0.05



Figures 4.10 The closed trajectory of cortisol and plasma ACTH levels of back-stepping method and comparison between old values of contr. gains L and correct values of L1 =0.1 and L2=0.05

4.2 Feedback Linearization Method Results

For controller gains L1 =5 and L2=0.5

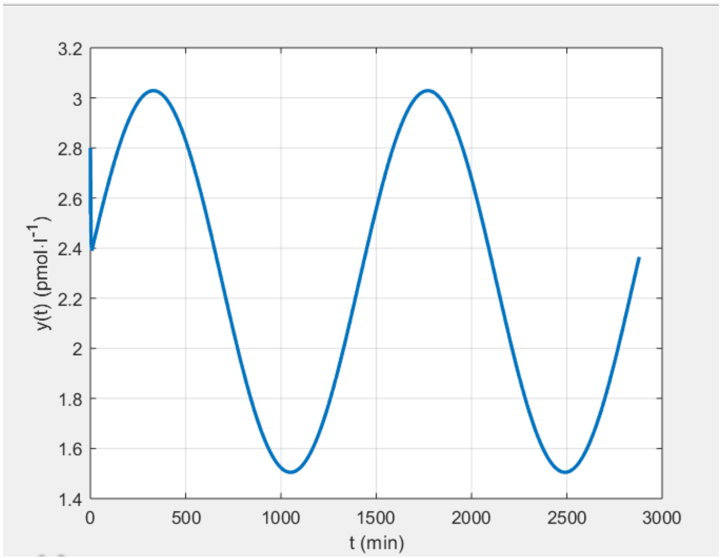


Figure 4.11 Variation of the plasma ACTH levels of feedback linearization method of controller gains L1 =5 and L2=0.5

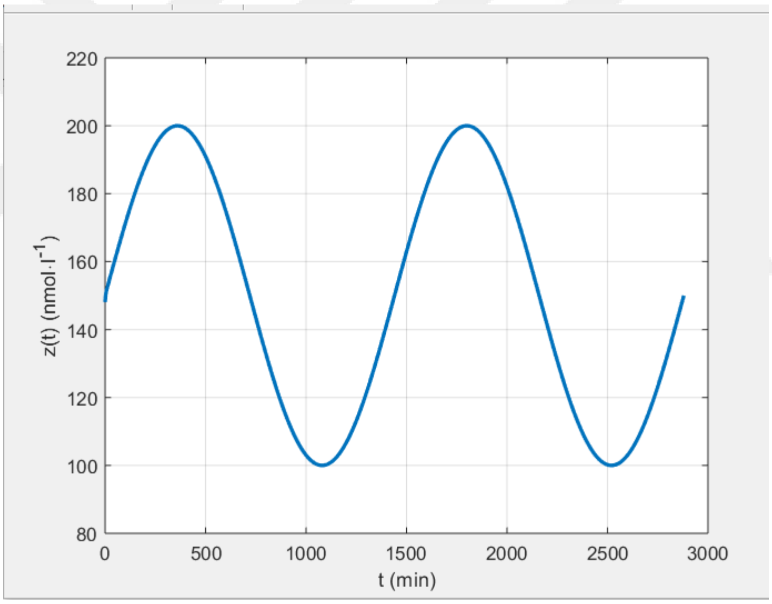


Figure 4.12 Variation of the plasma cortisol levels feedback linearization method of controller gains L1 =5 and L2=0.5

