EFFECTS OF ESTROGEN AND PROGESTERONE ON MENSTRUAL CYCLE BASED ON MATHEMATICAL MODELING

WANNISSA MUMTONG

A THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN APPLIED MATHEMATICS

DEPARTMENT OF MATHEMATICS
FACULTY OF SCIENCE
KING MONGKUT'S INSTITUTE OF TECHNOLOGY LADKRABANG

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ผลของเอสโตรเจนและโปรเจสเตอโรนต่อการมีประจำเดือนโดยแบบจำลองทางคณิตศาสตร์

EFFECTS OF ESTROGEN AND PROGESTERONE ON MENSTRUAL CYCLE BASED ON MATHEMATICAL MODELING

วรรณิศศา มุมทอง
WANNISSA MUMTONG

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตร
ปริญญาปรัชญาดุษฎีบัณฑิต สาขาวิชา คณิตศาสตร์ประยุกต์
ภาควิชาคณิตศาสตร์ คณะวิทยาศาสตร์
สถาบันเทคโนโลยีพระจอมเกล้าเจ้าคุณทหารลาดกระบัง
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หัวข้อวิทยานิพนธ์	ผลของเอสโตรเจนและโปรเจสเตอโรนต่อการมีประจำเดือนโดยแบบจำลองทางคณิตศาสตร์
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บทคัดย่อ

ในรอบประจำเดือนเกิดจากการทำงานร่วมกันของไฮโพทาลามัส ต่อมใต้สมองส่วนหน้าและการตอบสนองของอวัยวะเพศภายในเมื่อได้รับ *FSH* และ *LH* โดยจะสร้างฮอร์โมน Estrogen กับ Progesterone จากรังไข่ซึ่งจะกระตุ้นการเปลี่ยนแปลงของเยื่อบุมดลูก ซึ่งระดับฮอร์โมนทั้งสองจะมีความสัมพันธ์กับการตกไข่จากรังไข่ ฮอร์โมน Estrogen แบบธรรมชาติมีอยู่ 3 ชนิดคือ *Estrone* , *Estradiol* , และ *Estriol* แต่ในช่วงวัยที่ยังมีประจำเดือนอยู่ร่างกายจะผลิตฮอร์โมน Estrogen แบบ *Estradiol* ฮอร์โมนเฉพาะที่มีบทบาทในการควบคุมรอบประจำเดือน คือ *Insulin like Growth Factor (IGF)* , *Activin* , *Inhibin* โดยแต่ละรอบเดือนจะมีช่วงเวลาประมาณ 28 วัน ขึ้นอยู่กับแต่ละบุคคล การมีประจำเดือน เกิดขึ้นเฉลี่ยเดือนละ 1 ครั้ง ฮอร์โมนที่สร้างและหลั่งจากรังไข่ประจำเดือนประกอบด้วยระยะต่างๆ ดังนี้ ระยะ *menstrual flow phase* เป็นระยะการหลุดลอกของผนังมดลูก ระยะ *preovulatory phase* เป็นระยะหนาตัวของผนังมดลูกชั้นเอนโดมีเทรียมก่อนไข่ตก ระยะ *postvulatory phase* เป็นระยะที่ผนังมดลูกชั้นเอนโดมีเทรียมมีความหนาเพิ่มขึ้นจากการที่มีเส้นเลือดมากขึ้นและต่อมต่างๆได้หลั่งสารอาหารเพิ่มขึ้นและพร้อมรองรับการฝังตัวของตัวอ่อน ถ้าไม่มีการปฏิสนธิเกิดขึ้น ผนังมดลูกชั้นที่หนาขึ้นนี้จะหลุดลอกออกมาปนกับเลือดกลายเป็นประจำเดือนเข้าสู่เวลาเริ่มต้นของการมีรอบเดือน งานวิจัยนี้ได้ทำการศึกษาเกี่ยวกับฮอร์โมนที่ส่งผลต่อภาวะของการมีประจำเดือนและได้นำปัจจัยที่ทำให้รอบเดือนเกิดความผิดปกติมาพิจารณาด้วย โดยการสร้างแบบจำลองทางคณิตศาสตร์ของการมีประจำเดือน การประยุกต์วิธีของการจำลองเชิงพลวัตมาตรฐาน (standard dynamical modeling) มาใช้ในการวิเคราะห์ลักษณะของคำตอบในแบบจำลองทางคณิตศาสตร์พร้อมทั้งแสดงเงื่อนไขของตัวแปรที่ทำให้เกิดความเสถียรภาพของจุดสมดุล ผลลัพธ์เชิงตัวเลขของแบบจำลองนำมาแสดง เพื่อใช้ในการสนับสนุนสมมติฐานในการศึกษา ผลของการศึกษานี้สามารถเป็นแนวทางการวิจัยสำหรับผู้ที่มีความสนใจเกี่ยวกับระบบฮอร์โมนในร่างกายของมนุษย์โดยเฉพาะฮอร์โมนที่ผลิตจากต่อมใต้สมองส่วนหน้าในเพศหญิง กระตุ้นการเจริญของรังไข่และควบคุมการหลั่งฮอร์โมน Estrogen และ Progesterone เพื่อกระตุ้นให้เกิดการตกไข่ ควบคู่ไปกับแนวความคิดเกี่ยวกับการสร้างแบบจำลองทางคณิตศาสตร์

คำสำคัญ: จุดสมดุล, ดัชนีมวลกาย, แบบจำลองทางคณิตศาสตร์, ประจำเดือน, ฮอร์โมน, ฮอร์โมนแอคติวิน

Thesis Title	Effects of Estrogen and Progesterone on Menstrual Cycle using Mathematical model.
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ABSTACT

Menstrual cycle caused by the interaction of the hypothalamus, the anterior pituitary and the response of the internal sex organ when getting *FSH* and *LH*. It creates *Estrogen* and *Progesterone* hormones from ovary. This will stimulate the transformation of the uterine lining. Both of these hormones associated with ovulation from the ovary. *Estrogen* hormone naturally contained three types; *Estrone, Estradiol* and *Estriol*. At the age of menstruation, the body will produce Estrogen hormone as Estradiol. Specific hormones that control menstrual cycle are *Insulin like Growth Factor (IGF), Activin* and *Inhibin*. Menstruation will occur approximately 28 days, depending on the individual. Menstruation will occur about one time per month. The hormones created and secreted by the ovary are divided into the following phases; *menstrual flow phase* is the shedding of uterine wall, *preovulatory phase* is the thickness of the uterine wall in endometrium before ovulation and *postvulatory phase* is the uterine wall thickness in endometrium that increased from more vessels and glands to secrete more nutrients and support implantation of the embryo. If there is no fertilization, uterine wall thicker layer will peel off and become menstruation. Thus, there is the start time of menstrual cycle. This research was conducted on hormones that affect the conditions of menstruation, and consider the factors that cause menstrual disorders by building the mathematical model of menstruation and apply the standard dynamical modeling in order to analyze the nature of answer to the mathematical models that show the condition of variables that contribute to the stability of equilibrium points and numerical results to support the assumptions in the study. The results of this study can be taken as a guide for people who are interested in the research of hormone system in the human body, especially the hormone produced by the anterior pituitary gland in females, to stimulate the growth of ovarian and control the secretion of hormones to stimulate ovulation, coupled with ideas about creating a mathematical model.

Keywords: equilibrium point, body mass index, mathematical model, menstrual cycle, hormone, hormone activin

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Wannissa Mumtong

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Chapter 1
Introduction

1.1 Research Motivation

In humans, the body is composed of tissue and contains glands that produce chemicals called hormones. Hormones control the body changes, and are sent into the bloodstream and spread throughout the body to regulate the function of organs. Important hormones in the human body are hormones from the pituitary gland, hormones from the islets of Langerhans, hormones from the adrenal glands, hormones from the thyroid gland, hormones from sexual organs and other tissues. The control of the hormones is associated with the nervous system. The hormones are regulated by the body. Various hormones that control changes in males and females are different. The menstrual cycle only occurs in women and is related to the hormones produced by the pituitary gland in the female body for stimulating the growth of the ovaries and controlling the secretion of estrogen and progesterone, hormones for stimulating ovulation. A condition of menstruation is important for women of childbearing age. We propose model to study the Hormones of menstrual cycle based on the study of Selgrade. Clark and Selgrade analyzed mathematical model of Inhibin. Hormone activin is also important in menstrual cycle. It enhances FSH hormone secretions and synthesis. Clark et al. studied dynamical model considering estrogen, progesterone and inhibin. Hormone activin effects luteal, progesterone. It is also important for synthesis of menstrual cycle, thus we replace inhibin by activin. Therefore our model consists of functions estrogen, progesterone and activin.

This study focuses on hormones which affect the condition of menstruation and factors that contribute to menstrual irregularities and compares the factors that affect the female's menstruation. Then, a mathematical model for menstruation is used as preliminary data for the study of hormonal factors in the transmission system is created and analyzed.

1.2 Objectives of the study

The purpose of this research is to study and develop a mathematical model of the cycle of menstruation and factors affecting the menstrual irregularities. We analyzed the model by studying the standard dynamical models to obtain conditions of parameters corresponding to the hormonal balance in females. The research objectives are as follows:

1. To indicate the type of key hormones affecting menstruation.
2. To create a mathematical model for the cycle of menstruation.
3. To describe the controls and mechanisms that control the secretion of menstrual hormones.
4. To describe the factors that affect hormone levels and identify the causes of menstrual irregularities.
5. To use the results as basic data for the study of factors that affect the hormonal system.

1.3 Scope of the study

Analysis of menstrual hormones and factors that affect the menstrual dysfunction is conducted in order to create a mathematical model for the menstruation cycle. We consider the hormone Activin that plays a role in controlling the menstrual cycle. Finally, we analyze the factors affecting the balance of Follicular Stimulating Hormones and Luteinizing Hormones that cause irregular menstruation.

1.4 Process of the study

Stages of the research are as follows:

Stage 1 - Search for documents related to the hormones in the human body and the menstruation.
Stage 2 - Search for the research on menstruation.
Stage 3 - Create a mathematical model of the cycle of menstruation.
Stage 4 - Analyze the mathematical model of factors that affect the menstrual irregularities.
Stage 5 - Test the model for suitability.
Stage 6 - Develop a new model if the model is not suitable.
Stage 7 - Summarize the results and recommend the development of the model in the future.
Stage 8 - Write the thesis.

1.5 Benefits of the study

This study can serve as a set of guidelines for researchers who are interested in the hormones in the human body, especially hormones produced by the pituitary gland of the female, which stimulate the growth of ovaries and control the estrogen and progesterone hormones that cause ovulation as well as present ideas on how to create a mathematical model.

Chapter 2

Literature Reviews

In this chapter, we study the research on modeling the mathematics of the menstrual cycle. Researchers have been studying this area and related research is used to support this research study.

2.1 Background of the Menstrual Cycle

Female reproductive organs include the uterus. The uterus is located between the bladder and colon. Inside of the uterus is a cavity with a thick lining for the implantation of the embryo. Delamination of the lining of the uterus occurs as a result of changes in female hormone levels and is associated with ovulation. Furthermore, it causes the lining of the uterus to break out and discharge liquid which is composed of the menstrual blood and mucus and expelled at the end of the uterus, which is called the cervix. It happens about once a month.

The normal menstrual cycle is about 28 days. The thickness of the uterine lining increases due to estrogen in the ovary in the middle of the cycle, that is about the 14^{th} day of the menstrual cycle, and receives the egg from the ovary of one side. When it is fertilized with sperm, the egg or embryo is implanted in the uterine lining.

After ovulation, the changes of the blood vessels and glands in the lining of the uterus which are the result of progesterone hormones occur in order to support implantation of the embryo, which will develop into a subsequent pregnancy. If no fertilization occurs, the progesterone hormone level from the ovaries is lowered and the lining of the uterus breaks up. This condition is called menstruation. After menstruation, the ovaries begin to create the hormone estrogen and start the process again.

During puberty, the hormone production is consistent with the above, but when there is aging, the ovaries will eventually stop production of the two types of hormones, resulting in no menstruation, a period known as menopause [1]-[5].

The menarche, which is the first menstrual cycle, indicates that girls have grown into adulthood and are capable of breeding. Age of the first menstruation is usually between 7 – 16 years, but in Thailand, the average girl‘s age is 11 – 12 years. During the first 1 – 2 years of menstruation, the occurrence may be irregular as a result of the control of testosterone levels not yet being complete.

Menstrual cycles consist of the following phases:

1) The menstrual flow phase takes about 2 – 3 days. It is the delamination of the inner uterine wall thickness mixed with blood which becomes the menstrual blood. The first day of the phase will find the secretion of GnRH hormone to stimulate the secretion of FSH and LH from the anterior lobe of the pituitary gland. FSH acts to stimulate the growth of follicles in the ovaries, and it will stimulate the transcription of genes on follicular cells for the synthesis of estrogen.

2) The proliferative phase or pre-ovulatory phase takes about 1 – 2 weeks. There is a thick wall of the uterus in the endometrium before ovulation; the hormone estrogen can stimulate the growth of blood vessels and glands in the endometrium.

3) The secretory phase or post-ovulatory phase takes about 2 weeks. The uterine wall is thicker than ever and ready for implantation of the embryo. If there is no fertilization, this uterine wall will break down mixed with blood and become menstruation. Hormones that stimulate the growth of endometrium wall are estrogen and progesterone. There is the stimulation of glands in the wall of the uterus to shed the nutrients out of the fluid [6]-[11].

The ovarian cycle is a cycle of egg development and follicles, which is divided into three phases:

1) Follicular phase: It is growing follicles with egg cells and cells that surround the cells proliferate more layers with the hormone estrogen. It was found that the FSH hormone stimulates the growth of follicles in the early stages. Later on, as the volume of the follicle growth hormone estrogen increases, as many as possible are shed. The increase of hormones can be traced to the urge to increase the secretion of LH hormone, which is called LH surge. It is considered a positive feedback mechanism and then both FSH and LH jointly stimulate growth when entering the Graafian follicle phase.

2) The ovulation phase, also known as the ovulation period, occurs around day 14 of the menstrual cycle and is caused by the influence of the LH hormone, which is secreted in large quantities and the LH hormone, which is stimulated by GnRH and estrogen as mentioned above.

3) The luteal phase occurs when follicles remain in the ovaries and grows as corpus luteum. LH is the hormone that stimulates and maintains it. Then, the corpus luteum will create and secrete hormones of 2 types; progesterone and estrogen. These two hormones inhibit the secretion of hormones and are considered as a negative feedback mechanism which results in decreasing of LH. In case of non–pregnancy, the corpus luteum will fail and stop the creation of both hormones. Blood vessel growth in the endometrium is destroyed and broken. It will decay the

menstruation. Later, there is the start of a new menstrual cycle, which continues [12]-[14].

Menstrual disorders in women of reproductive age are found in approximately 30% and they can be found in many forms such as hypermenorrhea, menorrhagia, hypomenorrhea, oligomenorrhea, menometrorhagia, metrorhagia, amenorrhea, and postmenopausal bleeding.

Due to irregular menstruation, the imbalance of hormone levels is one of the most common results and is usually caused by irregular ovulation or dysfunctional uterine bleeding (DUB). Factors that cause hormone imbalance are as follows:

- Changes in hormones level during adolescence or early in menopause
- Diabetes, disorders of the thyroid or pituitary gland or other abnormalities
- Obesity
- Stress
- Excessive exercise
- Eating disorders such as Anorexia nervosa

The rare causes for the other menstrual disorders include ectopic pregnancy, effects of certain medication (hormone pill or oral contraceptive pill), diseases of blood clotting, infection or genital cancer, problems of inserting of IUD and thin lining of the vagina and inflammation.

Premenstrual symptoms - The symptoms occur regularly 1 – 2 weeks before menstruation. Common symptoms include abdominal pain, back aches, headaches, fatigue, gained weight, bigger breasts, tight pain in the breast, increased appetite, bloating, diarrhea and acne. In addition, there are changes in behavior, mind and emotions such as nervousness, irritability, emotional tension, anxiety, forgetfulness, lack of concentration, feeling sadness and insomnia. These symptoms will decrease and disappear after a period of 1 – 4 days. Although the exact cause is unknown, it is believed to be associated with changes and the imbalance of hormones in the menstrual cycle, especially the progesterone, which increases after ovulation.

Studies have found that women with premenstrual syndrome tend to have a high progesterone level. It is also believed to be associated with thyroid hormones, prostaglandin norepinephrine, estradiol gonadotropin and serotonin, chemicals in the brain, and stress as well as poor nutrition and a lack of certain vitamins or minerals such as fatty acids, linolenic acid, vitamin E, vitamin C, calcium, magnesium and manganese. During the menstruation, 75 – 80% of women will experience one or more of these symptoms simultaneously. The severity of symptoms can be classified as mild, moderate or severe, and affect health and daily life.

After menstruation, the ovaries begin to create the hormone estrogen increasingly and start the cycle again. During puberty, the hormone production will be consistent with the above, but when there is aging, the ovaries will eventually stop production of two types of hormones, resulting in a period known as menopause.

Hormonal disorders can cause menstrual irregularities and may be caused by lack of hormones for the endometrium when it squeezed into a menstruation. The main cause is obesity because obesity is a disorder in the production of hormones that regulate ovulation. Thus, it is a disorder of menstrual cycle. When there is no ovulation, menstrual cycle will not occur. Because testosterone is produced from fat, when the body has too much fat, the hormones are abnormal. The ovaries are responsible for creating estrogen. This will begin to build up during a girl's teenage years. It is a hormone that can change the shape of the children to become young women and ready for reproduction. When the level of estrogen of a girl's body is higher in the early teens, it causes larger breasts, skin with fat, a healthy look and changes in the shape of the body. The girl's menstruation is a sign that she is ready for reproduction.

During each menstrual cycle, the tissue in the uterus becomes increasingly thicker, to make the uterus ready for the eggs that may be fertilized and contribute to nourishment of the fetus. If there is no implantation of the embryo in the uterus tissue occurs, it will come out as menstruation. It is preparation of new tissue in the uterus, which evolves into a cycle and eventually ends as the menopause. When girls enter adolescence and estrogen hormone levels are reduced, they must adjust to the increasing familiarity with hormone levels in the body. At menopause, estrogen is lowered as the body has to adjust again. This change is called the 'golden age'.

Medical criteria used to measure the degree of obesity is known as Body Mass Index (BMI). It is a relationship between weight and height and is used to determine if someone who overweight or obese. The unit of weight is kilograms and the unit of height is meters. The mean BMI of an individual is equal to the weight divided by height squared. It can be written as the following equation:

$$BMI = \frac{w}{h^2}$$

where:

w represents weight (kg), and

h represents height (m).

World Health Organization and the Asian Medical Group divided obesity into 3 levels to indicate the severity of the condition or disease, which are moderate obesity, severe obesity and very severe obesity. A severe level of obesity is defined as a body mass index of 40 or more and from 30 up for Asians (WHO) [15]-[24].

A normal period of menstruation for every month is a sign of good health of mothers and all women. Menstruation is the indication of the reproductive system and the balance of the inner working of the bodies. Moreover, the menstruation also serves as an indicator of the health of the body. We can easily observe the types of color, odor and signs as follows:

1. Dark and fewer menstrual symptoms with tiredness, weakness and dizziness may indicate a sign of anemia.
2. Menstruation with blood clots and excessive internal bleeding could be a warning sign of pelvic inflammatory disease.
3. Irregular menstrual odor or itching and soreness of the vagina with a vaginal discharge indicates a vaginal infection, or bacterial, fungal or parasitic vaginal infections in the uterus and pelvic inflammation.
4. If there are malfunctions of the menstruation; such as headaches, the eyes growing dim, or unnatural proliferation of hair, facial hair and abnormal milk, women should see a doctor to check for tumors of the ovary or abnormalities of the adrenal or pituitary glands.
5. Hypomenorrhea with fatigue, flat breasts, or armpit and genital hair loss may lead to bleeding or fainting while giving birth, so women should to a the doctor to check for Sheehan's syndrome, a disease of the pituitary gland or brain ischemia.
6. If menstrual blood is very pale, women should see a doctor. If there is a smell of the blood and pain in the abdomen, they must be aware of salpingitis.
7. Hypermenorrhea and period pain or pain during intercourse and presence of a lump in the abdomen may be a sign of a tumor in the uterus.

8. Period pain and paleness or overall pain, could be a possible symptom of anomalous endometrial growth or chocolate cyst.

9. An unusually long period beyond 7 days is considered normal after childbirth or use of an intrauterine device. In the same way, menstruation is not normal if it is unusually long when there is no pregnancy, which is usually a result of being too fat, stress or excessive exercise.

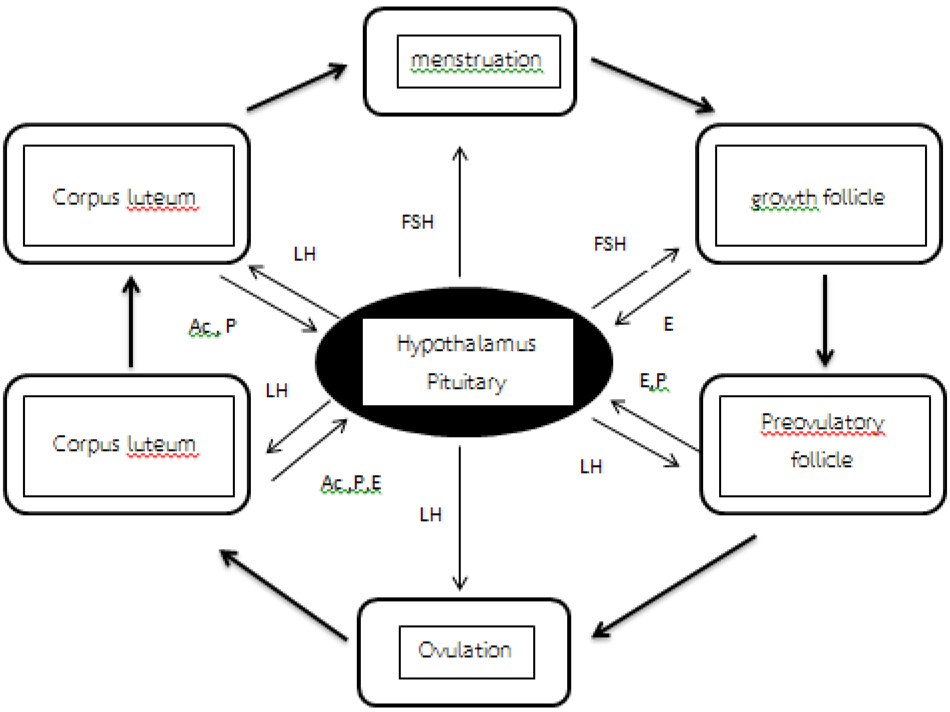


Figure 2.1: Phases of the menstrual cycle with gonadotropin hormones, LH and FSH, and ovarian hormones, E, P, and Ac [26].

The menstrual cycle occurs from a collaboration of the hypothalamus, the pituitary gland and the response of the pineal gland when it is caused by FSH and the LH hormone estrogen with progesterone, which stimulate the transition of the uterine lining. The sequence is as follows:

1. The hormone FSH is secreted by the thalamus and LH from the pituitary gland stimulates.

2. FHS and LH cause the growth of follicular Kelso Oval and encourage follicular Clemente growth to shed estrogen, which is able to make the uterine lining begins to thicken. Meanwhile, if a large amount of is secreted, this hormone is sent back to the thalamus to control the secretion of FSH and LH from the pituitary gland. Various stages of the cycle are shown in the figure 2.9 [26].

2.2 Literature Review

Andrew S. Rowland [15] described medical and lifestyle factors associated with menstrual cycle characteristics among 3941 menstruating women participating in a large study of the health of farm families.

Maite Vallejo [18] described this group of women, whose age was a major determinant of cardiac autonomic nervous modulation followed by the BMI. HRV may be better understood using a multivariable analysis that could mimic physiological conditions.

Selgrade and Schlosser [26] developed a nine-dimensional system of ordinary differential equations for the ovarian hormones E_2, P_4 and IHN.

James F. Selgrade [27] examined bifurcation diagrams with respect to K_{mLH}, a parameter in the LH synthesis term, and c_2, an ovarian mass transfer parameter.

Schlosser and Selgrade [28] constructed a four-dimensional system for the pituitary hormones LH and FSH. Margolskee and Selgrade studied parameters effect on the menstrual cycle and analyzed bifurcation with inhibin delay.

Kristen A Hahn [29] made a study on behavior, increasing age, and higher BMI. These factors affect the balance and hormone levels of the menstrual cycle.

Richard Bertrama and Yue-Xian Li [30] described the actions of activin, inhibin, and follistatin are consistent with LH/FSH secretion patterns, and likely complement other factors in the production of the characteristic secretion patterns in female rats.

James F. Selgrade [31] described the mathematical model of the menstrual cycle and parameters that affect the mathematical model.

Susanna Roblitz [32] describes the hormone profiles (LH, FSH, P4, E2) throughout the menstrual cycle in 12 healthy women. Moreover, her study correctly predicts the changes in the cycle following single and multiple dose administration of Nafarelin or Cetrorelix at different stages in the cycle.

Rasa Grigolienė and Donatas Švitra [33] modified the mathematical model of the menstrual cycle to include the mathematical model with a time delay depending on the functions that have been researched and the mathematical model with a dispersed time delay.

In this thesis, we consider a mathematical model of the menstrual cycle. We modified the model of James F. Selgrade [34]. His model considered the hormone inhibin, a hormone that acts with a specific hormone FSH. But in our research the aim was to study models of the menstrual cycle with only the hormone progesterone, a hormone that acts as an Activin stimulation. In inhibiting hormone secretion and FSH, we have studied the factors that affect the hormone system.

CHAPTER 3
Research methodology

This chapter discusses the origin of the mathematical model of the cycle. Since we are interested in a woman's menstrual cycle, we have studied the information that is related with the system in the body. From the study, we found that in the first period, it was the function of hormones in relation to organ parts. The mathematical model can be written as a continuous dynamical system model. Before explaining the details of our mathematical model, we introduce some mathematical theories used in this study.

3.1 Dynamical system model

A dynamical system model is a mathematical model that describes the dynamics of an event. There are two types: discrete and continuous dynamical system models. A mathematical model that represents a change of time that occurs intermittently is in the form:

$$X_{t+1} = rX_t + b$$

when r,b is constant.

A continuous dynamical system model is a mathematical model that represents a change of values as the time arises constantly. This model is in the form:

$$\frac{dX}{dt} = f(X,t)$$

3.2 Mathematical Model

Menstruation is related to two main hormones, LH and FSH, which are considered when creating a mathematical model of the cycle as follows.

3.2.1 System for the Pituitary Hormones

Systems of ordinary differential equations are used to create models that show the FSH processes of synthesis, release, and clearance. Each system is a two compartment model consisting of the pituitary gland and the blood. Gonadotropin synthesis occurs in the pituitary, where it is held in a reserve pool for release into the blood stream. $PL_{LH}(t)$ and $PL_{FSH}(t)$ denote the functions of time which represent the amounts of LH and FSH, respectively, in the releasable pool. $LH(t)$ and $FSH(t)$ denote the concentrations of hormones in the blood. The differential equations for $PL_{LH}(t)$ and $PL_{FSH}(t)$ contain terms for synthesis and for release; the differential equations for $LH(t)$ and $FSH(t)$ contain terms for assimilation and for clearance [35]-[43].

The system of differential equations governing the synthesis (sy_{LH}), release (re_{LH}) and clearance (cl_{LH}) of LH has the form:

$$\frac{d}{dt}PL_{LH} = sy_{LH}(E,P) - re_{LH}(E,P,PL_{LH}) \quad (1)$$

$$\frac{d}{dt}LH = \frac{1}{v}re_{LH}(E,P,PL_{LH}) - cl_{LH}(LH) \quad (2)$$

where:

$$sy_{LH}(E,P) = \frac{V_{1,LH} + \dfrac{V_{2,LH}[E(t)]^8}{[K_{nLH}]^8 + [E(t)]^8}}{1 + P(t)/K_{aLH,P}}$$

$$re_{LH}(E,P,PL_{LH}) = \frac{k_{LH}[1 + cl_{LH,p}P(t)]PL_{LH}}{1 + cl_{LH,E}E(t)}$$

$$cl_{LH}(LH) = A_{LH}LH$$

The pair of differential equations for synthesis and release of FSH have a form similar to (1)-(2):

$$\frac{d}{dt}PL_{FSH} = sy_{FSH}(Ac) - re_{FSH}(E,P,PL_{FSH}) \quad (3)$$

$$\frac{d}{dt}FSH = \frac{1}{v}re_{FSH}(E,P,PL_{FSH}) - cl_{FSH}(FSH) \quad (4)$$

where:

$$sy_{FSH}(Ac) = \frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}$$

$$re_{FSH}(E,P,P_{FSH}) = \frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^2}$$

$$cl_{FSH}(FSH) = A_{FSH}FSH$$

3.2.2 System for the Ovarian Hormones

The model for the ovaries divides the follicular phase and the luteal phase into 9 distinct states based on the capacity of each state to produce hormones before ovulation until the date of ovulation (follicular phase).

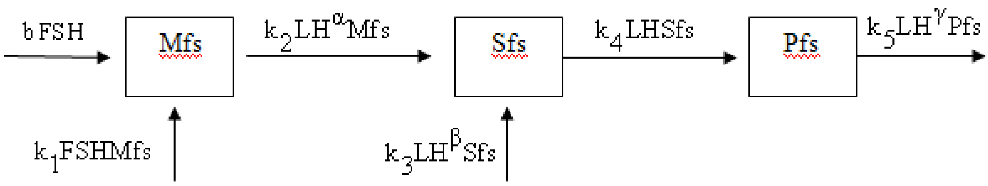


Figure 3.1: Diagram of the hormones before ovulation until the day of ovulation (follicular phase).

The dynamical equations of the hormones before ovulation until the day of ovulation (follicular phase) are described by:

$$\frac{d}{dt}Mfs = bFSH+\left[k_1FSH-k_2LH^{\alpha}\right]Mfs \quad (5)$$

$$\frac{d}{dt}Sfs = k_2LH^{\alpha}Mfs+\left[k_3LH^{\beta}-k_4LH\right]Sfs \quad (6)$$

$$\frac{d}{dt}Pfs = k_4LHSfs-k_5LH^{\gamma}Pfs \quad (7)$$

Changes occur during the transition period before ovulation until the day of ovulation (follicular phase) into the period after ovulation until the day before menstruation (luteal phase).

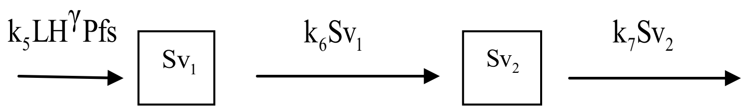


Figure 3.2: Diagram of the hormonal changes of ovulation prior to the date of ovulation (follicular phase) into the period after ovulation until the day before menstruation (luteal phase).

The dynamical equations of the hormonal changes of ovulation prior to the date of ovulation (follicular phase) to the period after ovulation until the day before menstruation (luteal phase) are described by:

$$\frac{d}{dt}Sv_1 = k_5 LH^{\gamma} Pfs - k_6 Sv_1 \tag{8}$$

$$\frac{d}{dt}Sv_2 = k_6 Sv_1 - k_7 Sv_2 . \tag{9}$$

After ovulation until the day before menstruation (luteal phase).

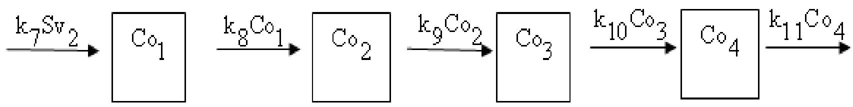


Figure3.3: Diagram of the hormones after ovulation until the day before menstruation (luteal phase).

The dynamical equations of the hormones after ovulation until the day before menstruation (luteal phase) are described by:

$$\frac{d}{dt}Co_1 = k_7 Sv_2 - k_8 Co_1 \tag{10}$$

$$\frac{d}{dt}Co_2 = k_8 Co_1 - k_9 Co_2 \tag{11}$$

$$\frac{d}{dt}Co_3 = k_9 Co_2 - k_{10} Co_3 \tag{12}$$

$$\frac{d}{dt}Co_4 = k_{10} Co_3 - k_{11} Co_4 \tag{13}$$

Table 3.1 The mathematical models of the menstrual cycle [44]-[45].

Parameters	Definition
PL_{LH}	The mass of stored LH in the pituitary
LH	The luteinizing hormone
PL_{FSH}	The mass of stored FSH in the pituitary
FSH	The follicle stimulating hormone
Mfs	The menstrual follicle state
Sfs	The secondary follicle state
Pfs	The pre-ovulatory follicle state
Sv_1	The early ovulatory scar
Sv_2	The late ovulatory scar
Co_1	The development stages of corpus luteum
Co_2	The development stages of corpus luteum
Co_3	The development stages of corpus luteum

Table 3.1 The mathematical models of the menstrual cycle (continued)

Parameters	Definition
Co_4	The development stages of corpus luteum
sy_{LH}	The *synthesis of LH*
re_{LH}	The *release of LH*
cl_{LH}	The *clearance of LH*
sy_{FSH}	The *synthesis of FSH*
re_{FSH}	The *release of FSH*
cl_{FSH}	The *clearance of FSH*
E	The estradiol
P	The progesterone
Ac	The concentration of activin in the blood
v	The blood volume
$\alpha,\beta,\gamma,b,k_1,k_2,k_3,k_4,k_5,k_6,k_7,k_8,k_9,k_{10},k_{11}$	Parameters for ovaries
$e_0,e_1,e_2,e_3,p_0,p_1,a_1,a_2,a_3$	Parameters for the auxiliary equations

Additional conditions of mathematical model for the normal menstrual cycle:

$$E(t) = e_0 + e_1 Sfs(t) + e_2 Pfs(t) + e_3 Co_4(t)$$

$$P(t) = p_0 Co_3(t) + p_1 Co_4(t)$$

$$Ac(t) = a_0 + a_1 Co_3(t) + a_2 Co_4(t)$$

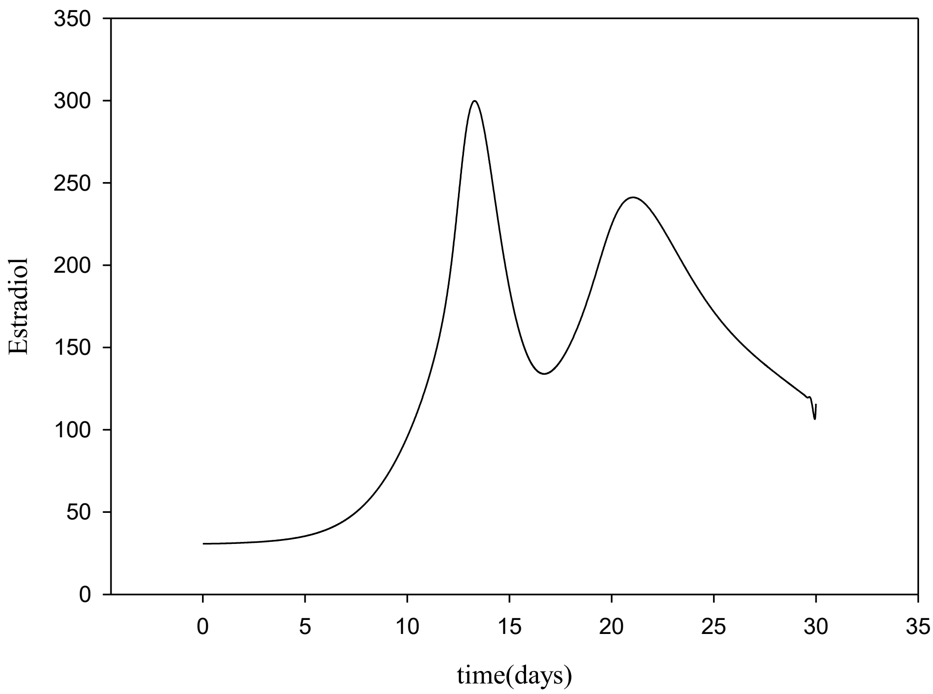
Additional conditions of mathematical model for irregular menstrual cycle:

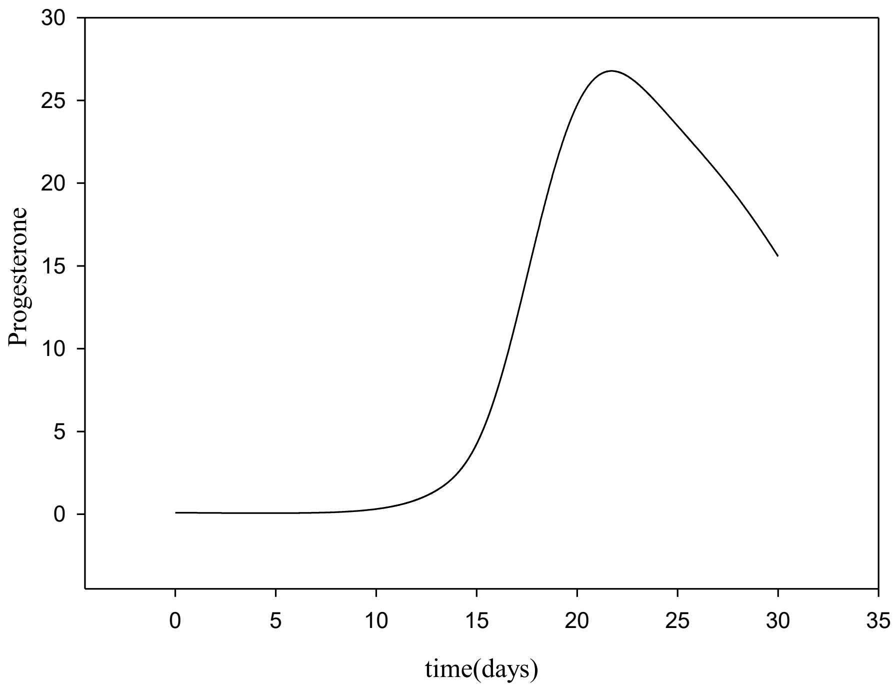
$$Es(t) = \left(\frac{e_0}{\eta_1} + \frac{e_1 MSe(t)}{\eta_2} + \frac{e_2 MPe(t)}{\eta_3} + \frac{e_3 MC_4(t)}{\eta_4} \right) BMI$$

$$Pr(t) = p_0 MC_3(t) + p_1 MC_4(t)$$

$$Ac(t) = a_0 + a_1 MC_3(t) + a_2 MC_4(t).$$

From our equations, LH and FSH are state variables and the functions P, E and Ac affect equations (1)-(13), P affects LH in equation (1) and there is a similar effect of Ac on FSH in equation (3). The simulation outputs are shown in the following figures:





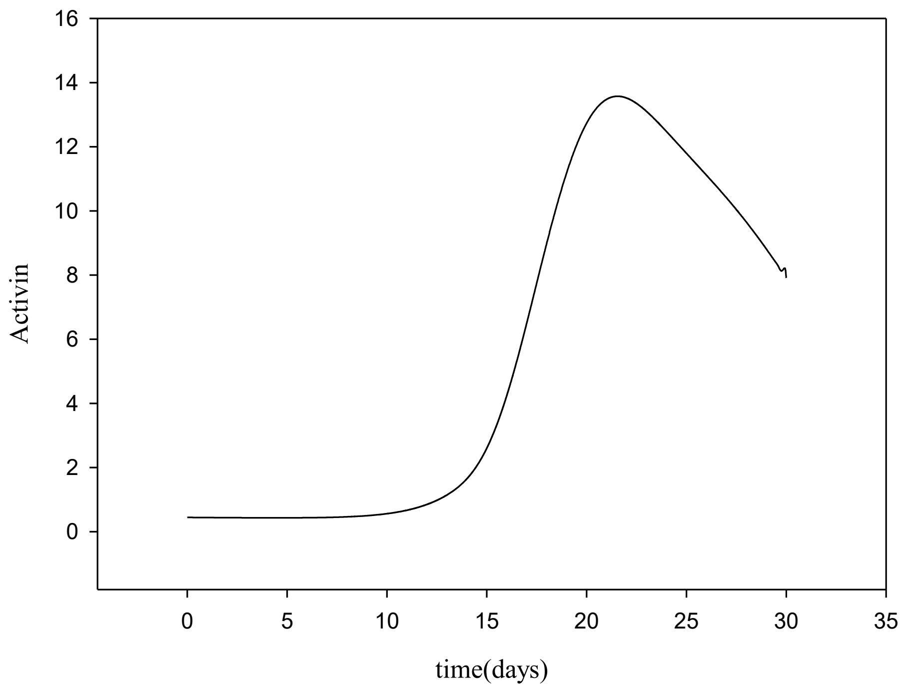


Figure 3.4: Time series solutions of Estradiol (E), Progesterone (P) and Activin (Ac).

From figure 3.4, we can see that both Progesterone and Activin hormone levels have the minimum volume levels on the 1^{st} to the 9^{th} day of menstruation and the maximum level on the 21^{st} to the 23^{rd} day of menstruation. The volume of Estradiol increases on the 6^{th} day.

CHAPTER 4
Main Results and Discussion

4. Analysis of the Mathematical Model

This chapter analyzes the mathematical model of the menstrual cycle. We analyze the balance of our equations, the stability of the equilibrium states, if all eigenvalues for each steady state have negative real parts, and that steady states are locally stable.

4.1 The Steady States

The steady state is defined as:

$$E=(LH^{*},PL^{*}_{LH},FSH^{*},PL^{*}_{FSH},Mfs^{*},,Sfs^{*},Pfs^{*},Sv^{*}_{1},Sv^{*}_{2},Co^{*}_{1},Co^{*}_{2},Co^{*}_{3},Co^{*}_{4}).$$

The steady states are obtained by setting the right hand side of eqs. (1)-(13) to zero.

From equation (1):

$$sy_{LH}(E,P)-re_{LH}\left(E,P,PL^{*}_{LH}\right)=0$$

$$sy_{LH}(E,P)=re_{LH}\left(E,P,PL^{*}_{LH}\right)$$

$$\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}}=\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)},$$

we get for PL^{*}_{LH}

$$PL^{*}_{LH}=\left[\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}}\right]\left[\frac{1+cl_{LH,E}E(t)}{k_{LH}\left[1+cl_{LH,p}P(t)\right]}\right].$$

From equation (2):

$$\frac{1}{v}re_{LH}\left(E,P,PL_{LH}\right)-cl_{LH}\left(LH\right)=0$$

$$\frac{1}{v}re_{LH}\left(E,P,PL_{LH}\right)=cl_{LH}\left(LH\right)$$

$$\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P\left(t\right)\right]PL^{*}_{LH}}{1+cl_{LH,E}E\left(t\right)}\right]=A_{LH}LH^{*}$$

$$LH^{*}=\frac{1}{vA_{LH}}\left[\frac{k_{LH}\left[1+cl_{LH,p}P\left(t\right)\right]PL^{*}_{LH}}{1+cl_{LH,E}E\left(t\right)}\right]$$

$$LH^{*}=\frac{1}{vA_{LH}}\left[\frac{k_{LH}\left[1+cl_{LH,p}P\left(t\right)\right]}{1+cl_{LH,E}E\left(t\right)}\right]\left[\frac{V_{1,LH}+\frac{V_{2,LH}\left[E\left(t\right)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E\left(t\right)\right]^{8}}}{1+P\left(t\right)/K_{aLH,p}}\right]\left[\frac{1+cl_{LH,E}E\left(t\right)}{k_{LH}\left[1+cl_{LH,p}P\left(t\right)\right]}\right],$$

we get for LH^{*}

$$LH^{*}=\frac{1}{vA_{LH}}\left[\frac{V_{1,LH}+\frac{V_{2,LH}\left[E\left(t\right)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E\left(t\right)\right]^{8}}}{1+P\left(t\right)/K_{aLH,p}}\right].$$

From equation (3):

$$sy_{FSH}\left(Ac\right)-re_{FSH}\left(E,P,PL_{FSH}\right)=0$$

$$sy_{FSH}\left(Ac\right)=re_{FSH}\left(E,P,PL_{FSH}\right)$$

$$\frac{V_{FSH}}{1+Ac\left(t\right)/K_{aFSH,Ac}}=\frac{k_{FSH}\left[1+cl_{FSH,p}P\left(t\right)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E\left(t\right)\right]^{2}},$$

we get for PL^{*}_{FSH}

$$PL^{*}_{FSH}=\left[\frac{V_{FSH}}{1+Ac\left(t\right)/K_{aFSH,Ac}}\right]\left[\frac{1+cl_{FSH,E}\left[E\left(t\right)\right]^{2}}{k_{FSH}\left[1+cl_{FSH,p}P\left(t\right)\right]}\right].$$

From equation (4):

$$\frac{1}{v}\,\mathrm{re}_{FSH}\left(E,P,PL_{FSH}\right) - \mathrm{cl}_{FSH}\left(FSH\right) = 0$$

$$\frac{1}{v}\,\mathrm{re}_{FSH}\left(E,P,PL_{FSH}\right) = \mathrm{cl}_{FSH}\left(FSH\right)$$

$$\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P\left(t\right)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E\left(t\right)\right]^{2}}\right]=A_{FSH}FSH^{*}$$

$$FSH^{*}=\frac{1}{vA_{FSH}}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P\left(t\right)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E\left(t\right)\right]^{2}}\right]$$

$$FSH^{*}=\frac{1}{vA_{FSH}}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P\left(t\right)\right]}{1+cl_{FSH,E}\left[E\left(t\right)\right]^{2}}\right]\left[\frac{V_{FSH}}{1+Ac\left(t\right)/K_{aFSH,Ac}}\right]\left[\frac{1+cl_{FSH,E}\left[E\left(t\right)\right]^{2}}{k_{FSH}\left[1+cl_{FSH,p}P\left(t\right)\right]}\right],$$

we get for FSH^{*}

$$FSH^{*}=\frac{1}{vA_{FSH}}\left[\frac{V_{FSH}}{1+Ac\left(t\right)/K_{aFSH,Ac}}\right].$$