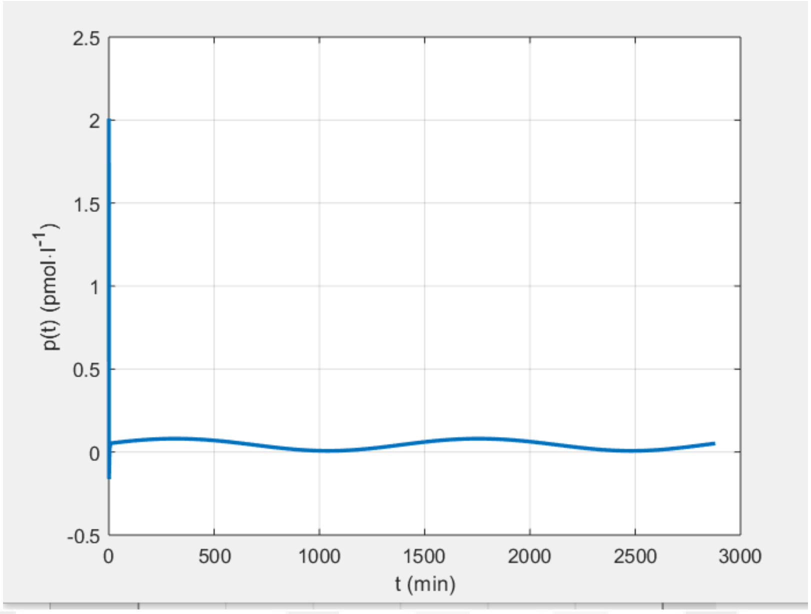


Figure 4.13 Variation of the tracking error between the reference plasma cortisol level of feedback linearization method of controller gains L1 =5 and L2=0.5

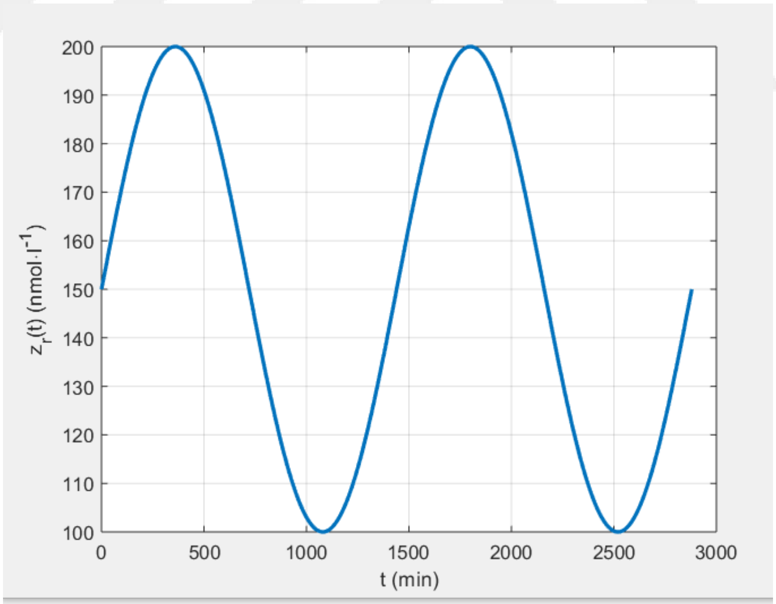
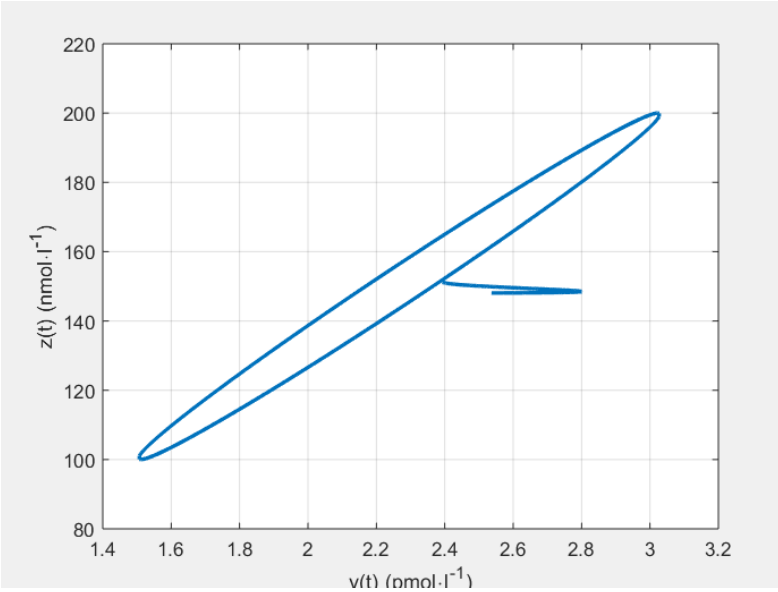