From equation (5):

$$bFSH^{*}+\left[k_{1}FSH^{*}-k_{2}LH^{*\alpha}\right]Mfs^{*}=0$$

$$\left[k_{1}FSH^{*}-k_{2}LH^{*\alpha}\right]Mfs^{*}=-bFSH^{*},$$

we get for Mfs^{*}

$$Mfs^{*}=\frac{bFSH^{*}}{k_{2}(LH^{*})^{\alpha}-k_{1}FSH^{*}}.$$

From equation (6):

$$k_{2}LH^{*\alpha}Mfs^{*}+\left[k_{3}LH^{*\beta}-k_{4}LH^{*}\right]Sfs^{*}=0$$

$$\left[k_{3}LH^{*\beta}-k_{4}LH^{*}\right]Sfs^{*}=-k_{2}LH^{*\alpha}Mfs^{*}$$

$$Sfs^* = \frac{-k_2 LH^{*\alpha} Mfs^*}{\left[k_3 LH^{*\beta} - k_4 LH^*\right]}$$

$$Sfs^* = \frac{-k_2 LH^{*\alpha}}{\left[k_3 LH^{*\beta} - k_4 LH^*\right]}\left[\frac{bFSH^*}{k_2 (LH^*)^{\alpha} - k_1 FSH^*}\right],$$

we get for Sfs^*

$$Sfs^* = \frac{bFSH^* k_2 (LH^*)^{\alpha}}{\left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}.$$

From equation (7):

$$k_4 LH^* Sfs^* - k_5 LH^{*\gamma} Pfs^* = 0$$

$$-k_5 LH^{*\gamma} Pfs^* = -k_4 LH^* Sfs^*$$

$$Pfs^* = \frac{-k_4 LH^* Sfs^*}{-k_5 LH^{*\gamma}}$$

$$Pfs^* = \frac{-k_4 LH^*}{-k_5 LH^{*\gamma}} \frac{-k_2 LH^{*\alpha}}{\left[k_3 LH^{*\beta} - k_4 LH^*\right]}\left[\frac{bFSH^*}{k_2 (LH^*)^{\alpha} - k_1 FSH^*}\right],$$

we get for Pfs^*

$$Pfs^* = \frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha-\gamma}}{k_5\left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}.$$

From equation (8):

$$k_5 LH^{*\gamma} Pfs^* - k_6 Sv^*_1 = 0$$

$$-k_6 Sv^*_1 = -k_5 LH^{*\gamma} Pfs^*$$

$$Sv^*_1 = \frac{-k_5 LH^{*\gamma} Pfs^*}{-k_6}$$

$$Sv^*_1 = \frac{-k_5 LH^{*\gamma}}{-k_6}\left[\frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha-\gamma}}{k_5\left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}\right],$$

we get for Sv^*_1

$$Sv^*_1 = \frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_6 \left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}.$$

From equation (9):

$$k_6 Sv^*_1 - k_7 Sv^*_2 = 0$$

$$-k_7 Sv^*_2 = -k_6 Sv^*_1$$

$$Sv^*_2 = \frac{-k_6 Sv^*_1}{-k_7}$$

$$Sv^*_2 = \frac{-k_6}{-k_7}\left[\frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_6 \left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}\right],$$

we get for Sv^*_2

$$Sv^*_2 = \frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_7 \left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}.$$

From equation (10):

$$k_7 Sv^*_2 - k_8 Co^*_1 = 0$$

$$-k_8 Co^*_1 = -k_7 Sv^*_2$$

$$Co^*_1 = \frac{-k_7 Sv^*_2}{-k_8}$$

$$Co^*_1 = \frac{-k_7}{-k_8}\left[\frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_7 \left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}\right],$$

we get for Co^{*}_{1}

$$Co^{*}_{1} = \frac{k_4 bFSH^{*} k_2 (LH^{*})^{1+\alpha}}{k_8 \left(k_1 FSH^{*} - k_2 (LH^{*})^{\alpha}\right)\left(k_3 (LH^{*})^{\beta} - k_4 LH^{*}\right)}.$$

From equation (11):

$$k_8 Co^{*}_{1} - k_9 Co^{*}_{2} = 0$$

$$-k_9 Co^{*}_{2} = -k_8 Co^{*}_{1}$$

$$Co^{*}_{2} = \frac{-k_8 Co^{*}_{1}}{-k_9}$$

$$Co^{*}_{2} = \frac{-k_8}{-k_9}\left[\frac{k_4 bFSH^{*} k_2 (LH^{*})^{1+\alpha}}{k_8 \left(k_1 FSH^{*} - k_2 (LH^{*})^{\alpha}\right)\left(k_3 (LH^{*})^{\beta} - k_4 LH^{*}\right)}\right],$$

we get for Co^{*}_{2}

$$Co^{*}_{2} = \frac{k_4 bFSH^{*} k_2 (LH^{*})^{1+\alpha}}{k_9 \left(k_1 FSH^{*} - k_2 (LH^{*})^{\alpha}\right)\left(k_3 (LH^{*})^{\beta} - k_4 LH^{*}\right)}.$$

From equation (12):

$$k_9 Co^{*}_{2} - k_{10} Co^{*}_{3} = 0$$

$$-k_{10} Co^{*}_{3} = -k_9 Co^{*}_{2}$$

$$Co^{*}_{3} = \frac{-k_9 Co^{*}_{2}}{-k_{10}}$$

$$Co^{*}_{3} = \frac{-k_9}{-k_{10}}\left[\frac{k_4 bFSH^{*} k_2 (LH^{*})^{1+\alpha}}{k_9 \left(k_1 FSH^{*} - k_2 (LH^{*})^{\alpha}\right)\left(k_3 (LH^{*})^{\beta} - k_4 LH^{*}\right)}\right],$$

we get for Co^*_3

$$Co^*_3 = \frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_{10}\left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}.$$

From equation (13):

$$\begin{aligned} k_{10}Co^*_3 - k_{11}Co^*_4 &= 0 \\ -k_{11}Co^*_4 &= -k_{10}Co^*_3 \\ Co^*_4 &= \frac{-k_{10}Co^*_3}{-k_{11}} \\ Co^*_4 &= \frac{-k_{10}}{-k_{11}}\left[\frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_{10}\left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}\right], \end{aligned}$$

we get for Co^*_4

$$Co^*_4 = \frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_{11}\left(k_1 FSH^* - k_2 (LH^*)^{\alpha}\right)\left(k_3 (LH^*)^{\beta} - k_4 LH^*\right)}.$$

Therefore, equations (1)-(13) have a positive steady state $E(LH^*, PL^*_{LH}, FSH^*, PL^*_{FSH}, Mfs^*, , Sfs^*, Pfs^*, Sv^*_1, Sv^*_2, Co^*_1, Co^*_2, Co^*_3, Co^*_4)$ and $LH^*, PL^*_{LH}, FSH^*, PL^*_{FSH}, Mfs^*, , Sfs^*, Pfs^*, Sv^*_1, Sv^*_2, Co^*_1, Co^*_2, Co^*_3, Co^*_4$ satisfies:

$$LH^* = \left[\frac{V_{1,LH} + \dfrac{V_{2,LH}\left[E(t)\right]^8}{\left[K_{nLH}\right]^8 + \left[E(t)\right]^8}}{1 + P(t)/K_{aLH,p}}\right]\left[\frac{1}{vA_{LH}}\right] \qquad (14)$$

$$PL^{*}_{LH} = \left[\frac{V_{1,LH} + \frac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8} + \left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} \right] \left[\frac{1+cl_{LH,E}E(t)}{k_{LH}\left[1+cl_{LH,p}P(t)\right]} \right] \tag{15}$$

$$FSH^{*} = \left[\frac{1}{vA_{FSH}} \right] \left[\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}} \right] \tag{16}$$

$$PL^{*}_{FSH} = \left[\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}} \right] \left[\frac{1+cl_{FSH,E}\left[E(t)\right]^{2}}{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]} \right] \tag{17}$$

$$Mfs^{*} = \frac{bFSH^{*}}{k_{2}(LH^{*})^{\alpha} - k_{1}FSH^{*}} \tag{18}$$

$$Sfs^{*} = \frac{bFSH^{*}k_{2}(LH^{*})^{\alpha}}{\left(k_{1}FSH^{*} - k_{2}(LH^{*})^{\alpha}\right)\left(k_{3}(LH^{*})^{\beta} - k_{4}LH^{*}\right)} \tag{19}$$

$$Pfs^{*} = \frac{k_{4}bFSH^{*}k_{2}(LH^{*})^{1+\alpha-\gamma}}{k_{5}\left(k_{1}FSH^{*}-k_{2}(LH^{*})^{\alpha}\right)\left(k_{3}(LH^{*})^{\beta}-k_{4}LH^{*}\right)} \tag{20}$$

$$Sv^{*}_{1} = \frac{k_{4}bFSH^{*}k_{2}(LH^{*})^{1+\alpha}}{k_{6}\left(k_{1}FSH^{*}-k_{2}(LH^{*})^{\alpha}\right)\left(k_{3}(LH^{*})^{\beta}-k_{4}LH^{*}\right)} \tag{21}$$

$$Sv^{*}_{2} = \frac{k_{4}bFSH^{*}k_{2}(LH^{*})^{1+\alpha}}{k_{7}\left(k_{1}FSH^{*}-k_{2}(LH^{*})^{\alpha}\right)\left(k_{3}(LH^{*})^{\beta}-k_{4}LH^{*}\right)} \tag{22}$$

$$Co^{*}_{1} = \frac{k_{4}bFSH^{*}k_{2}(LH^{*})^{1+\alpha}}{k_{8}\left(k_{1}FSH^{*}-k_{2}(LH^{*})^{\alpha}\right)\left(k_{3}(LH^{*})^{\beta}-k_{4}LH^{*}\right)} \tag{23}$$

$$Co^*_2 = \frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_9\left(k_1FSH^* - k_2(LH^*)^{\alpha}\right)\left(k_3(LH^*)^{\beta} - k_4LH^*\right)} \tag{24}$$

$$Co^*_3 = \frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_{10}\left(k_1FSH^* - k_2(LH^*)^{\alpha}\right)\left(k_3(LH^*)^{\beta} - k_4LH^*\right)} \tag{25}$$

$$Co^*_4 = \frac{k_4 bFSH^* k_2 (LH^*)^{1+\alpha}}{k_{11}\left(k_1FSH^* - k_2(LH^*)^{\alpha}\right)\left(k_3(LH^*)^{\beta} - k_4LH^*\right)} \tag{26}$$

4.2 Stability Analysis

The local stability of an equilibrium point is determined from the Jacobian matrix of the right hand side of differential equations at the equilibrium point. If all eigenvalues for each the equilibrium point have negative real parts then that equilibrium point is locally stable. From equations (1)-(13), we assign:

$$x_1\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = sy_{LH}(E,P) - re_{LH}(E,P,PL^*_{LH})$$

$$x_2\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = \frac{1}{v}re_{LH}(E,P,PL^*_{LH}) - cl_{LH}(LH^*)$$

$$x_3\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = sy_{FSH}(Ac) - re_{FSH}\left(E,P,PL^*_{FSH}\right)$$

$$x_4\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = \frac{1}{v}re_{FSH}\left(E,P,PL^*_{FSH}\right) - cl_{FSH}\left(FSH^*\right)$$

$$x_5\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = bFSH^* + \left[k_1FSH^* - k_2LH^{*\alpha}\right]Mfs^*$$

$$x_6\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = k_2LH^{*\alpha}Mfs + \left[k_3LH^{*\beta} - k_4LH^*\right]Sfs^*$$

$$x_7\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = k_4LH^*Sfs^* - k_5LH^{*\gamma}Pfs^*$$

$$x_8\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = k_5LH^{*\gamma}Pfs^* - k_6Sv_1^*$$

$$x_9\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = k_6Sv_1^* - k_7Sv_2^*$$

$$x_{10}\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = k_7Sv_2^* - k_8Co_1^*$$

$$x_{11}\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = k_8Co_1^* - k_9Co_2^*$$

$$x_{12}\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = k_9Co_2^* - k_{10}Co_3^*$$

$$x_{13}\left(LH^*,PL^*_{LH},FSH^*,PL^*_{FSH},Mfs^*,Sfs^*,Pfs^*,Sv^*_1,Sv^*_2,Co^*_1,Co^*_2,Co^*_3,Co^*_4\right) = k_{10}Co_3^* - k_{11}Co_4^*$$

We obtain the following Jacobian matrix at the equilibrium point:

$$J=\begin{bmatrix}
x_{1PL_{LH}} & x_{1LH} & x_{1PL_{FSH}} & x_{1FSH} & x_{1Mfs} & x_{1Sfs} & x_{1Pfs} & x_{1Sv_1} & x_{1Sv_2} & x_{1Co_1} & x_{1Co_2} & x_{1Co_3} & x_{1Co_4} \\
x_{2PL_{LH}} & x_{2LH} & x_{2PL_{FSH}} & x_{2FSH} & x_{2Mfs} & x_{2Sfs} & x_{2Pfs} & x_{2Sv_1} & x_{2Sv_2} & x_{2Co_1} & x_{2Co_2} & x_{2Co_3} & x_{2Co_4} \\
x_{3PL_{LH}} & x_{3LH} & x_{3PL_{FSH}} & x_{3FSH} & x_{3Mfs} & x_{3Sfs} & x_{3Pfs} & x_{3Sv_1} & x_{3Sv_2} & x_{3Co_1} & x_{3Co_2} & x_{3Co_3} & x_{3Co_4} \\
x_{4PL_{LH}} & x_{4LH} & x_{4PL_{FSH}} & x_{4FSH} & x_{4Mfs} & x_{4Sfs} & x_{4Pfs} & x_{4Sv_1} & x_{4Sv_2} & x_{4Co_1} & x_{4Co_2} & x_{4Co_3} & x_{4Co_4} \\
x_{5PL_{LH}} & x_{5LH} & x_{5PL_{FSH}} & x_{5FSH} & x_{5Mfs} & x_{5Sfs} & x_{5Pfs} & x_{5Sv_1} & x_{5Sv_2} & x_{5Co_1} & x_{5Co_2} & x_{5Co_3} & x_{5Co_4} \\
x_{6PL_{LH}} & x_{6LH} & x_{6PL_{FSH}} & x_{6FSH} & x_{6Mfs} & x_{6Sfs} & x_{6Pfs} & x_{6Sv_1} & x_{6Sv_2} & x_{6Co_1} & x_{6Co_2} & x_{6Co_3} & x_{6Co_4} \\
x_{7PL_{LH}} & x_{7LH} & x_{7PL_{FSH}} & x_{7FSH} & x_{7Mfs} & x_{7Sfs} & x_{7Pfs} & x_{7Sv_1} & x_{7Sv_2} & x_{7Co_1} & x_{7Co_2} & x_{7Co_3} & x_{7Co_4} \\
x_{8PL_{LH}} & x_{8LH} & x_{8PL_{FSH}} & x_{8FSH} & x_{8Mfs} & x_{8Sfs} & x_{8Pfs} & x_{8Sv_1} & x_{8Sv_2} & x_{8Co_1} & x_{8Co_2} & x_{8Co_3} & x_{8Co_4} \\
x_{9PL_{LH}} & x_{9LH} & x_{9PL_{FSH}} & x_{9FSH} & x_{9Mfs} & x_{9Sfs} & x_{9Pfs} & x_{9Sv_1} & x_{9Sv_2} & x_{9Co_1} & x_{9Co_2} & x_{9Co_3} & x_{9Co_4} \\
x_{10PL_{LH}} & x_{10LH} & x_{10PL_{FSH}} & x_{10FSH} & x_{10Mfs} & x_{10Sfs} & x_{10Pfs} & x_{10Sv_1} & x_{10Sv_2} & x_{10Co_1} & x_{10Co_2} & x_{10Co_3} & x_{10Co_4} \\
x_{11PL_{LH}} & x_{11LH} & x_{11PL_{FSH}} & x_{11FSH} & x_{11Mfs} & x_{11Sfs} & x_{11Pfs} & x_{11Sv_1} & x_{11Sv_2} & x_{11Co_1} & x_{11Co_2} & x_{11Co_3} & x_{11Co_4} \\
x_{12PL_{LH}} & x_{12LH} & x_{12PL_{FSH}} & x_{12FSH} & x_{12Mfs} & x_{12Sfs} & x_{12Pfs} & x_{12Sv_1} & x_{12Sv_2} & x_{12Co_1} & x_{12Co_2} & x_{12Co_3} & x_{12Co_4} \\
x_{13PL_{LH}} & x_{13LH} & x_{13PL_{FSH}} & x_{13FSH} & x_{13Mfs} & x_{13Sfs} & x_{13Pfs} & x_{13Sv_1} & x_{13Sv_2} & x_{13Co_1} & x_{13Co_2} & x_{13Co_3} & x_{13Co_4}
\end{bmatrix}$$

Members of the Jacobian matrix in each row are as follows:

In the 1st row:

$$x_{1PL_{LH}} = \frac{-k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)}$$

$$x_{1LH} = 0$$

$$x_{1PL_{FSH}} = 0$$

$$x_{1FSH} = 0$$

$$x_{1Mfs} = 0$$

$$x_{1Sfs} = 0$$

$$x_{1Pfs} = 0$$

$$x_{1Sv_1} = 0$$

$$x_{1Sv_2} = 0$$

$$x_{1Co_1} = 0$$

$$x_{1Co_2} = 0$$

$$x_{1Co_3} = 0$$

$$x_{1Co_4} = 0.$$

In the 2nd row:

$$x_{2PL_{LH}} = \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)}$$

$$x_{2LH} = -vA_{LH}$$

$$x_{2PL_{FSH}} = 0$$

$$x_{2FSH} = 0$$

$$x_{2Mfs} = 0$$

$$x_{2Sfs} = 0$$

$$x_{2Pfs} = 0$$

$$x_{2Sv_1} = 0$$

$$x_{2Sv_2} = 0$$

$$x_{2Co_1} = 0$$

$$x_{2Co_2} = 0$$

$$x_{2Co_3} = 0$$

$$x_{2Co_4} = 0.$$

In the 3rd row:

$$x_{3PL_{LH}} = 0$$

$$x_{3LH} = 0$$

$$x_{3PL_{FSH}} = \frac{-k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2}$$

$$x_{3FSH} = 0$$

$$x_{3Mfs} = 0$$

$$x_{3Sfs} = 0$$

$$x_{3Pfs} = 0$$

$$x_{3Sv_1} = 0$$

$$x_{3Sv_2} = 0$$

$$x_{3Co_1} = 0$$

$$x_{3Co_2} = 0$$

$$x_{3Co_3} = 0$$

$$x_{3Co_4} = 0.$$

In the 4th row:

$$x_{4PL_{LH}} = 0$$

$$x_{4LH} = 0$$

$$x_{4PL_{FSH}} = \frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2}$$

$$x_{4FSH} = -vA_{FSH}$$

$$x_{4Mfs} = 0$$

$$x_{4Sfs} = 0$$

$$x_{4Pfs} = 0$$

$$x_{4Sv_1} = 0$$

$$x_{4Sv_2} = 0$$

$$x_{4Co_1} = 0$$

$$x_{4Co_2} = 0$$

$$x_{4Co_3} = 0$$

$$x_{4Co_4} = 0.$$

In the 5th row:

$$x_{5PL_{LH}} = 0$$
$$x_{5LH} = k_2\alpha\left(LH^*\right)^{\alpha-1} Mfs^*$$
$$x_{5PL_{FSH}} = 0$$
$$x_{5FSH} = b+k_1 Mfs^*$$
$$x_{5Mfs} = k_1 FSH^* - k_2\left(LH^*\right)^{\alpha}$$
$$x_{5Sfs} = 0$$
$$x_{5Pfs} = 0$$
$$x_{5Sv_1} = 0$$
$$x_{5Sv_2} = 0$$
$$x_{5Co_1} = 0$$
$$x_{5Co_2} = 0$$
$$x_{5Co_3} = 0$$
$$x_{5Co_4} = 0.$$

In the 6th row:

$$x_{6PL_{LH}} = 0$$
$$x_{6LH} = k_2\alpha\left(LH^*\right)^{\alpha-1} Mfs^* + \left[k_3\beta\left(LH^*\right)^{\beta-1} - k_4\right] Sfs^*$$
$$x_{6PL_{FSH}} = 0$$
$$x_{6FSH} = 0$$
$$x_{6Mfs} = k_2\left(LH^*\right)^{\alpha}$$
$$x_{6Sfs} = k_3\left(LH^*\right)^{\beta} - k_4 LH^*$$
$$x_{6Pfs} = 0$$
$$x_{6Sv_1} = 0$$
$$x_{6Sv_2} = 0$$
$$x_{6Co_1} = 0$$
$$x_{6Co_2} = 0$$
$$x_{6Co_3} = 0$$
$$x_{6Co_4} = 0.$$

In the 7th row:

$$x_{7PL_{LH}} = 0$$
$$x_{7LH} = k_4 Sfs^* - k_5\gamma\left(LH^*\right)^{\gamma-1} Pfs^*$$
$$x_{7PL_{FSH}} = 0$$
$$x_{7FSH} = 0$$
$$x_{7Mfs} = 0$$
$$x_{7Sfs} = k_4 LH^*$$
$$x_{7Pfs} = -k_5\left(LH^*\right)^{\gamma}$$
$$x_{7Sv_1} = 0$$
$$x_{7Sv_2} = 0$$
$$x_{7Co_1} = 0$$
$$x_{7Co_2} = 0$$
$$x_{7Co_3} = 0$$
$$x_{7Co_4} = 0.$$

In the 8th row:

$$x_{8PL_{LH}} = 0$$
$$x_{8LH} = k_5\gamma\left(LH^*\right)^{\gamma-1} Pfs^*$$
$$x_{8PL_{FSH}} = 0$$
$$x_{8FSH} = 0$$
$$x_{8Mfs} = 0$$
$$x_{8Sfs} = 0$$
$$x_{8Pfs} = k_5\left(LH^*\right)^{\gamma}$$
$$x_{8Sv_1} = 0$$
$$x_{8Sv_2} = 0$$
$$x_{8Co_1} = 0$$
$$x_{8Co_2} = 0$$
$$x_{8Co_3} = 0$$
$$x_{8Co_4} = 0.$$

In the 9th row:

$$x_{9PL_{LH}} = 0$$
$$x_{9LH} = 0$$
$$x_{9PL_{FSH}} = 0$$
$$x_{9FSH} = 0$$
$$x_{9Mfs} = 0$$
$$x_{9Sfs} = 0$$
$$x_{9Pfs} = 0$$
$$x_{9Sv_1} = k_6$$
$$x_{9Sv_2} = -k_7$$
$$x_{9Co_1} = 0$$
$$x_{9Co_2} = 0$$
$$x_{9Co_3} = 0$$
$$x_{9Co_4} = 0.$$

In the 10th row:

$$x_{10PL_{LH}} = 0$$
$$x_{10LH} = 0$$
$$x_{10PL_{FSH}} = 0$$
$$x_{10FSH} = 0$$
$$x_{10Mfs} = 0$$
$$x_{10Sfs} = 0$$
$$x_{10Pfs} = 0$$
$$x_{10Sv_1} = 0$$
$$x_{10Sv_2} = k_7$$
$$x_{10Co_1} = -k_8$$
$$x_{10Co_2} = 0$$
$$x_{10Co_3} = 0$$
$$x_{10Co_4} = 0.$$

In the 11th row:

$x_{11PL_{LH}} = 0$

$x_{11LH} = 0$

$x_{11PL_{FSH}} = 0$

$x_{11FSH} = 0$

$x_{11Mfs} = 0$

$x_{11Sfs} = 0$

$x_{11Pfs} = 0$

$x_{11Sv_1} = 0$

$x_{11Sv_2} = 0$

$x_{11Co_1} = k_8$

$x_{11Co_2} = -k_9$

$x_{11Co_3} = 0$

$x_{11Co_4} = 0.$

In the 12th row:

$x_{12PL_{LH}} = 0$

$x_{12LH} = 0$

$x_{12PL_{FSH}} = 0$

$x_{12FSH} = 0$

$x_{12Mfs} = 0$

$x_{12Sfs} = 0$

$x_{12Pfs} = 0$

$x_{12Sv_1} = 0$

$x_{12Sv_2} = 0$

$x_{12Co_1} = 0$

$x_{12Co_2} = k_9$

$x_{12Co_3} = -k_{10}$

$x_{12Co_4} = 0.$

In the 13th row:

$x_{13PL_{LH}} = 0$

$x_{13LH} = 0$

$x_{13PL_{FSH}} = 0$

$x_{13FSH} = 0$

$x_{13Mfs} = 0$

$x_{13Sfs} = 0$

$x_{13Pfs} = 0$

$x_{13Sv_1} = 0$

$x_{13Sv_2} = 0$

$x_{13Co_1} = 0$

$x_{13Co_2} = 0$

$x_{13Co_3} = k_{10}$

$x_{13Co_4} = -k_{11}.$

We obtain the following Jacobian matrix at the equilibrium point:

$$J=\begin{bmatrix}
\frac{-k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)} & -vA_{LH} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{-k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2} & -vA_{FSH} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -k_2\alpha\left(LH^*\right)^{\alpha-1}Mfs^* & 0 & b+k_1Mfs^* & k_1FSH^*-k_2\left(LH^*\right)^{\alpha} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_2\alpha\left(LH^*\right)^{\alpha-1}Mfs^*+\left[k_3\beta\left(LH^*\right)^{\beta-1}-k_4\right]Sfs^* & 0 & 0 & k_2\left(LH^*\right)^{\alpha} & k_3\left(LH^*\right)^{\beta}-k_4LH^* & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_4Sfs^*-k_5\gamma\left(LH^*\right)^{\gamma-1}Pfs^* & 0 & 0 & 0 & k_4LH^* & -k_5\left(LH^*\right)^{\gamma} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_5\gamma\left(LH^*\right)^{\gamma-1}Pfs^* & 0 & 0 & 0 & 0 & k_5\left(LH^*\right)^{\gamma} & -k_6 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & k_6 & -k_7 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_7 & -k_8 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_8 & -k_9 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_9 & -k_{10} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{10} & -k_{11}
\end{bmatrix}$$

The eigenvalues are obtained by solving the characteristic equation:

$$\det\left(J-\lambda I_{13}\right)=0$$

where I_{13} is the identity matrix dimension 13×13 and is defined as:

$$I_{13}=\begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}.$$

If all eigenvalues for each the steady states have negative real parts, then steady states are locally stable.