Figure 4.14 Variation of the tracking error between the reference plasma cortisol level of feedback linearization method of controller gains L1 =5 and L2=0.5



Figures 4.15 The closed trajectory of cortisol and plasma ACTH levels of feedback linearization method of controller gains L1 =5 and L2=0.5

But also, when we check it for negative values then it had negative concentrations and more than in back-stepping method and this is physically wrong and lead that controller gains L1 and L2 values not suitable

and after changing controller gains L1 and L2 values lead to threshold with L1=4.89 and L2=0.01

we merge two plots.

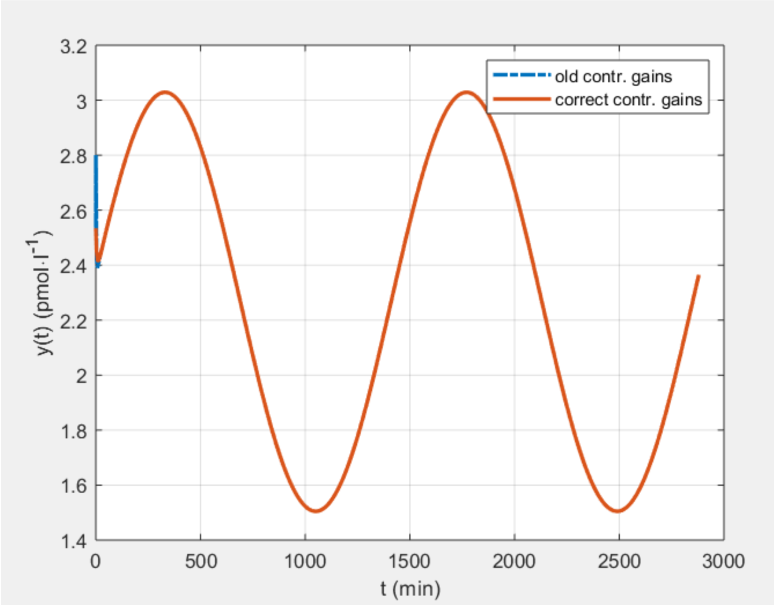


Figure 4.16 Variation of the plasma ACTH levels of feedback linearization method and comparison between old values of contr. gains L and correct values of L1 =4.89 and L2=0.01

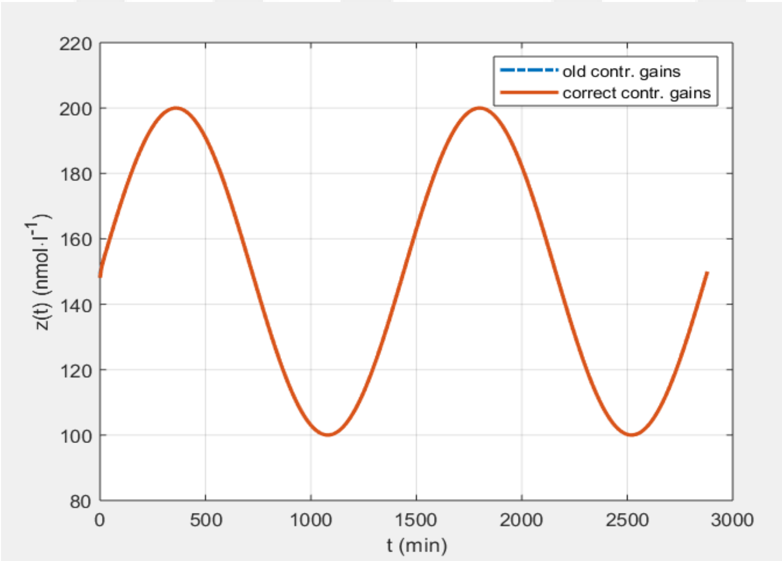


Figure 4.17 Variation of the plasma cortisol levels of feedback linearization method and comparison between old values of contr. gains L and correct values of L1 =4.89 and L2=0.01

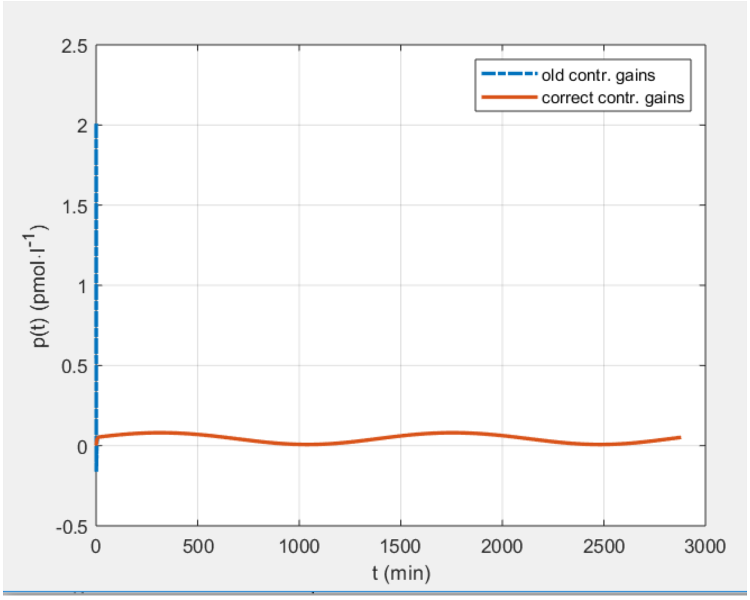


Figure 4.18 Variation of the tracking error between the reference plasma cortisol level of feedback linearization method and comparison between old values of contr. gains L and correct values of L1 =4.89 and L2=0.01

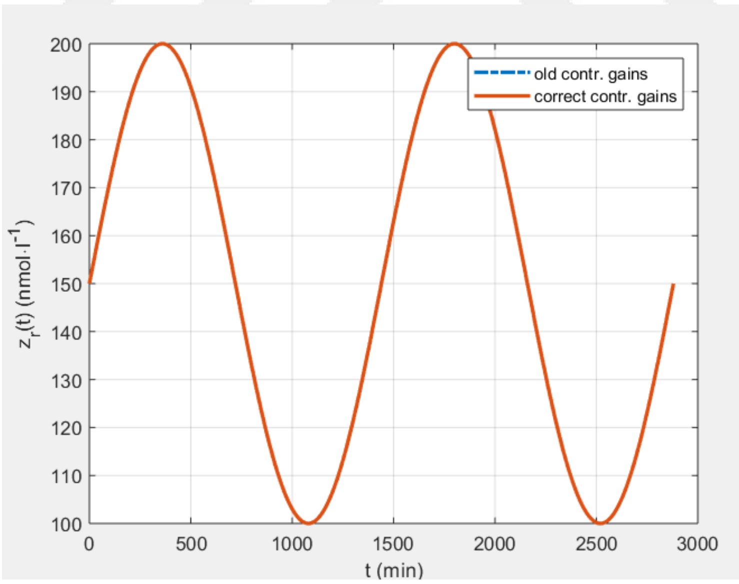
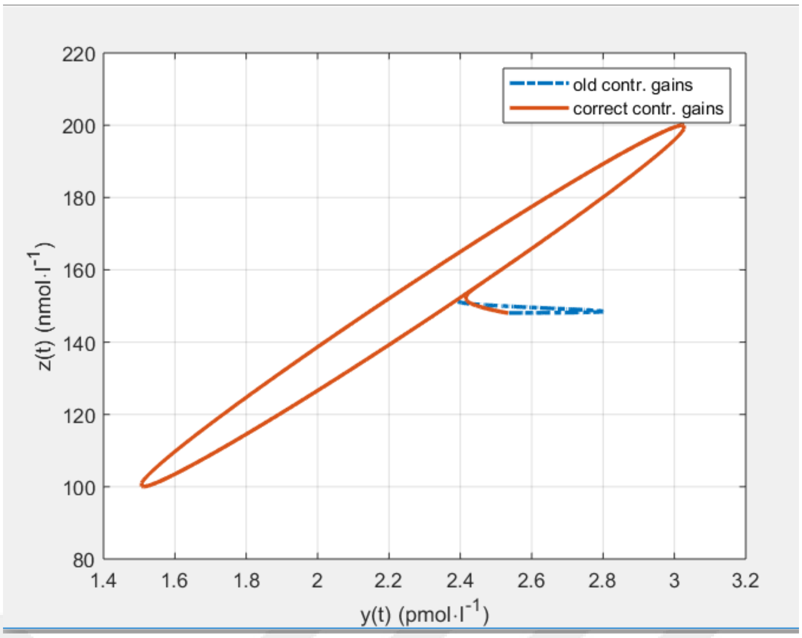