Consider:

$$J-\lambda I_{13} =$$

$$\begin{bmatrix}
\frac{-k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)} & -vA_{LH}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{-k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2} & -vA_{FSH}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -k_2\alpha\left(LH^*\right)^{\alpha-1}Mfs^* & 0 & b+k_1Mfs^* & k_1FSH^*-k_2\left(LH^*\right)^{\alpha}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_2\alpha\left(LH^*\right)^{\alpha-1}Mfs^*+\left[k_3\beta\left(LH^*\right)^{\beta-1}-k_4\right]Sfs^* & 0 & 0 & k_2\left(LH^*\right)^{\alpha} & k_3\left(LH^*\right)^{\beta}-k_4LH^*-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_4Sfs^*-k_5\gamma\left(LH^*\right)^{\gamma-1}Pfs^* & 0 & 0 & 0 & k_4LH^* & -k_5\left(LH^*\right)^{\gamma}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_5\gamma\left(LH^*\right)^{\gamma-1}Pfs^* & 0 & 0 & 0 & 0 & k_5\left(LH^*\right)^{\gamma} & -k_6-\lambda & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & k_6 & -k_7-\lambda & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_7 & -k_8-\lambda & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_8 & -k_9-\lambda & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_9 & -k_{10}-\lambda & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{10} & -k_{11}-\lambda
\end{bmatrix}$$

$$\det\left(J-\lambda I_{13}\right) =$$

$$\begin{vmatrix}
\frac{-k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)} & -vA_{LH}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{-k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2} & -vA_{FSH}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -k_2\alpha\left(LH^*\right)^{\alpha-1}Mfs^* & 0 & b+k_1Mfs^* & k_1FSH^*-k_2\left(LH^*\right)^{\alpha}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_2\alpha\left(LH^*\right)^{\alpha-1}Mfs^*+\left[k_3\beta\left(LH^*\right)^{\beta-1}-k_4\right]Sfs^* & 0 & 0 & k_2\left(LH^*\right)^{\alpha} & k_3\left(LH^*\right)^{\beta}-k_4LH^*-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_4Sfs^*-k_5\gamma\left(LH^*\right)^{\gamma-1}Pfs^* & 0 & 0 & 0 & k_4LH^* & -k_5\left(LH^*\right)^{\gamma}-\lambda & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_5\gamma\left(LH^*\right)^{\gamma-1}Pfs^* & 0 & 0 & 0 & 0 & k_5\left(LH^*\right)^{\gamma} & -k_6-\lambda & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & k_6 & -k_7-\lambda & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_7 & -k_8-\lambda & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_8 & -k_9-\lambda & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_9 & -k_{10}-\lambda & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{10} & -k_{11}-\lambda
\end{vmatrix}$$

The characteristic equation for the steady states is given by:

$$\det\left(J - \lambda I_{13}\right) = \left(\frac{-k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)} - \lambda\right)\left(-vA_{LH} - \lambda\right)\left(\frac{-k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2} - \lambda\right)\left(-vA_{FSH} - \lambda\right)$$

$$\left(k_1 FSH^* - k_2\left(LH^*\right)^{\alpha} - \lambda\right)\left(k_3\left(LH^*\right)^{\beta} - k_4 LH^* - \lambda\right)\left(-k_5\left(LH^*\right)^{\gamma} - \lambda\right)\left(-k_6 - \lambda\right)$$

$$\left(-k_7 - \lambda\right)\left(-k_8 - \lambda\right)\left(-k_9 - \lambda\right)\left(-k_{10} - \lambda\right)\left(-k_{11} - \lambda\right)$$

$$= 0.$$

That is:

$$\lambda_1 = \frac{-k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)} \quad , \quad \lambda_2 = -vA_{LH}$$

$$\lambda_3 = \frac{-k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2} \quad , \quad \lambda_4 = -vA_{FSH}$$

$$\lambda_5 = k_1 FSH^* - k_2 LH^{*\alpha} \quad , \quad \lambda_6 = k_3 LH^{*\beta} - k_4 LH^*$$

$$\lambda_7 = -k_5 LH^{*\gamma} \quad , \quad \lambda_8 = -k_6$$

$$\lambda_9 = -k_7 \quad , \quad \lambda_{10} = -k_8$$

$$\lambda_{11} = -k_9 \quad , \quad \lambda_{12} = -k_{10}$$

$$\lambda_{13} = -k_{11}$$

We can see that all eigenvalues are negative except λ_5 and λ_6, as shown in Figures 4.1-4.10.

From: $\lambda_5 = k_1 FSH^* - k_2 LH^{*\alpha}$,

consider: $k_1 FSH^* - k_2 LH^{*\alpha} < 0$

when: $k_2 LH^{*\alpha} - k_1 FSH^* > 0$

$$k_2 LH^{*\alpha} > k_1 FSH^*$$

$$\frac{k_2 LH^{*\alpha}}{k_1 FSH^*} > 1.$$

From: $\lambda_6 = k_3 LH^{*\beta} - k_4 LH^*$,

consider: $$k_3 LH^{*\beta} - k_4 LH^* < 0$$

when: $$k_4 LH^* - k_3 LH^{*\beta} > 0$$

$$k_4 LH^* > k_3 LH^{*\beta}$$

$$\frac{k_4 LH^*}{k_3 LH^{*\beta}} > 1.$$

the $P = k_2 LH^{*\alpha} - k_1 FSH^*$ and $P_1 = k_4 LH^* - k_3 LH^{*\beta}$.

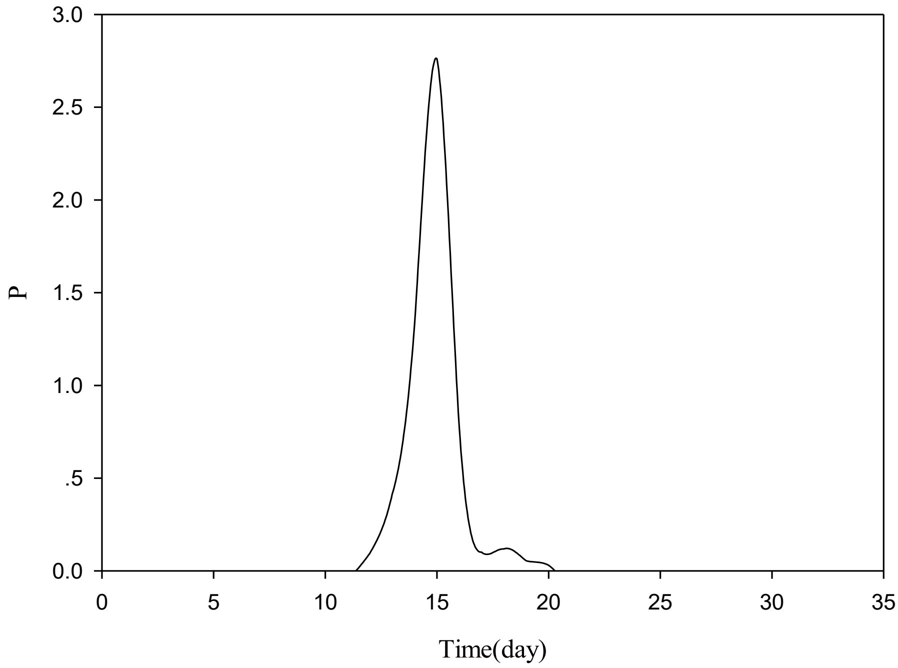


Figure 4.1: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.0058, k_2=0.048 , k_3=0.004, k_4=0.0061 , α=0.7736 , β=0.6.

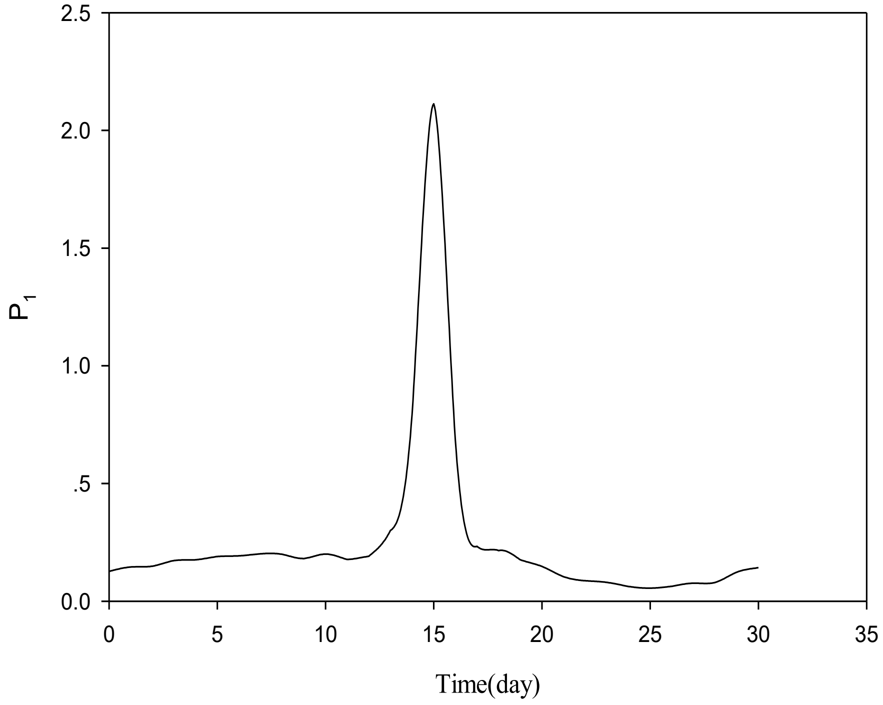


Figure 4.2: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.0058, k_2=0.048 , k_3=0.004, k_4=0.0061 , α=0.7736 , β=0.6

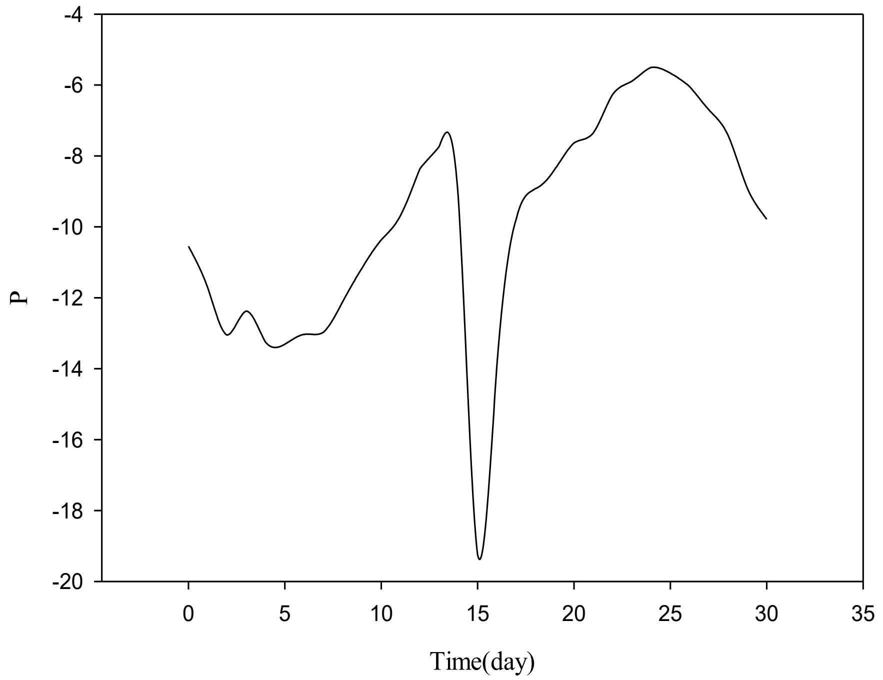


Figure 4.3: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.08, k_2=0.07 , k_3=0.13, k_4=0.027 , α=0.7736 , β=0.6, $k_2 < k_1$

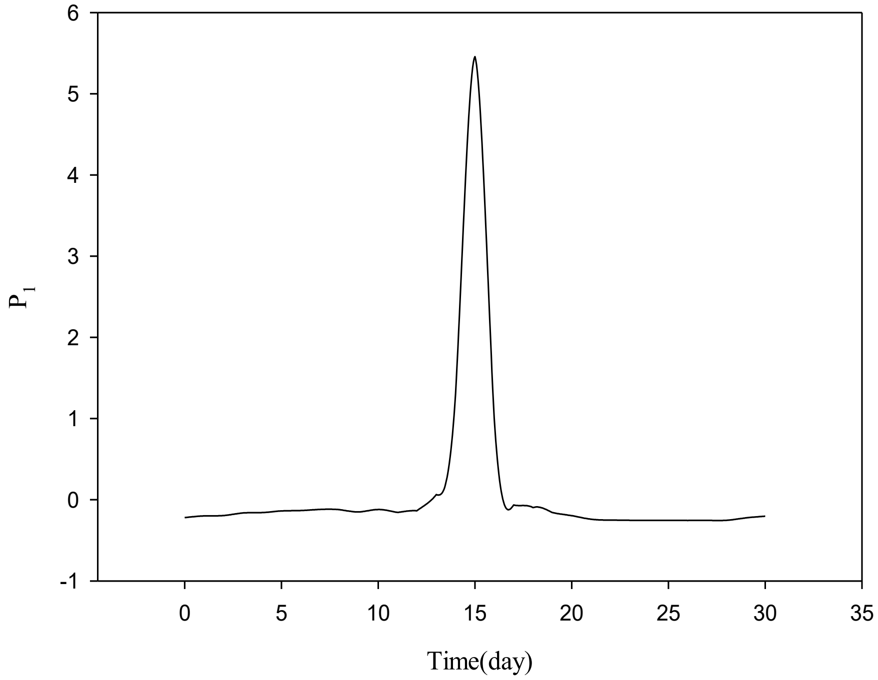


Figure 4.4: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.08, k_2=0.07 , k_3=0.13, k_4=0.027 , α=0.7736 , β=0.6, $k_4 < k_3$

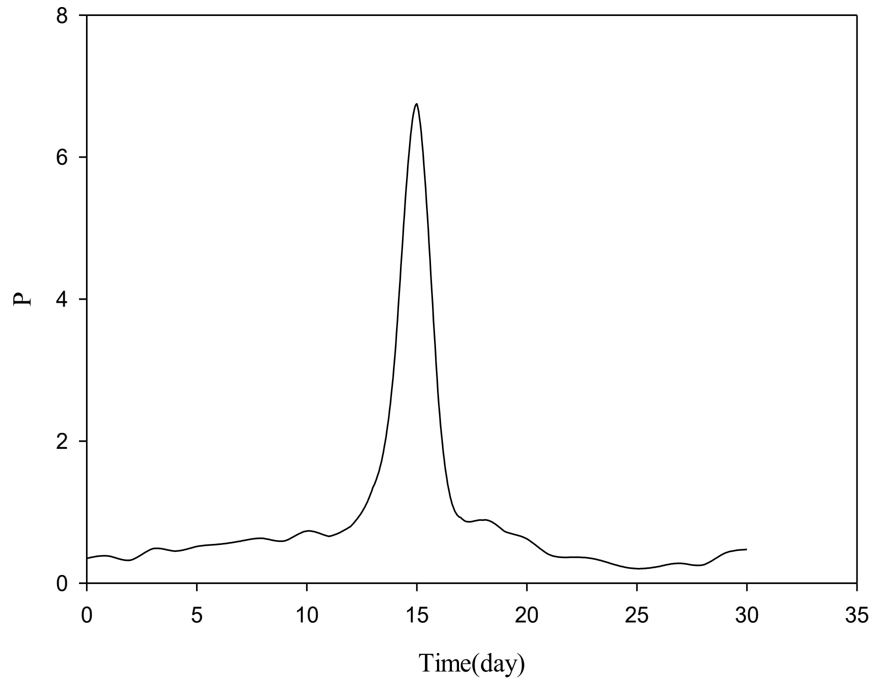


Figure 4.5: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.0045, k_2=0.077 , k_3=0.006, k_4=0.008 , α=0.79 , β=0.16, $k_2 > k_1$

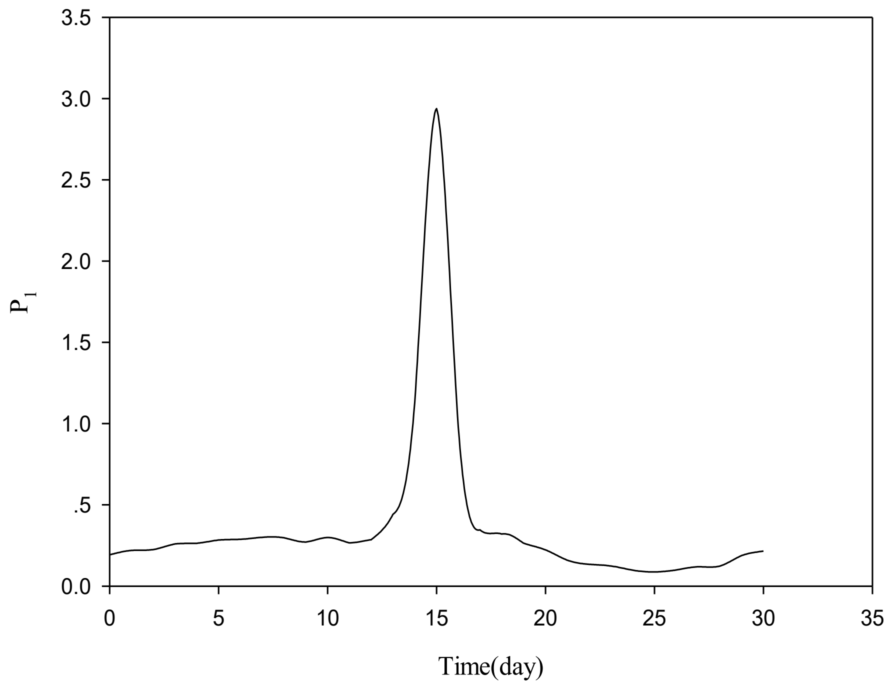


Figure 4.6: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.0045, k_2=0.077 , k_3=0.006, k_4=0.008 , α=0.79 , β=0.16, k_4>k_3

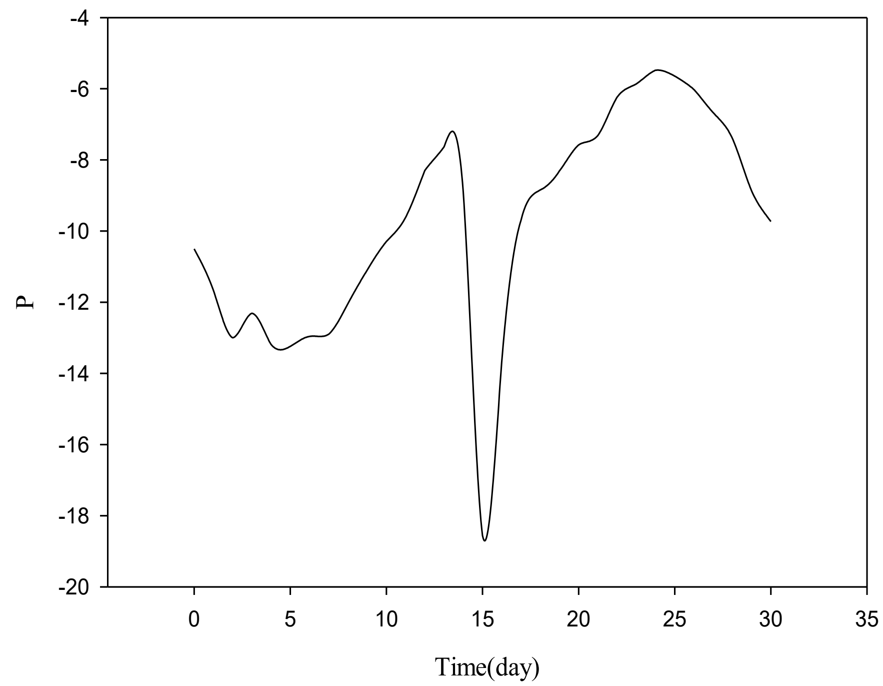


Figure 4.7: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.08, k_2=0.07 , k_3=0.13, k_4=0.027 , α=0.79 , β=0.16, k_2<k_1

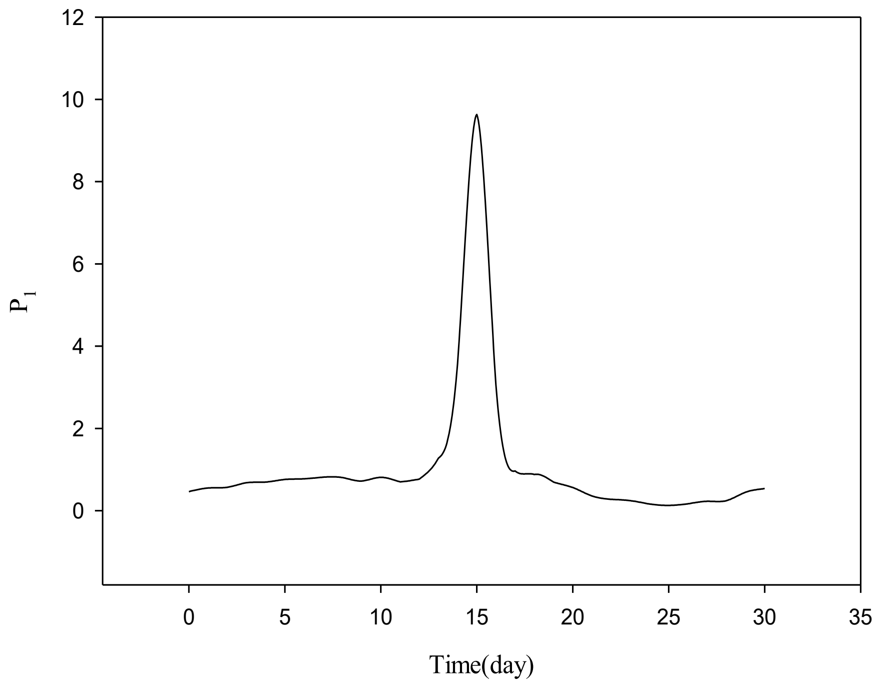


Figure 4.8: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.08, k_2=0.07 , k_3=0.13, k_4=0.027 , α=0.79 , β=0.16, k_4<k_3

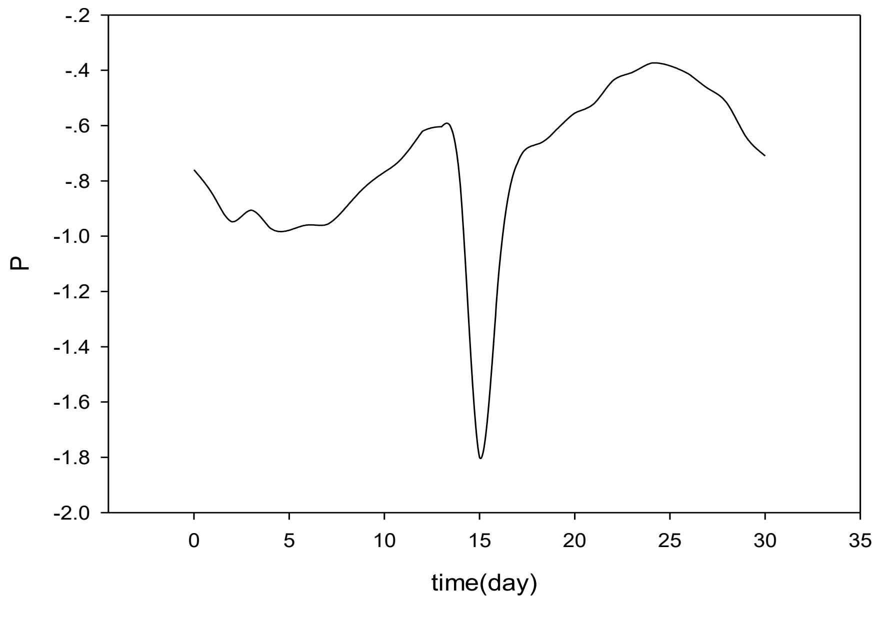


Figure 4.9: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.0058, k_2=0.048 , k_3=0.004, k_4=0.0061 , α=0.1 , β=0.06, k_4>k_3, k_2>k_1

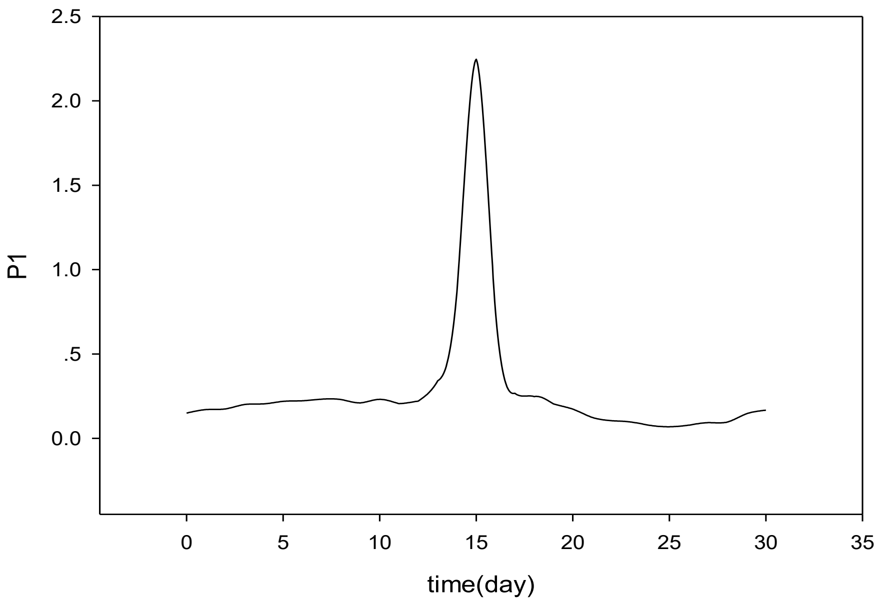


Figure 4.10: Graphs of parameters corresponding to the equilibrium conditions of stability on: k_1=0.0058, k_2=0.048 , k_3=0.004, k_4=0.0061 , α=0.1 , β=0.06, $k_4>k_3$, $k_2>k_1$

The graphs above show that the parameters for a balance that makes compliance with the conditions of stability on $k_2 < k_1$ means to create a mathematical model of the period. The parameters should be set in accordance with the conditions mentioned above. The above provisions apply to writing the form of the theories below.

Theorem 4.1 Assume that:

$$w_{01} = \frac{k_2(LH^*)^{\alpha}}{k_1 FSH^*} \text{ and } w_{02} = \frac{k_4 LH^*}{k_3(LH^*)^{\beta}}.$$

If $w_{01} > 1$ and $w_{02} > 1$, then the positive steady state $E(LH^*, PL^*_{LH}, FSH^*, PL^*_{FSH}, Mfs^*, Sfs^*, Pfs^*, Sv^*_1, Sv^*_2, Co^*_1, Co^*_2, Co^*_3, Co^*_4)$
is a locally stable state.

Proof. The Jacobian matrix of eqs. (1) - (13) at:

$$E(LH^*, PL_{LH}^*, FSH^*, PL_{FSH}^*, Mfs^*, Sfs^*, Pfs^*, Sv_1^*, Sv_2^*, Co_1^*, Co_2^*, Co_3^*, Co_4^*)$$ is

$$J=\begin{bmatrix}
\frac{-k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)} & -vA_{LH} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{-k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2} & -vA_{FSH} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -k_2\alpha\left(LH^*\right)^{\alpha-1}Mfs^* & 0 & b+k_1Mfs^* & k_1FSH^*-k_2\left(LH^*\right)^{\alpha} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_2\alpha\left(LH^*\right)^{\alpha-1}Mfs^*+\left[k_3\beta\left(LH^*\right)^{\beta-1}-k_4\right]Sfs^* & 0 & 0 & k_2\left(LH^*\right)^{\alpha} & k_3\left(LH^*\right)^{\beta}-k_4LH^* & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_4Sfs^*-k_5\gamma\left(LH^*\right)^{\gamma-1}Pfs^* & 0 & 0 & 0 & k_4LH^* & -k_5\left(LH^*\right)^{\gamma} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_5\gamma\left(LH^*\right)^{\gamma-1}Pfs^* & 0 & 0 & 0 & 0 & k_5\left(LH^*\right)^{\gamma} & -k_6 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & k_6 & -k_7 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_7 & -k_8 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_8 & -k_9 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_9 & -k_{10} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{10} & -k_{11}
\end{bmatrix}$$

.

The characteristic equation is defined by $\det\left(J_E-\lambda I_{13}\right)=0$, where I_{13} is the 13×13 identity matrix:

$$\left(\lambda+\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)}\right)\left(\lambda+\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2}\right)\left(\lambda+vA_{LH}\right)\left(\lambda+vA_{FSH}\right)$$
$$\left(\lambda+k_2LH^{*\alpha}-k_1FSH^*\right)\left(\lambda+k_4LH^*-k_3LH^{*\beta}\right)\left(\lambda+k_5LH^{*\gamma}\right)\left(\lambda+k_6\right)\left(\lambda+k_7\right)\left(\lambda+k_8\right)$$
$$\left(\lambda+k_9\right)\left(\lambda+k_{10}\right)\left(\lambda+k_{11}\right)=0 \qquad (27)$$

From the characteristic equation (27), eigenvalues are given by:

$$\lambda_1 = \frac{-k_{LH}\left[1+cl_{LH,p}P(t)\right]}{1+cl_{LH,E}E(t)}, \quad \lambda_2 = -vA_{LH}, \quad \lambda_3 = \frac{-k_{FSH}\left[1+cl_{FSH,p}P(t)\right]}{1+cl_{FSH,E}\left[E(t)\right]^2},$$

$\lambda_4 = -vA_{FSH}$, $\lambda_5 = k_1 FSH^* - k_2 LH^{*\alpha}$, $\lambda_6 = k_3 LH^{*\beta} - k_4 LH^*$,

$\lambda_7 = -k_5 LH^{*\gamma}$, $\lambda_8 = -k_6$, $\lambda_9 = -k_7$,

$\lambda_{10} = -k_8$, $\lambda_{11} = -k_9$, $\lambda_{12} = -k_{10}$,

$\lambda_{13} = -k_{11}$

The steady state is a locally stable state when all eigenvalues have negative real parts. From the above eigenvalues, we can see that all eigenvalues have negative signs except λ_5 and λ_6. Consider λ_5 and λ_6:

$$\lambda_5 = k_1 FSH^* - k_2 LH^{*\alpha} < 0 \text{ when } w_{01} > 1 \quad (28)$$

$$\lambda_6 = k_3 LH^{*\beta} - k_4 LH^* < 0 \text{ when } w_{02} > 1 . \quad (29)$$

We can see that (28) and (29) are satisfied when $w_{01} > 1$ and $w_{02} > 1$.

Thus, the steady states are locally stable when $w_{01} > 1$ and $w_{02} > 1$. In the next section, we show the numerical results of the model.

4.3 Numerical results

In this section, we analyze the model given by equations (1) - (13). The trajectories of the solutions when the parameter values lead to equilibrium state are shown in fig. 4.11-4.23. The parameters used in this study are:

$K_{aLH,p} = 31.22$ ng/mL, $k_{LH} = 2.49$ day^{-1}, $V_{1,LH} = 1263.4$ IU/day, $\beta = 0.1566$,

$cl_{LH,p} = 0.07$ mL/ng, $cl_{LH,E} = 0.0049$ mL/pg, $A_{LH} = 14$ day^{-1}, $\gamma = 0.0202$,

$A_{FSH} = 8.21$ day^{-1}, $V_{FSH} = 5700$ IU/day, $K_{aFSH,Ac} = 641$ IU/mL, $\alpha = 0.7736$,

$k_{FSH} = 7.29$ day^{-1}, $cl_{FSH,p} = 644$mL/ng, $cl_{FSH,E} = 0.16$ mL/pg

corresponding to the study of [11], $K_{nLH} = 360$pg/mL, $V_{2,LH} = 91000$ IU/day,

LH[0]=40, PL_{LH}[0]=12, FSH[0]=20, PL_{FSH}[0]=11Mfs[0]=5 $Co_1[0]=1$, $Co_2[0]=1$,

$Co_3[0]=1$, $Co_4[0]=1$.

Numerical Solutions:

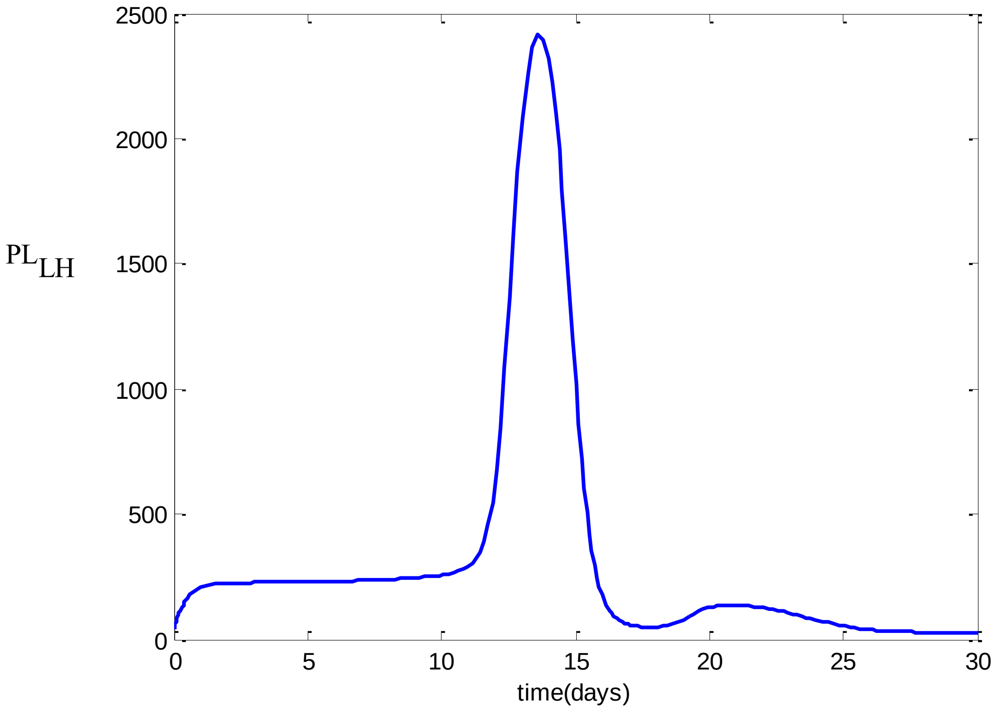


Figure 4.11: The graph shows the proportion of PL_{LH} with time. PL_{LH} is the highest volume on day 13 of the menstrual cycle.

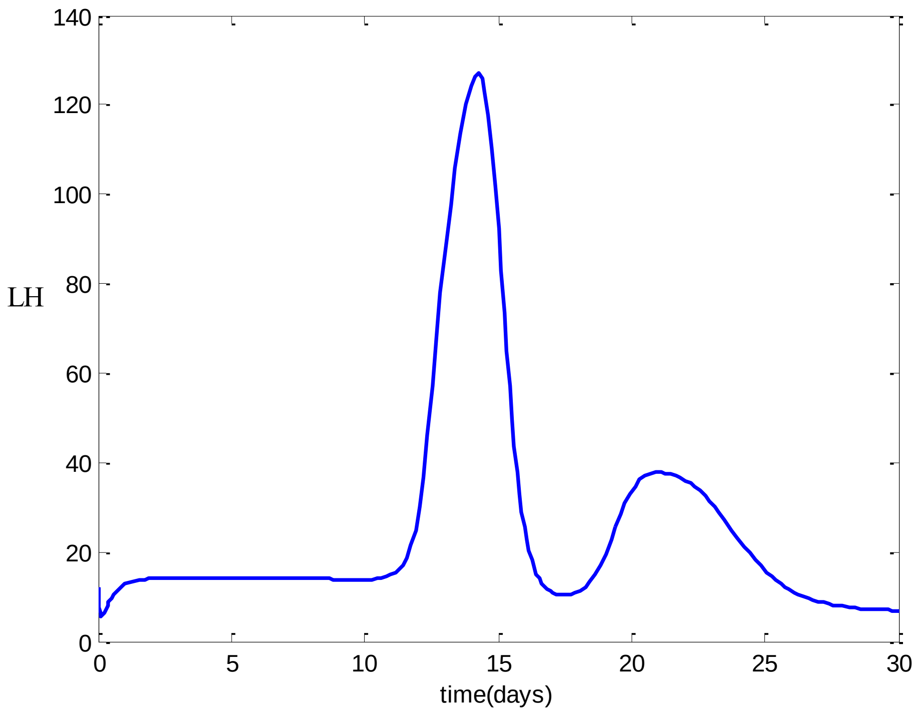


Figure 4.12: The graph shows the proportion of LH with time. LH is the highest volume on the 14th day, which is the stage of late follicular phase.

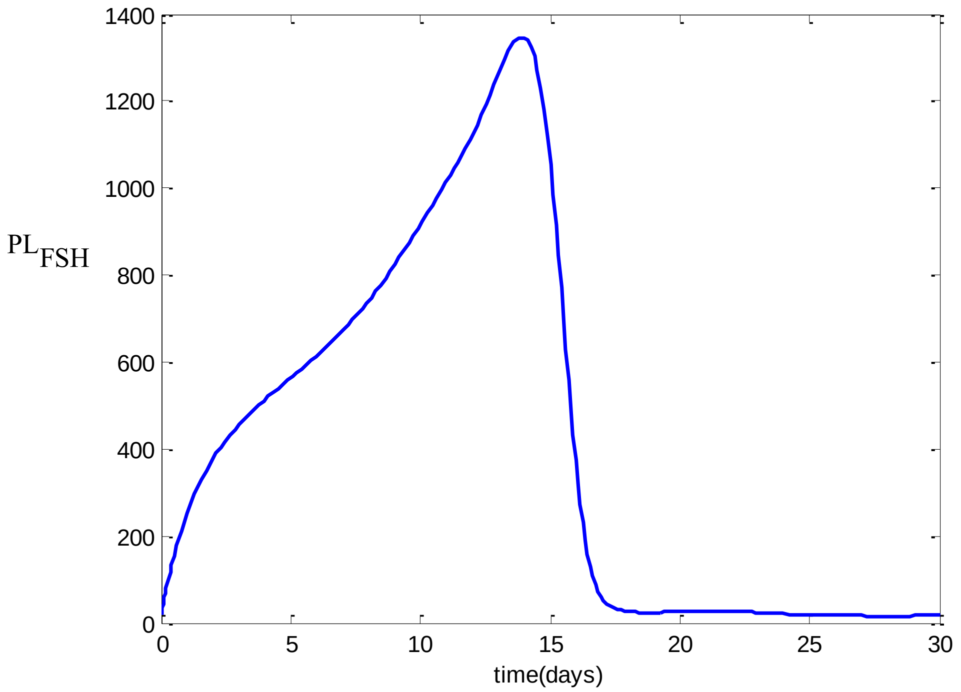


Figure 4.13: The graph shows the proportion of PL_{FSH} with time. PL_{FSH} is the highest volume on day 13 of the menstrual cycle.

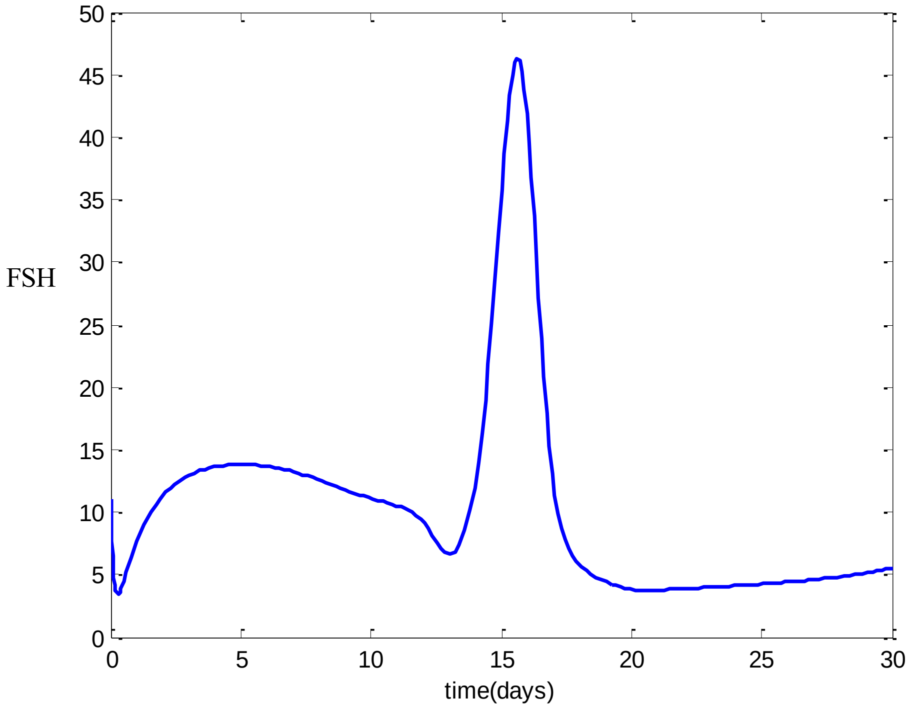


Figure 4.14: The graph shows the proportion of FSH with time. FSH is the highest volume on the 14th day, which is the stage of late follicular phase.

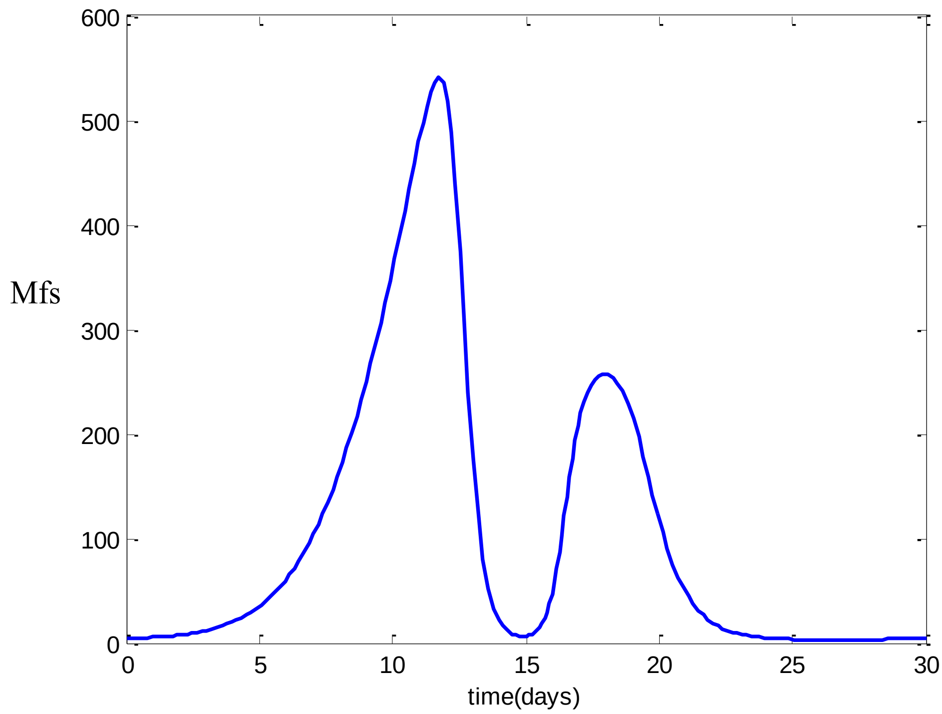


Figure 4.15: The graph shows the proportion of Mfs with time. Mfs is the highest volume on day 12 of the menstrual cycle.