Figure 4.19 Variation of the tracking error between the reference plasma cortisol level of feedback linearization method and comparison between old values of contr. gains L and correct values of L1 =4.89 and L2=0.01



Figures 4.20 The closed trajectory of cortisol and plasma ACTH levels of feedback linearization method and comparison between old values of contr. gains L and correct values of L1 =4.89 and L2=0.01

4.3 Back-Stepping and Feedback Linearization Comparison Results

We make the comparison with correct values of controller gains L of two methods

For back-stepping method of controller gains L1 =0.1, L2=0.05 and for Feedback Linearization method of controller gains L1 =4.89 and L2=0.01

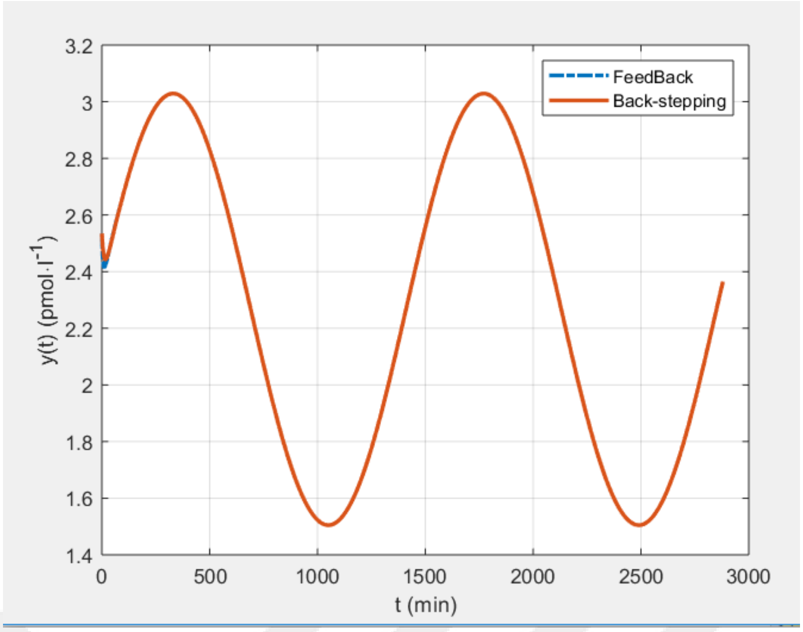


Figure 4.21 Variation of the plasma ACTH levels comparison of back-stepping and Feedback Linearization methods