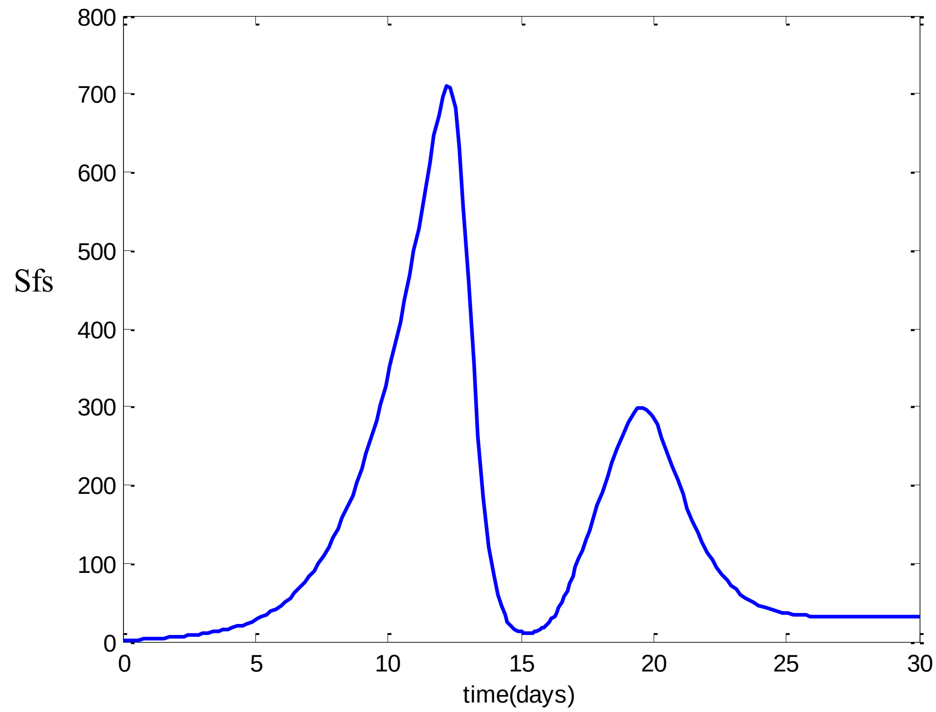


Figure 4.16: The graph shows the proportion of Sfs with time. Sfs is the highest volume on day 12 of the menstrual cycle.

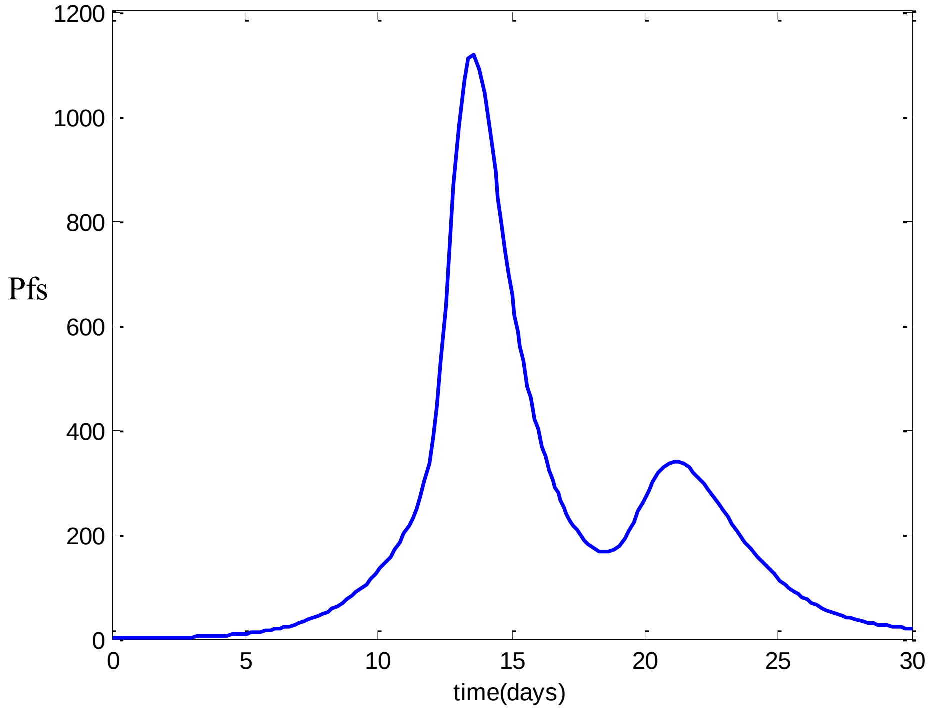


Figure 4.17: The graph shows the proportion of Pfs with time. Pfs is the highest volume on day 14 of the menstrual cycle.

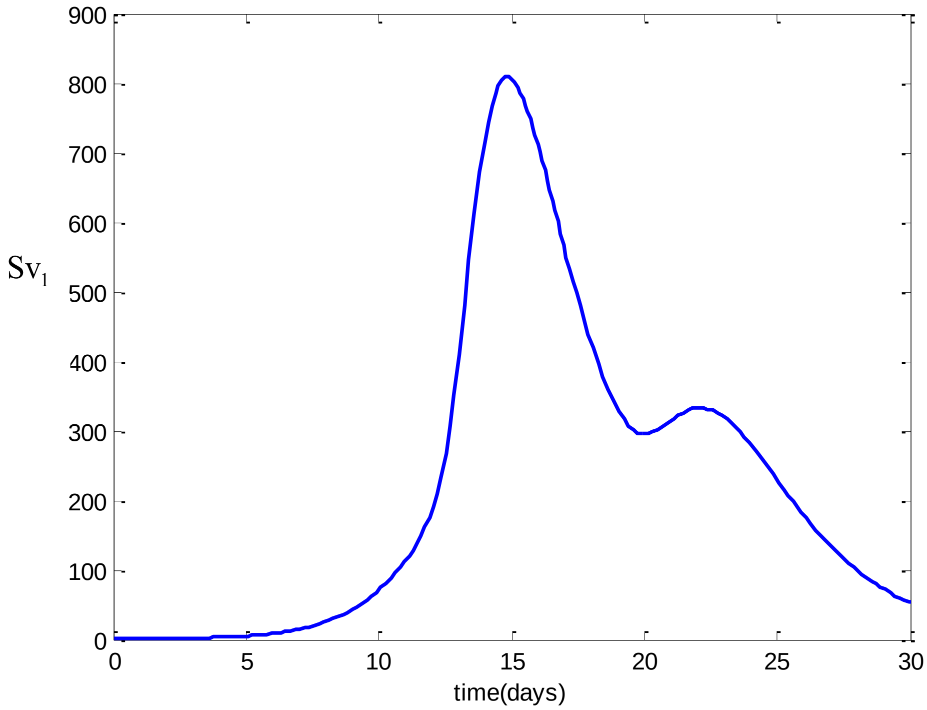


Figure 4.18: The graph shows the proportion of Sv_1 with time. Sv_1 is the highest volume on day 15 of the menstrual cycle.

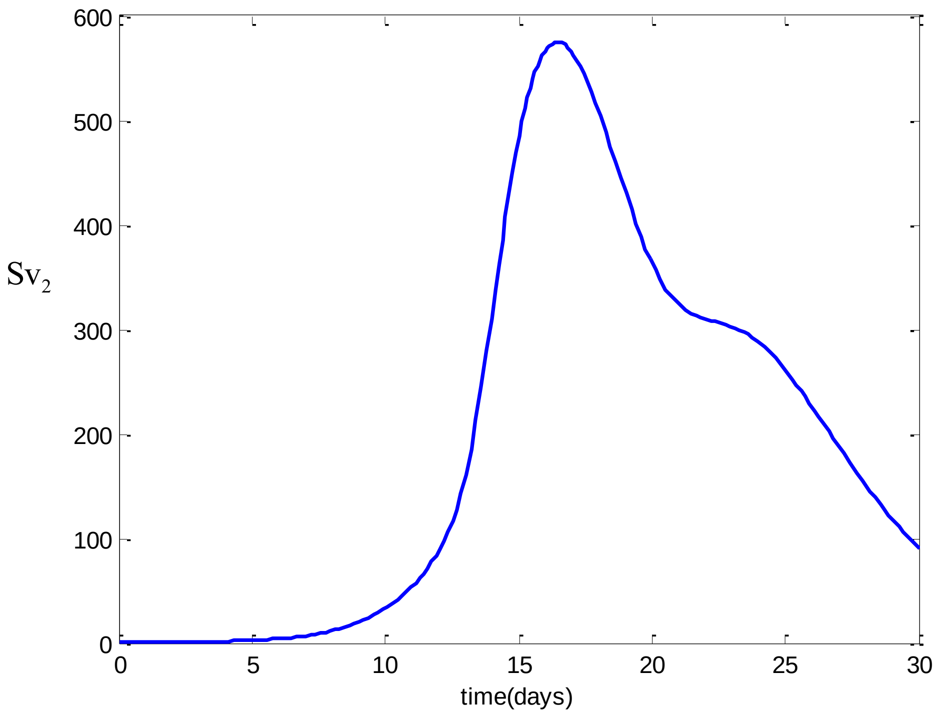


Figure 4.19: The graph shows the proportion of Sv_2 with time. Sv_2 is the highest volume on day 17 of the menstrual cycle.

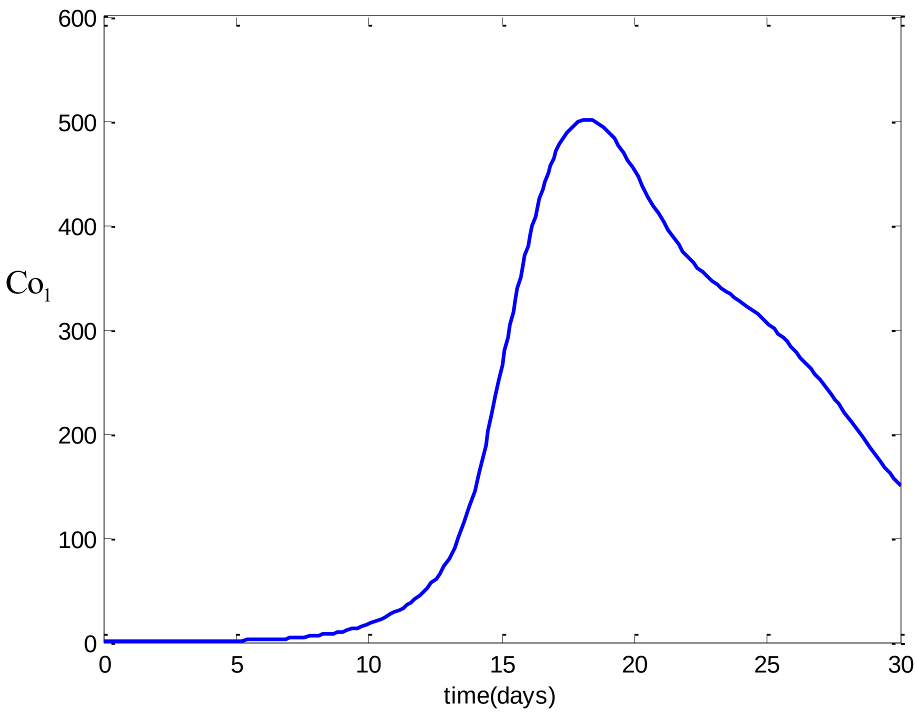


Figure 4.20: The graph shows the proportion of Co_1 with time. Co_1 is the highest volume on day 17 of the menstrual cycle.

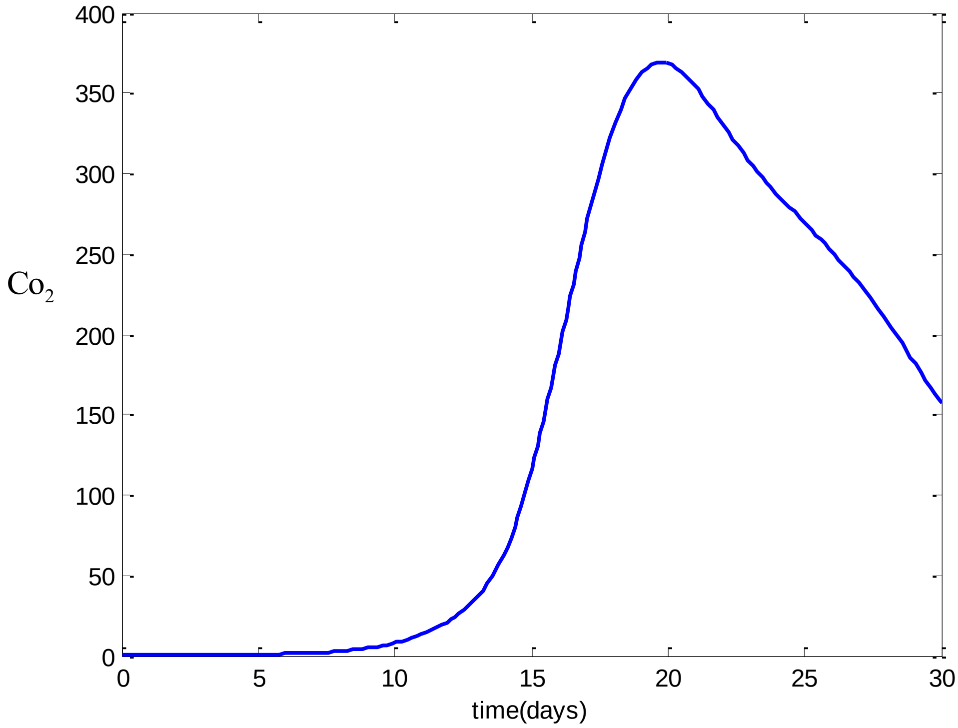


Figure 4.21: The graph shows the proportion of Co_2 with time. Co_2 is the highest volume on day 20 of the menstrual cycle.

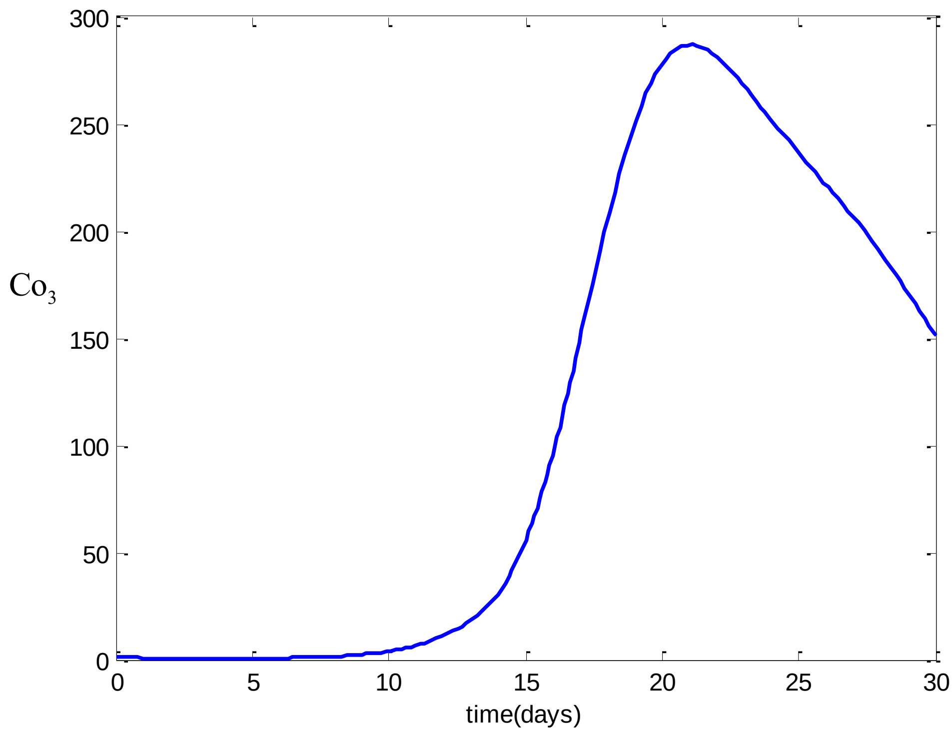


Figure 4.22: The graph shows the proportion of Co_3 with time. Co_3 is the highest volume on day 21 of the menstrual cycle.

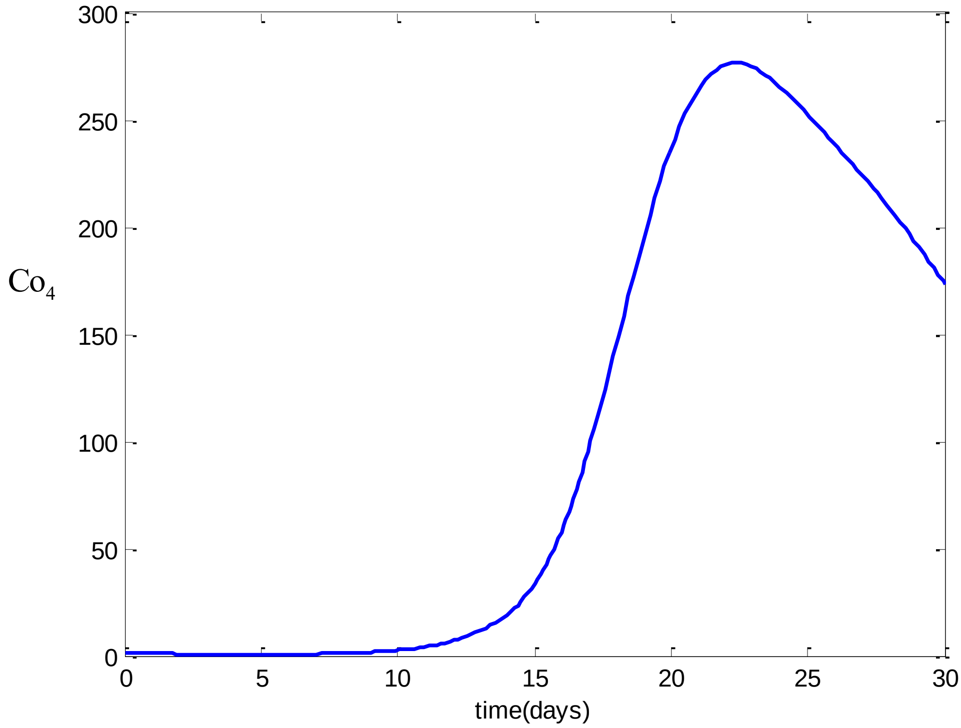


Figure 4.23: The graph shows the proportion of Co_4 with time. Co_4 is the highest volume on day 22 of the menstrual cycle.

The time series solutions of eqs. (1) to eqs. (13) are shown in fig. 4.11 to 4.23. The simulation outputs are calculated at 31 days .The values of parameters are: $K_{aLH,p} = 31.22\,ng/mL$, $k_{LH} = 2.49\ day^{-1}$, $V_{1,LH} = 1263.4\ IU/day$, $cl_{LH,p} = 0.07\,mL/ng$, $cl_{LH,E} = 0.0049\ mL/pg$, $A_{LH} = 14\ day^{-1}$, $A_{FSH} = 8.21\ day^{-1}$, $V_{FSH} = 5700\ IU/day$, $K_{aFSH,Ac} = 641\ IU/mL$, $k_{FSH} = 7.29\ day^{-1}$, $cl_{FSH,p} = 644mL/ng$, $\gamma = 0.0202$, $\alpha = 0.7736$, $cl_{FSH,E} = 0.16\ mL/pg$ corresponding to the study of [11], $\beta = 0.1566$, $K_{nLH} = 360pg/mL$, $V_{2,LH} = 91000\ IU/day$, Mfs[0]=5 $Co_1[0] = 1$, $Co_2[0] = 1$,$Co_3[0] = 1$, $Co_4[0] = 1$ LH[0]=40 , $PL_{LH}[0]$=12, FSH[0]=20,$PL_{FSH}[0]$=11, $Co_1[0] = 1$,$Co_2[0] = 1$, $Co_3[0] = 1$, $Co_4[0] = 1$

According to the outputs, a higher volume of Estradiol causes continuously higher LH during the 13th day, which is the stage of late follicular phase. FSH decreases to the minimum level on the 12th day of menstruation, considered as the lowest point of pre-ovulation period. The remaining graphs are the results from simulations.

Limit Cycles:

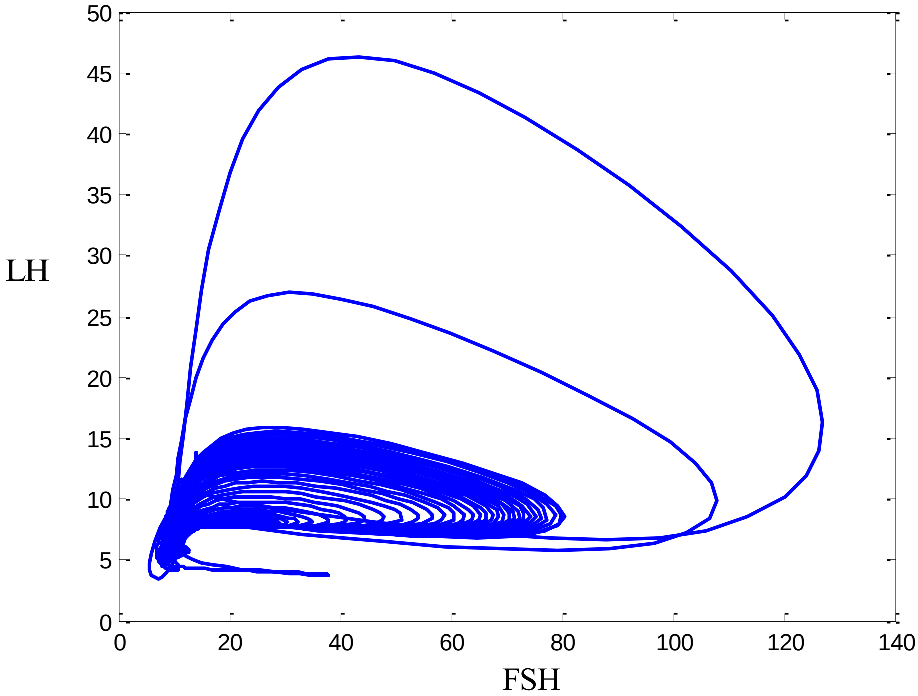


Figure 4.24: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space (FSH, LH).

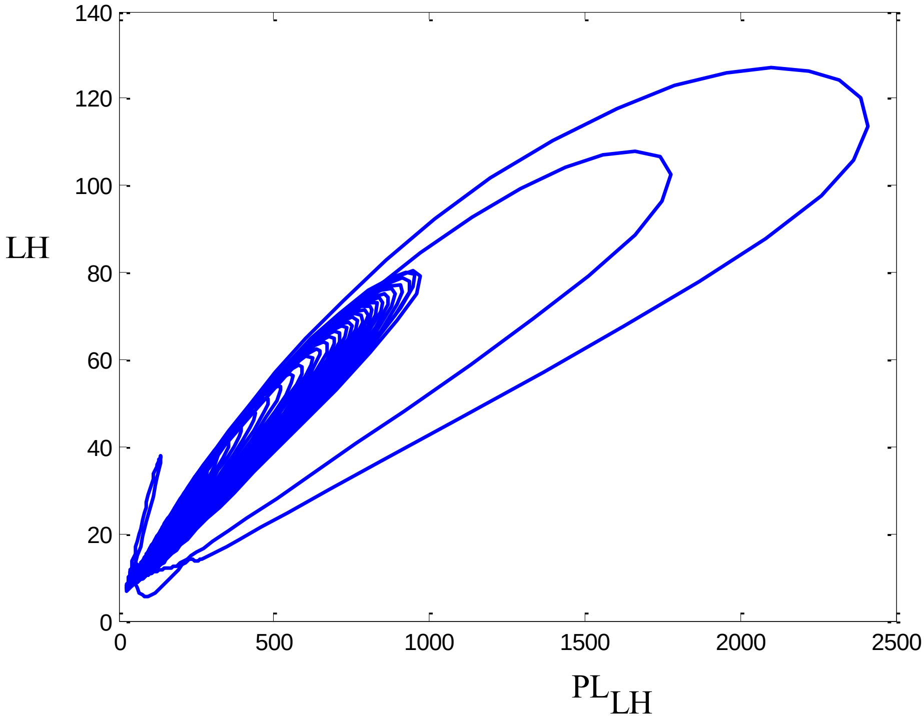


Figure 4.25: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space (PL_{LH}, LH).

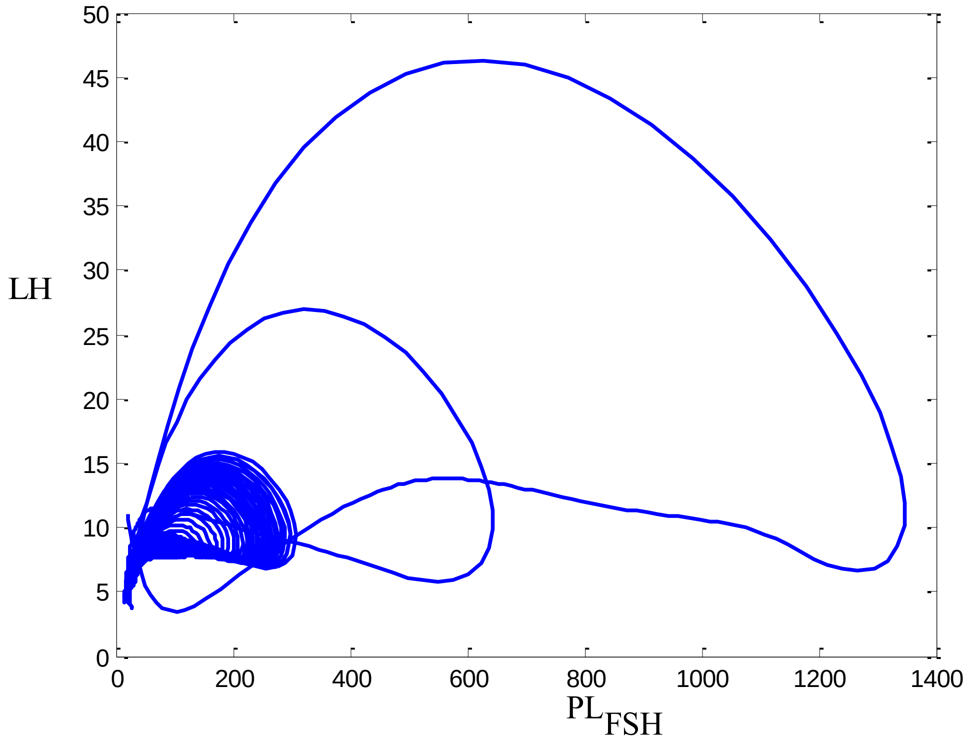


Figure 4.26: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space $\left(PL_{FSH}, LH\right)$.

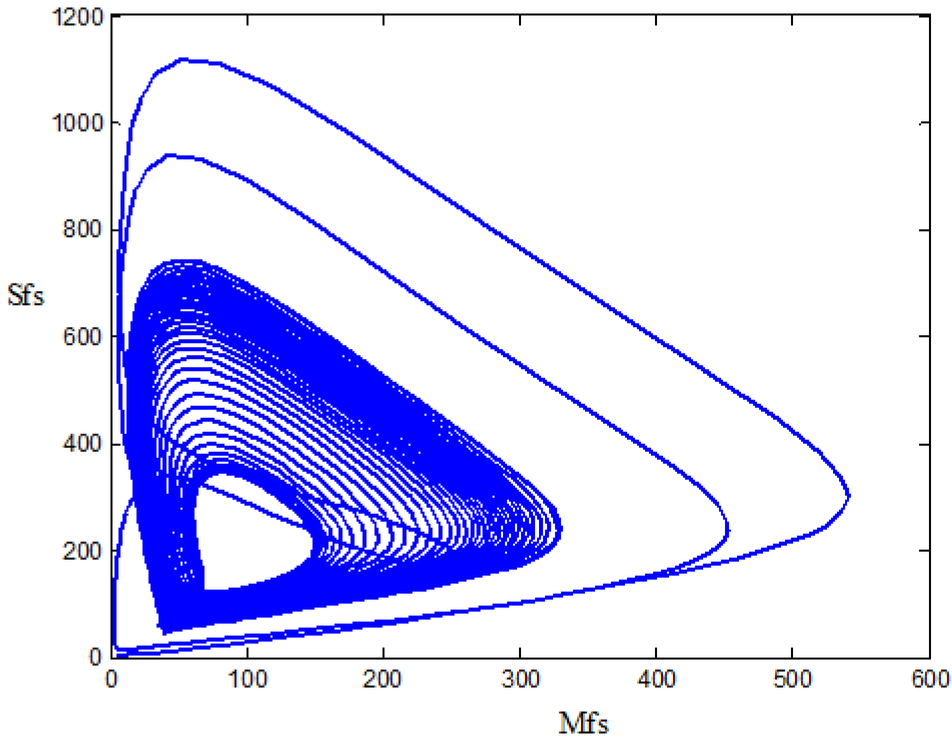


Figure 4.27: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space $\left(Mfs, Sfs\right)$.

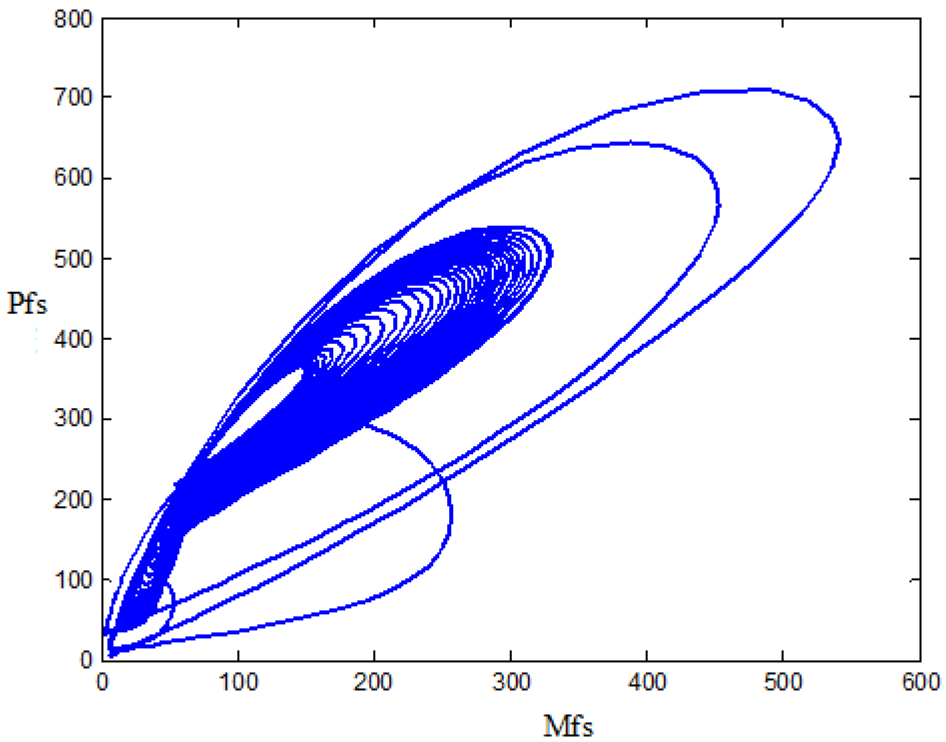


Figure 4.28: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space $(\mathrm{Mfs},\mathrm{Pfs})$.

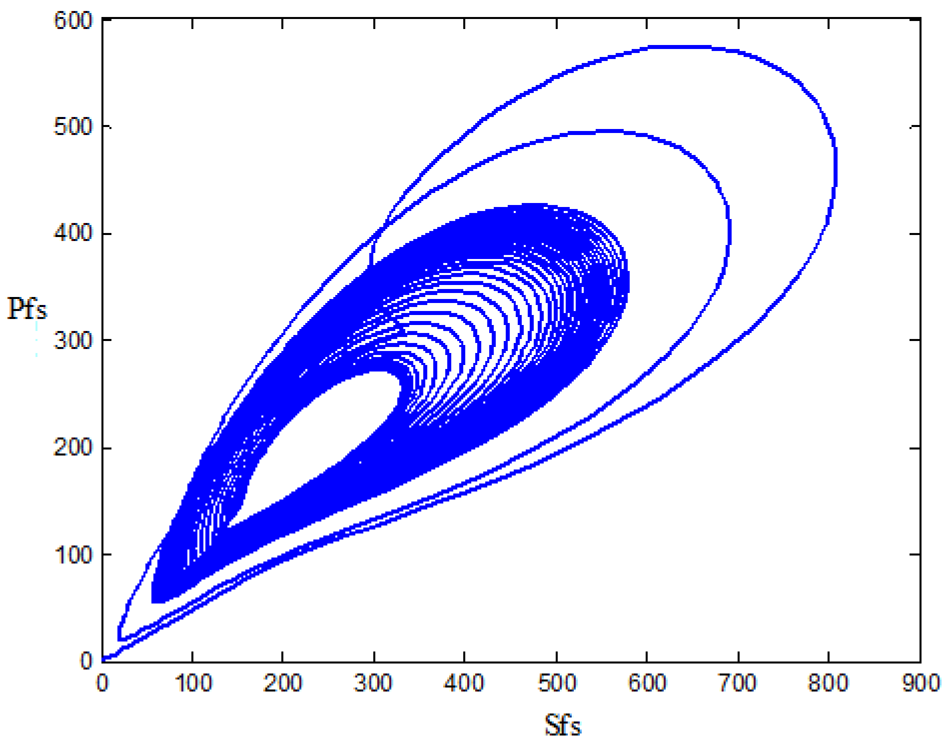


Figure 4.29: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space $(\mathrm{Sfs},\mathrm{Pfs})$.

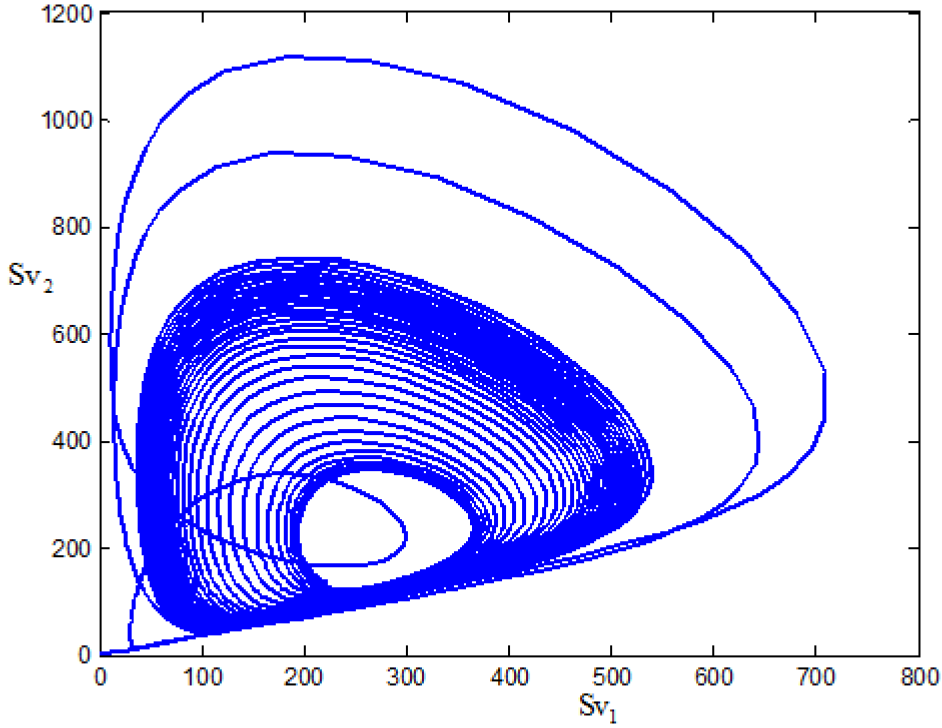


Figure 4.30: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space (Sv_1, Sv_2).

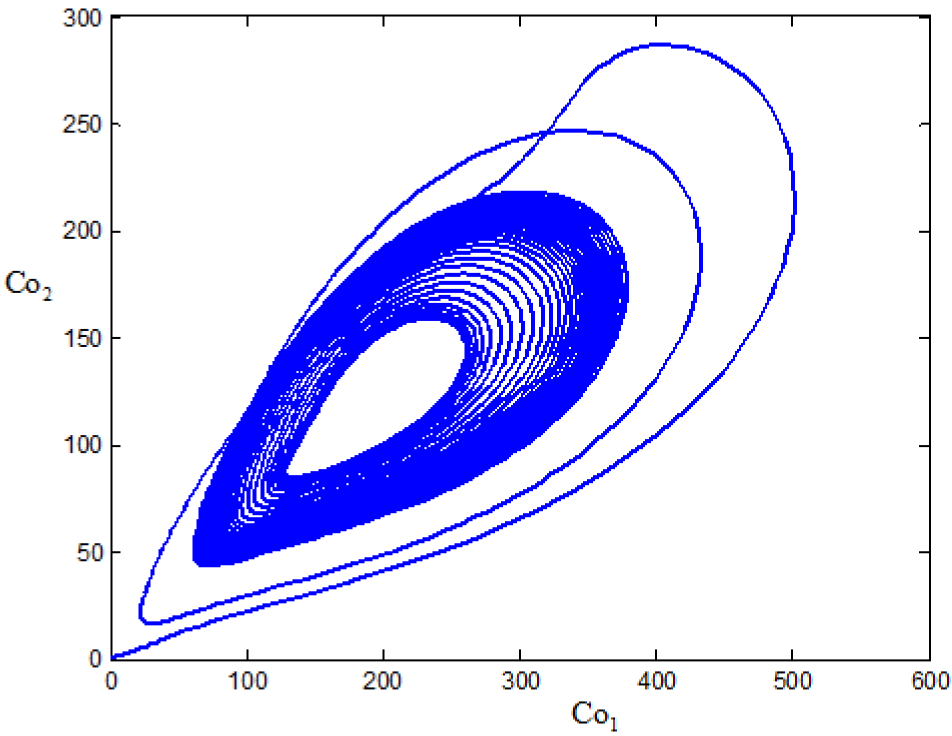


Figure 4.31: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space (Co_1, Co_2).

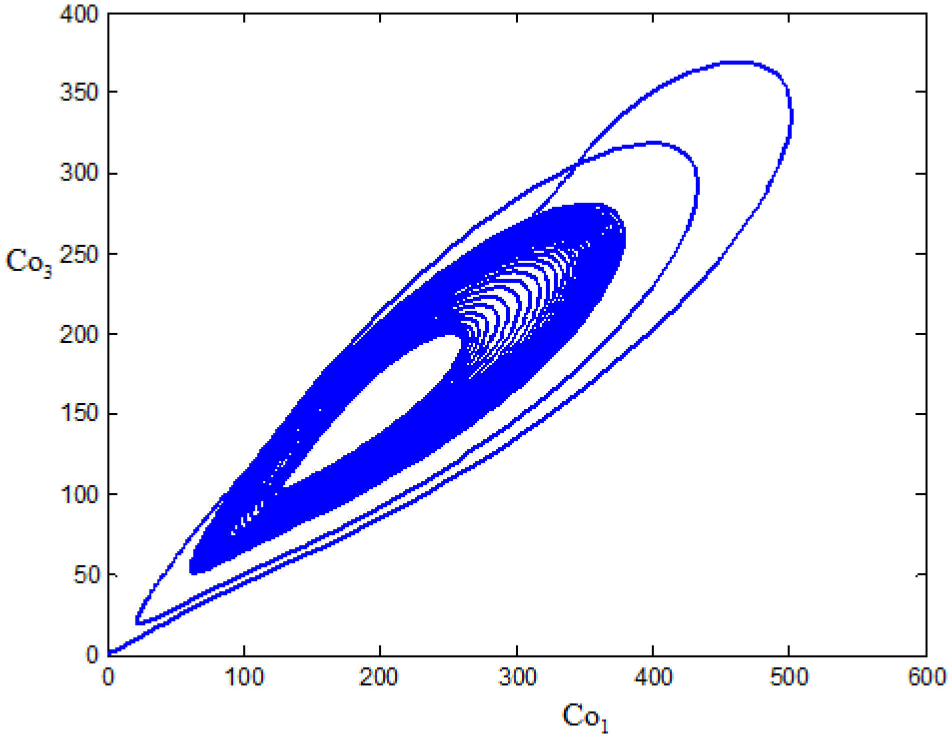


Figure 4.32: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space (Co_1, Co_3).

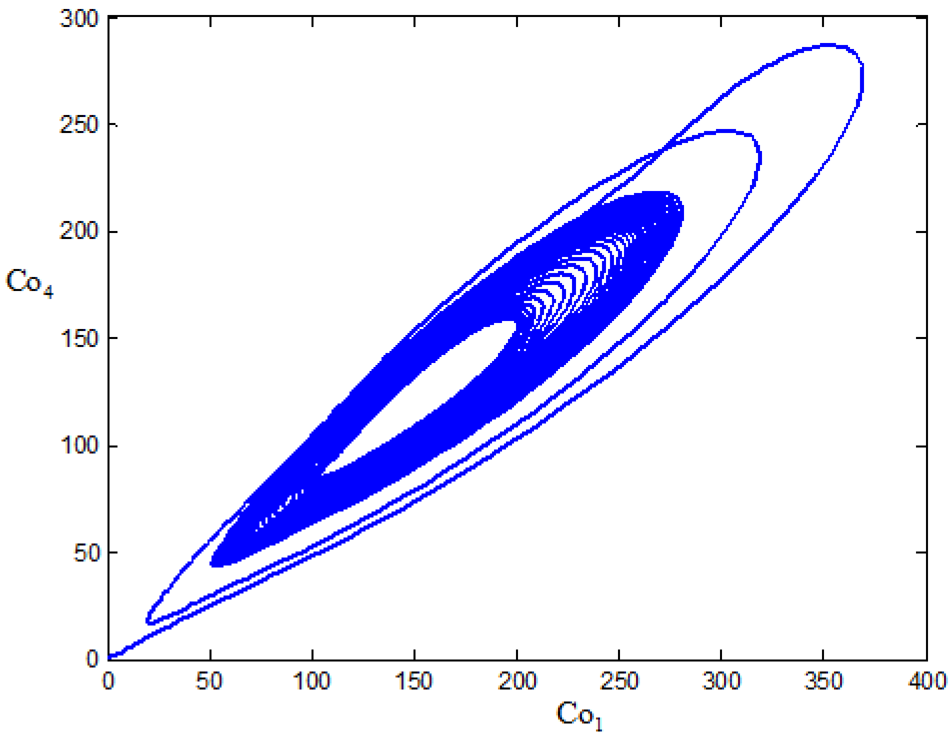


Figure 4.33: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space (Co_1, Co_4).

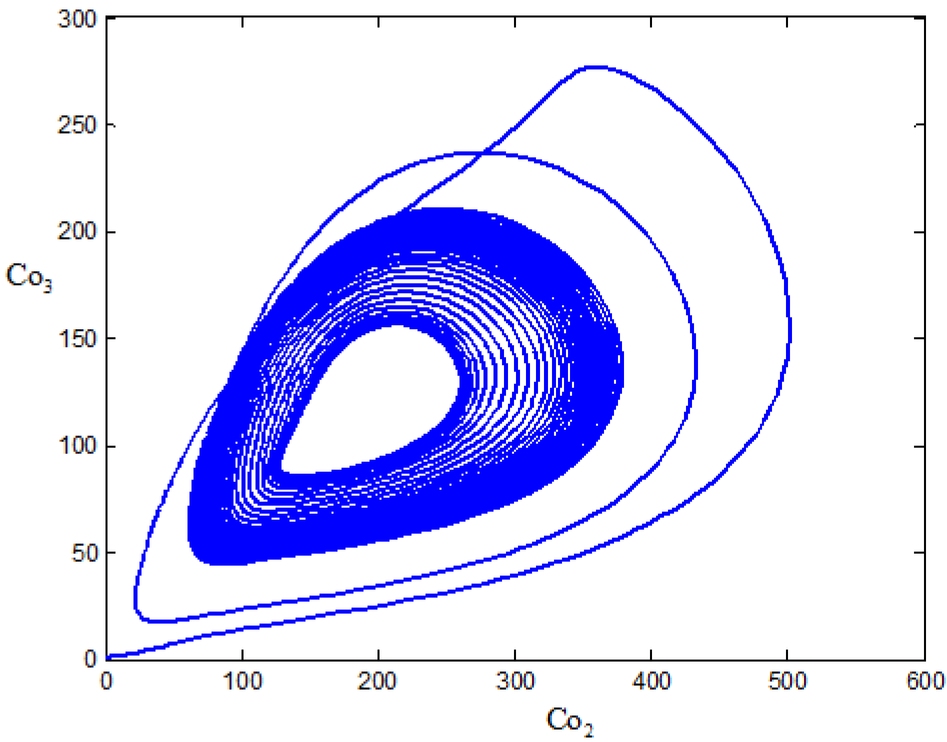


Figure 4.34: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space (Co_2, Co_3).