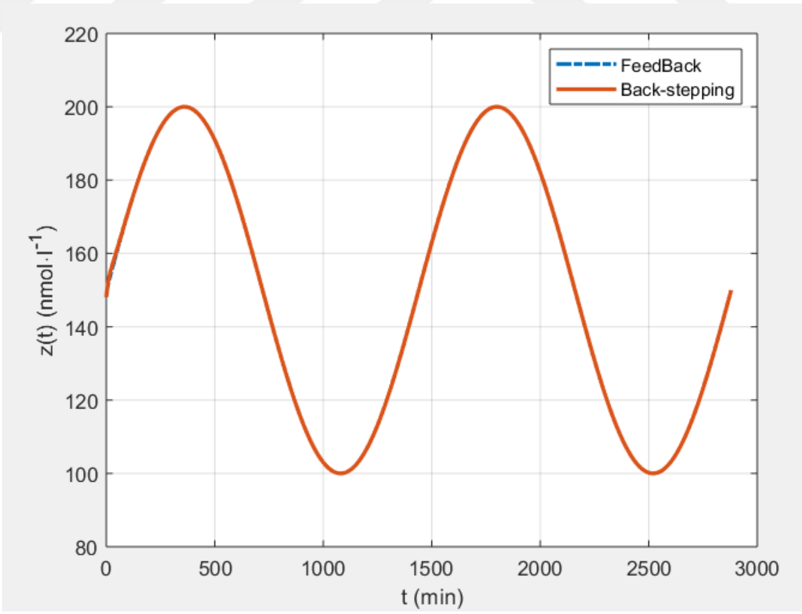


Figure 4.22 Variation of the plasma cortisol levels comparison of back-stepping and Feedback Linearization methods

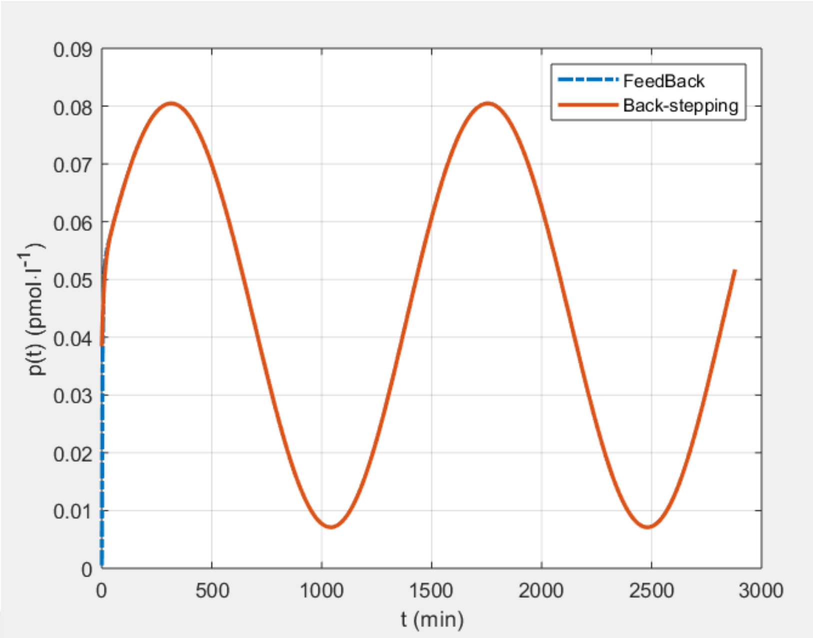


Figure 4.23 Variation of the tracking error between the reference plasma cortisol level of comparison of back-stepping and Feedback Linearization methods

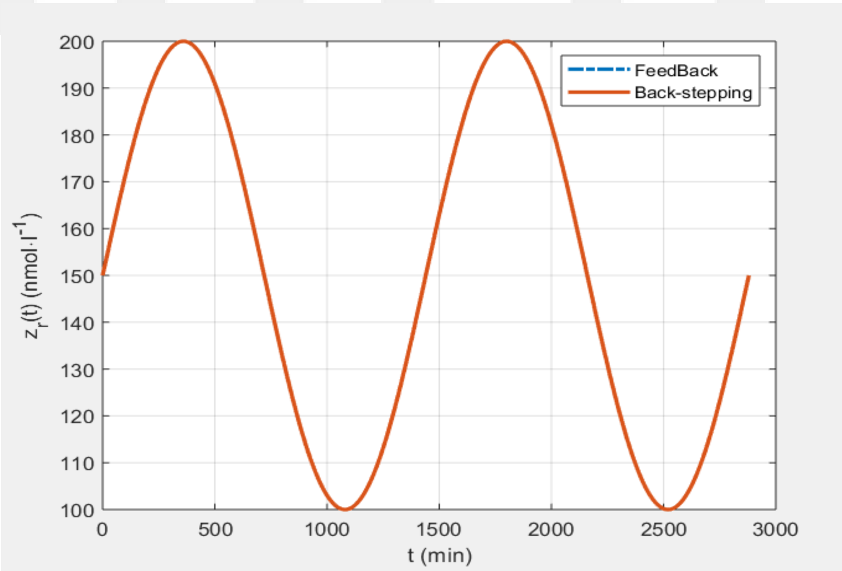
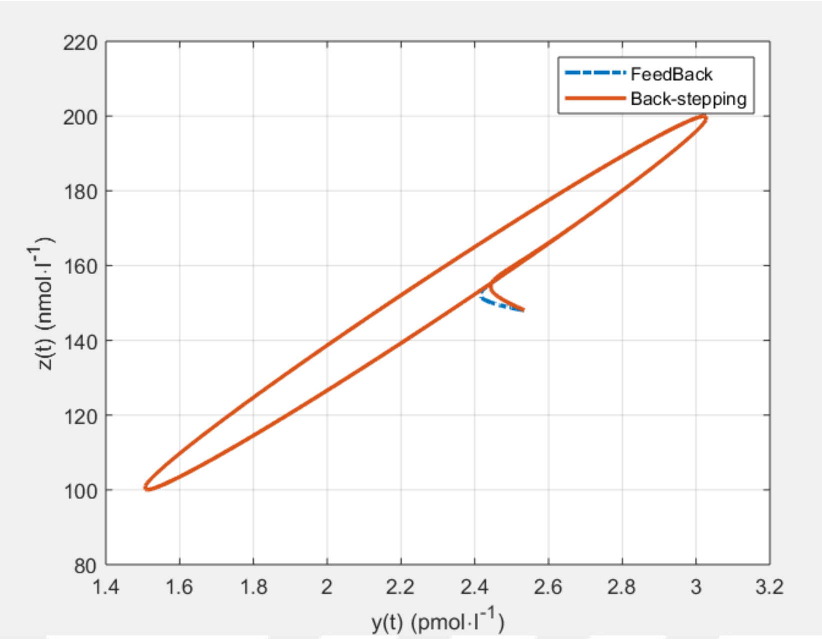


Figure 4.24 Variation of the tracking error between the reference plasma cortisol level of comparison of back-stepping and Feedback Linearization methods



Figures 4.25 The closed trajectory of cortisol and plasma ACTH levels of comparison of back-stepping and Feedback Linearization methods

CHAPTER 5

DISCUSSION AND CONCLUSIONS

5.1 Discussion

We can make the differential equation of system models to linear equations but to do that we have to neglect many coefficients to linearize it, instead we go to nonlinear controller methods such as back-stepping method and feedback linearization.

In figure 4.1 to 4.10 the back-stepping method with different controller gains (L1, L2) and the purpose from that to get results does not contain any negative values because it is wrong physically and there are no cortisol values in negative.

So that we make program to check values of results variables if negative or not and to overcome we choose values randomly until get threshold positive values in all outputs and we notice that negative values in beginning of figure 4.6- 4.8 and 4.10 in beginning in back-stepping and then take positive values until end of domain [A.1-A.4].

The feedback linearization has same negative values until we give proper controller gains values to make negative values disappear.

We notice that back-stepping is fewer negative values than feedback linearization and it show clearly from plots and from negative numbers values of checking program and we will put it in appendix [A.1-A.4].

5.2 Conclusion

For designing a model for the hypothalamus–pituitary–adrenal (HPA) axis, we choose two methods for nonlinear equations of model back-stepping and feedback linearization.

The back-stepping results after controller gains (L1, L2) changing it show perfect performance of cortisol and the feedback linearization method show good performance.

The stability of model in back-stepping show satisfy results and also the stability of feedback linearization is good, but the back-stepping is more stable than feedback linearization and that show clearly from comparison between them of cortisol levels.

It clearly shows the stability and behavior of overall system performance related to type of controller and correctness of design and choosing proper initial conditions and for our case controller gains (L1, L2).

5.3 Limitation of Study

In the first case of controller gains (L1, L2) values for both back-stepping and feedback linearization and this led to less stable and less performance of overall system model and led to series faults in working of model, then when correcting controller gains individually for each method it shows improvement in both stability and performance and led to minimum error bound for outputs.

5.4 Future Work

My goal in future works to re-derive new equations that describe Hypothalamus–Pituitary–Adrenal (HPA) axis.

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APPENDIX A

Back-Stepping Check

For controller gains L1=5 and L2=0.5

```
>> anyNegativeA = any(pa(:,[754:2880001])<0)

anyNegativeA =

  logical

   1

>> anyNegativeA = any(pa(:,[755:2880001])<0)

anyNegativeA =

  logical

   0

>> %pa values of backstepping method
```

Figures A.1 of back-stepping method of for controller gains L1 =5 and L2=0.5 check

For controller gains L1=0.1 and L2=0.05

```
Command Window
>> anyNegativeA = any(pa(:,[1:2880001])<0)

anyNegativeA =

  logical

   0
```

Figures A.2 of back-stepping method of controller gains
L1 =0.1 and L2=0.05 check

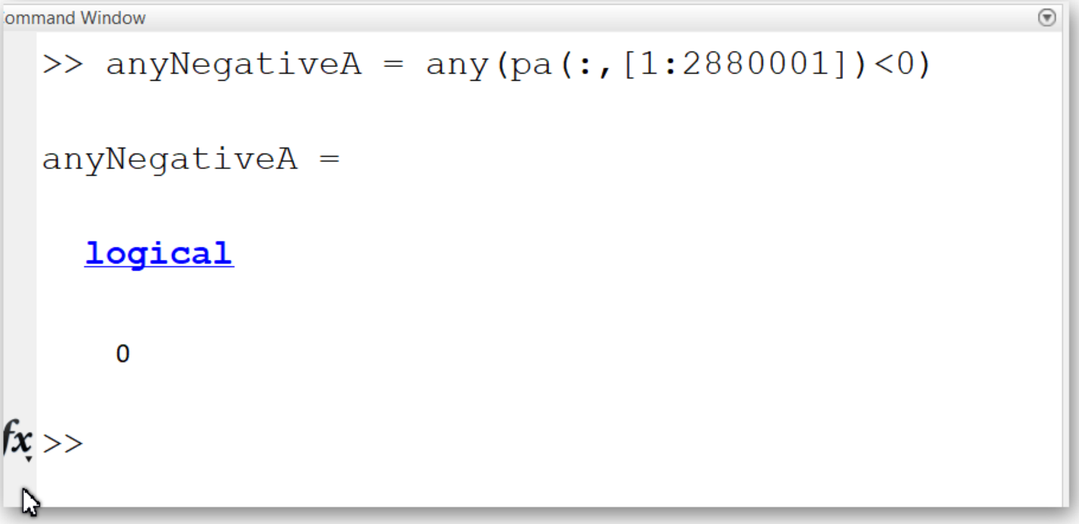
Feedback Linearization Check

For controller gains L1 =5 and L2=0.5

```
anyNegativeA =

  logical

   1

>> anyNegativeA = any(pa1(:,[9800:2880001])<0)

anyNegativeA =

  logical

   0

>> %pa1 for feedback linearization
```

Figures A.3 of Feedback Linearization method of controller gains L1
=5 and L2=0.5 check

For controller gains L1=4.89 and L2=0.01



Figures A.4 of Feedback Linearization method of controller gains L1=4.89 and L2=0.01 check