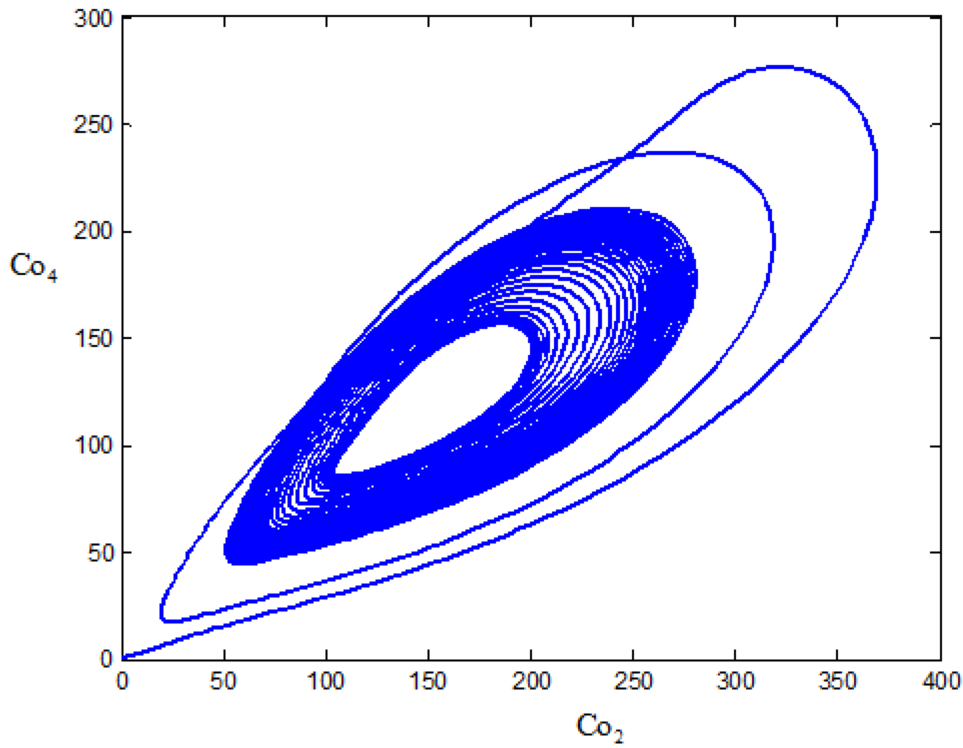


Figure 4.35: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space (Co_2, Co_4).

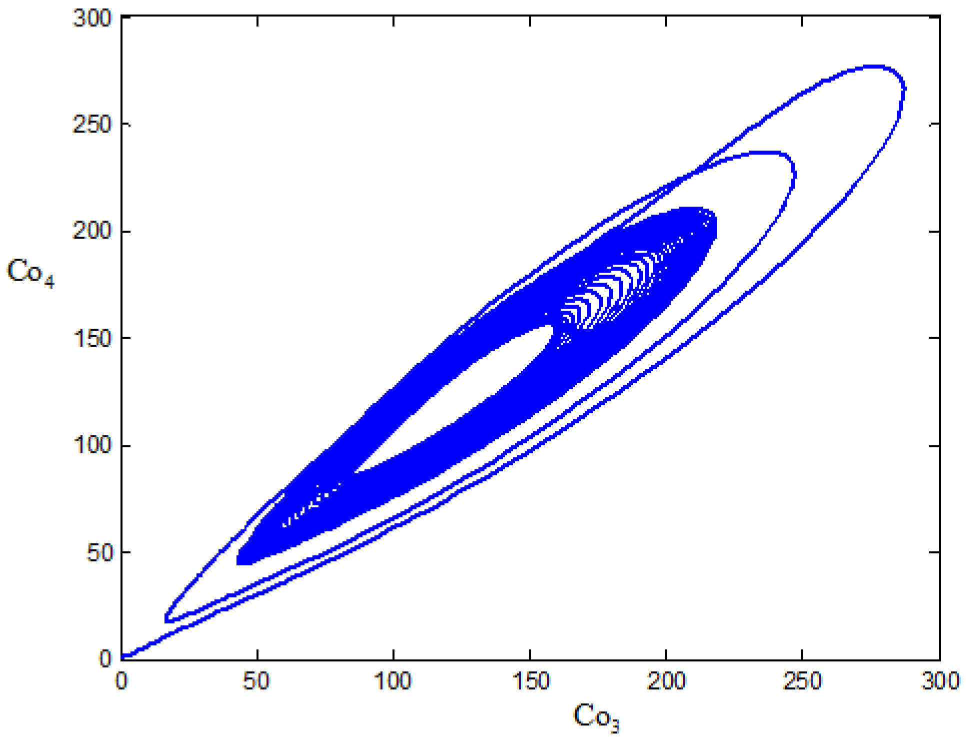


Figure 4.36: Numerical solutions demonstrate the solution trajectories, projected into the 2D-space $\left(Co_3, Co_4\right)$.

Numerical solutions that demonstrate the solution trajectories, projected into the 2D-space are shown in fig. 4.24 to 4.36. The limit cycles occur within the parameters,

$K_{nLH} = 360 pg/mL$, $K_{aLH,p} = 31.22$ ng/mL, $V_{2,LH} = 91000$ IU/day, $k_{LH} = 2.49$ day^{-1}, $V_{1,LH} = 1263.4$ IU/day, $cl_{LH,p} = 0.07$ mL/ng, $cl_{LH,E} = 0.0049$ mL/pg, $A_{LH} = 14$ day^{-1}, $A_{FSH} = 8.21$ day^{-1}, $\gamma = 0.0202$, $V_{FSH} = 5700$ IU/day, $K_{aFSH,Ac} = 641$ IU/mL, $\alpha = 0.7736$, $k_{FSH} = 7.29$ day^{-1}, $cl_{FSH,p} = 644$ mL/ng, $cl_{FSH,E} = 0.16$ mL/pg, $\beta = 0.1566$, and in accordance with conditions $w_{01} > 1$ and $w_{02} > 1$.The limit cycles can occur with a different set of parameters.

Moreover, for this model, we studied the global behavior of equilibrium points for the equations (1)-(13) by using Lyapunov functions.

Theorem 4.2 Assume that:

$$w_{01}=\frac{k_2(LH^*)^\alpha}{k_1FSH^*} \text{ and } w_{02}=\frac{k_4LH^*}{k_3(LH^*)^\beta},$$

if $w_{01}>1$ and $w_{02}>1$, then the positive steady state $E(LH^*, PL^*_{LH}, FSH^*, PL^*_{FSH}, Mfs^*, Sfs^*, Pfs^*, Sv_1^*, Sv_2^*, Co_1^*, Co_2^*, Co_3^*, Co_4^*)$ is globally asymptotically stable when it satisfies the following conditions:

$$\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^8}{\left[K_{nLH}\right]^8+\left[E(t)\right]^8}}{1+P(t)/K_{aLH,p}}-\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}>0$$

$$\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH>0$$

$$\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]MP_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^2}>0$$

$$\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^2}\right]-A_{FSH}FSH>0$$

Proof. Let us consider a possible Lyapunov function:

$$\psi(t)=\cos PL_{LH}+\cos LH+\cos PL_{FSH}+\cos FSH-Mfs-Sfs-Pfs-Sv_1-Sv_2-Co_1-Co_2-Co_3-Co_4$$

Its derivative along the trajectories of equations is given by:

$$\psi'(t)=-\sin PL_{LH}PL'_{LH}-\sin LH\,LH'-\sin PL_{FSH}PL'_{FSH}-\sin FSH\,FSH'-Mfs'-Sfs'-Pfs'-Sv'_1-Sv'_2-Co'_1-Co'_2-Co'_3-Co'_4 \quad (30)$$

We substitute:

$$PL'_{LH}, LH', PL'_{FSH}, FSH', Mfs', Sfs', Pfs', Sv'_1, Sv'_2, Co'_1, Co'_2, Co'_3, Co'_4$$

into (30). Thus, we obtain:

$$\psi'(t) = -\sin PL_{LH}\left(\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]MP_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH\right)$$

$$-\sin PL_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right)$$

$$-\sin FSH\left(\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right]-A_{FSH}FSH\right)$$

$$-\left(bFSH+\left[k_1FSH-k_2LH^{\alpha}\right]Mfs\right)-\left(k_2LH^{\alpha}Mfs+\left[k_3LH^{\beta}-k_4LH\right]Sfs\right)$$

$$-\left(k_4LHSfs-k_5LH^{\gamma}Pfs\right)-\left(k_5LH^{\gamma}Pfs-k_6Sv_1\right)-\left(k_6Sv_1-k_7Sv_2\right)$$

$$-\left(k_7Sv_2-k_8Co_1\right)-\left(k_8Co_1-k_9Co_2\right)-\left(k_9Co_2-k_{10}Co_3\right)-\left(k_{10}Co_3-k_{11}Co_4\right)$$

$$\psi'(t) = -\sin PL_{LH}\left(\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH\right)$$

$$-\sin PL_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right)$$

$$-\sin FSH\left(\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right]-A_{FSH}FSH\right)$$

$$-bFSH-\left[k_1FSH-k_2LH^{\alpha}\right]Mfs-k_2LH^{\alpha}Mfs-\left[k_3LH^{\beta}-k_4LH\right]Sfs$$

$$-k_4LHSfs+k_5LH^{\gamma}Pfs-k_5LH^{\gamma}Pfs+k_6Sv_1-k_6Sv_1+k_7Sv_2-k_7Sv_2$$

$$+k_8Co_1-k_8Co_1+k_9Co_2-k_9Co_2+k_{10}Co_3-k_{10}Co_3+k_{11}Co_4$$

$$\psi'(t) = -\sin PL_{LH}\left(\frac{V_{1,LH}+\frac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH\right)$$

$$-\sin PL_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right)$$

$$-\sin FSH\left(\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right]-A_{FSH}FSH\right)$$

$$-bFSH - k_1 FSHMfs + k_2 LH^{\alpha} Mfs - k_2 LH^{\alpha} Mfs - k_3 LH^{\beta} Sfs + k_4 LHSfs$$

$$-k_4 LHSfs + k_5 LH^{\gamma} Pfs - k_5 LH^{\gamma} Pfs + k_6 Sv_1 - k_6 Sv_1 + k_7 Sv_2 - k_7 Sv_2 + k_8 Co_1$$

$$-k_8 Co_1 + k_9 Co_2 - k_9 Co_2 + k_{10} Co_3 - k_{10} Co_3 + k_{11} Co_4$$

$$\psi'(t) = -\sin PL_{LH}\left(\frac{V_{1,LH}+\frac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH\right)$$

$$-\sin PL_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right)$$

$$-\sin FSH\left(\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right]-A_{FSH}FSH\right)$$

$$-bFSH - k_1 FSHMfs - k_3 LH^{\beta} Sfs + k_{11} Co_4$$

At the positive steady state:

$$E(LH^{*}, PL_{LH}^{*}, FSH^{*}, PL_{FSH}^{*}, Mfs^{*}, Sfs^{*}, Pfs^{*}, Sv_1^{*}, Sv_2^{*}, Co_1^{*}, Co_2^{*}, Co_3^{*}, Co_4^{*}),$$

we get:

$$\psi^{/}(t) = -\sin PL^{*}_{LH}\left(\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH^{*}\left(\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH^{*}\right)$$

$$-\sin PL^{*}_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right)$$

$$-\sin FSH^{*}\left(\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right]-A_{FSH}FSH^{*}\right)$$

$$-\left(b+\ k_{1}Mfs^{*}\right)FSH^{*}-k_{3}LH^{*\beta}Sfs^{*}+k_{11}Co^{*}_{4}$$

$$\psi^{/}(t) = -\sin PL^{*}_{LH}\left(\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH^{*}\right)$$

$$-\sin PL^{*}_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right)$$

$$-\sin FSH^{*}\left(\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right]-A_{FSH}FSH^{*}\right)$$

$$-b\,FSH^{*}-\frac{k_{1}b\left(FSH^{*}\right)^{2}}{k_{2}(LH^{*})^{\alpha}-k_{1}FSH^{*}}-\frac{k_{3}bFSH^{*}k_{2}(LH^{*})^{\alpha+\beta}}{\left(k_{2}(LH^{*})^{\alpha}-k_{1}FSH^{*}\right)\left(k_{4}LH^{*}-k_{3}(LH^{*})^{\beta}\right)}$$

$$+\frac{k_{4}bFSH^{*}k_{2}(LH^{*})^{1+\alpha}}{\left(k_{2}(LH^{*})^{\alpha}-k_{1}FSH^{*}\right)\left(k_{4}LH^{*}-k_{3}(LH^{*})^{\beta}\right)}$$

$$\psi^{/}(t) = -\sin PL^{*}_{LH}\left(\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH^{*}\right)$$

$$-\sin PL^{*}_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right)$$

$$-\sin FSH^{*}\left(\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right]-A_{FSH}FSH^{*}\right)$$

$$+\frac{-b\,FSH^{*}\left(k_2(LH^{*})^{\alpha}-k_1FSH^{*}\right)\left(k_4LH^{*}-k_3(LH^{*})^{\beta}\right)}{\left(k_2(LH^{*})^{\alpha}-k_1FSH^{*}\right)\left(k_4LH^{*}-k_3(LH^{*})^{\beta}\right)}$$

$$\frac{-k_1b\left(FSH^{*}\right)^{2}\left(k_4LH^{*}-k_3(LH^{*})^{\beta}\right)-k_3bFSH^{*}k_2(LH^{*})^{\alpha+\beta}+k_4bFSH^{*}k_2(LH^{*})^{1+\alpha}}{\left(k_2(LH^{*})^{\alpha}-k_1FSH^{*}\right)\left(k_4LH^{*}-k_3(LH^{*})^{\beta}\right)}$$

$$\psi^{/}(t) = -\sin PL^{*}_{LH}\left(\frac{V_{1,LH}+\dfrac{V_{2,LH}\left[E(t)\right]^{8}}{\left[K_{nLH}\right]^{8}+\left[E(t)\right]^{8}}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}P(t)\right]PL^{*}_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH^{*}\right)$$

$$-\sin PL^{*}_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right)$$

$$-\sin FSH^{*}\left(\frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}P(t)\right]PL^{*}_{FSH}}{1+cl_{FSH,E}\left[E(t)\right]^{2}}\right]-A_{FSH}FSH^{*}\right)$$

$$+\frac{-k_4k_2b\,FSH^{*}(LH^{*})^{\alpha+1}+k_3k_2b\,FSH^{*}(LH^{*})^{\alpha+\beta}+k_1k_4b\,LH^{*}\left(FSH^{*}\right)^{2}-k_1k_3b(LH^{*})^{\beta}\left(FSH^{*}\right)^{2}-k_4LH^{*}k_1b\left(FSH^{*}\right)^{2}}{\left(k_2(LH^{*})^{\alpha}-k_1FSH^{*}\right)\left(k_4LH^{*}-k_3(LH^{*})^{\beta}\right)}$$

$$+\frac{k_3(LH^{*})^{\beta}k_1b\left(FSH^{*}\right)^{2}-k_3bFSH^{*}k_2(LH^{*})^{\alpha+\beta}+k_4bFSH^{*}k_2(LH^{*})^{1+\alpha}}{\left(k_2(LH^{*})^{\alpha}-k_1FSH^{*}\right)\left(k_4LH^{*}-k_3(LH^{*})^{\beta}\right)}$$

$$\psi'(t) = -\sin PL^*_{LH}\left(\frac{V_{1,LH}+\dfrac{V_{2,LH}[E(t)]^8}{[K_{nLH}]^8+[E(t)]^8}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}[1+cl_{LH,p}P(t)]PL^*_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}[1+cl_{LH,p}P(t)]PL^*_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH^*\right)$$

$$-\sin PL^*_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}[1+cl_{FSH,p}P(t)]PL^*_{FSH}}{1+cl_{FSH,E}[E(t)]^2}\right)$$

$$-\sin FSH^*\left(\frac{1}{v}\left[\frac{k_{FSH}[1+cl_{FSH,p}P(t)]PL^*_{FSH}}{1+cl_{FSH,E}[E(t)]^2}\right]-A_{FSH}FSH^*\right)$$

$$+\frac{0}{\left(k_2(LH^*)^{\alpha}-k_1FSH^*\right)\left(k_4LH^*-k_3(LH^*)^{\beta}\right)}$$

$$\psi'(t) = -\sin PL^*_{LH}\left(\frac{V_{1,LH}+\dfrac{V_{2,LH}[E(t)]^8}{[K_{nLH}]^8+[E(t)]^8}}{1+P(t)/K_{aLH,p}} - \frac{k_{LH}[1+cl_{LH,p}P(t)]PL^*_{LH}}{1+cl_{LH,E}E(t)}\right)$$

$$-\sin LH\left(\frac{1}{v}\left[\frac{k_{LH}[1+cl_{LH,p}P(t)]PL^*_{LH}}{1+cl_{LH,E}E(t)}\right]-A_{LH}LH^*\right)$$

$$-\sin PL^*_{FSH}\left(\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}-\frac{k_{FSH}[1+cl_{FSH,p}P(t)]PL^*_{FSH}}{1+cl_{FSH,E}[E(t)]^2}\right)$$

$$-\sin FSH^*\left(\frac{1}{v}\left[\frac{k_{FSH}[1+cl_{FSH,p}P(t)]PL^*_{FSH}}{1+cl_{FSH,E}[E(t)]^2}\right]-A_{FSH}FSH^*\right)$$

We can see that all terms in the above equation are always negative. By using the Lyapunov's stability theorem [46], we have $\psi'(t) \le 0$, then the function $\psi'(t)$ is negative definite. LaSalle's invariant principle implies that the positive steady state:

$$E(LH^*, PL^*_{LH}, FSH^*, PL^*_{FSH}, Mfs^*, Sfs^*, Pfs^*, Sv^*_1, Sv^*_2, Co^*_1, Co^*_2, Co^*_3, Co^*_4)$$

is globally asymptotically stable.

CHAPTER 5

Mathematical model for the menstrual cycle with the effect of body mass index

In this chapter, we present a mathematical model of the menstrual cycle including the effect of obesity, which is a factor that causes an imbalance of hormones, and is one of the most common causes of irregular menstruation or dysmenorrhea.

5.1 Mathematical Model

We present a mathematical model for the menstrual cycle in accordance with the factors that cause abnormal hormone doses. The mathematical model for the menstrual cycle is formulated by defining the variables as follows.

$\frac{dMP_{LH}}{dt}$ is the rate of change for the mass of stored LH in the pituitary at time t,

$\frac{dLH}{dt}$ is the rate of change for the luteinizing hormone at time t,

$\frac{dMP_{FSH}}{dt}$ is the rate of change for the mass of stored FSH in the pituitary at time t,

$\frac{dFSH}{dt}$ is the rate of change for the follicle stimulating hormone at time t,

$\frac{dMMe}{dt}$ is the rate of change for the menstrual follicle state at time t,

$\frac{dMSe}{dt}$ is the rate of change for the secondary follicle state at time t,

$\frac{dMPe}{dt}$ is the rate of change for the preovulatory follicle state at time t,

$\frac{dMS_1}{dt}$ is the rate of change for the early ovulatory scar at time t,

$\frac{dMS_2}{dt}$ is the rate of change for the late ovulatory scar at time t,

$\frac{dMC_1}{dt}$ is the rate of change for the development stages of corpus luteum at time t,

$\frac{dMC_2}{dt}$ is the rate of change for the development stages of corpus luteum at time t,

$\frac{dMC_3}{dt}$ is the rate of change for the development stages of corpus luteum at time t,

$\frac{dMC_4}{dt}$ is the rate of change for the development stages of corpus luteum at time t.

Dynamical equations of the mathematical model for the menstrual cycle can be explained as follows:

$$\frac{dMP_{LH}}{dt} = \frac{V_{1,LH} + \dfrac{V_{2,LH}\left[Es(t)\right]^8}{\left[K_{nLH}\right]^8 + \left[Es(t)\right]^8}}{1+Pr(t)/K_{aLH,p}} - \frac{k_{LH}\left[1+cl_{LH,p}Pr(t)\right]MP_{LH}}{1+cl_{LH,E}Es(t)} \tag{1}$$

$$\frac{dLH}{dt} = \frac{1}{v}\left[\frac{k_{LH}\left[1+cl_{LH,p}Pr(t)\right]MP_{LH}}{1+cl_{LH,E}Es(t)}\right] - A_{LH}LH \tag{2}$$

$$\frac{dMP_{FSH}}{dt} = \frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}} - \frac{k_{FSH}\left[1+cl_{FSH,p}Pr(t)\right]MP_{FSH}}{1+cl_{FSH,E}\left[Es(t)\right]^2} \tag{3}$$

$$\frac{dFSH}{dt} = \frac{1}{v}\left[\frac{k_{FSH}\left[1+cl_{FSH,p}Pr(t)\right]MP_{FSH}}{1+cl_{FSH,E}\left[Es(t)\right]^2}\right] - A_{FSH}FSH \tag{4}$$

$$\frac{dMMe}{dt} = bFSH + \left[k_1FSH - k_2LH^{\alpha}\right]MMe \tag{5}$$

$$\frac{dMSe}{dt} = k_2LH^{\alpha}MMe + \left[k_3LH^{\beta} - k_4LH\right]MSe \tag{6}$$

$$\frac{dMPe}{dt}=k_4 LHMSe-k_5 LH^{\gamma} MPe \tag{7}$$

$$\frac{dMS_1}{dt}=k_5 LH^{\gamma} MPe-k_6 MS_1 \tag{8}$$

$$\frac{dMS_2}{dt}=k_6 MS_1-k_7 MS_2 \tag{9}$$

$$\frac{dMC_1}{dt}=k_7 MS_2-k_8 MC_1 \tag{10}$$

$$\frac{dMC_2}{dt}=k_8 MC_1-k_9 MC_2 \tag{11}$$

$$\frac{dMC_3}{dt}=k_9 MC_2-k_{10} MC_3 \tag{12}$$

$$\frac{dMC_4}{dt}=k_{10} MC_3-k_{11} MC_4 \tag{13}$$

where:

$$Es(t)=\left(\frac{e_0}{\eta_1}+\frac{e_1 MSe(t)}{\eta_2}+\frac{e_2 MPe(t)}{\eta_3}+\frac{e_3 MC_4(t)}{\eta_4}\right)BMI$$

$$Pr(t)=p_0 MC_3(t)+p_1 MC_4(t)$$

$$Ac(t)=a_0+a_1 MC_3(t)+a_2 MC_4(t),$$

and where the parameters in the above equations are defined as follows:

Es is the estradiol

Pr is the progesterone

Ac is the activin concentration in the blood

v is the blood volume

$\alpha,\beta,\gamma,b,k_1,k_2,k_3,k_4,k_5,k_6,k_7,k_8,k_9,k_{10},k_{11}$ are the parameters for the ovaries

$e_0, e_1, e_2, e_3, p_0, p_1, a_0, a_1, a_2$ are the parameters for the auxiliary equations (1)-(13)

5.2 Analysis of the Mathematical Model

We analyze the body mass index that affects the abnormal production of hormones which influence the menstrual irregularities. By analyzing the dynamical equation of the menstrual cycle, we obtain the steady state:

$E=(LH^*, MP^*_{LH}, FSH^*, MP^*_{FSH}, MMe^*, MSe^*, MPe^*, MS^*_1, MS^*_2, MC^*_1, MC^*_2, MC^*_3, MC^*_4)$. The steady state is obtained by setting the right hand side of $(1)-(13)$ equal to zero. The equilibrium point is:

$E=(LH^*, MP^*_{LH}, FSH^*, MP^*_{FSH}, MMe^*, MSe^*, MPe^*, MS^*_1, MS^*_2, MC^*_1, MC^*_2, MC^*_3, MC^*_4)$ and $LH^*, MP^*_{LH}, FSH^*, MP^*_{FSH}, MMe^*, MSe^*, MPe^*, MS^*_1, MS^*_2, MC^*_1, MC^*_2, MC^*_3, MC^*_4$ satisfies (14) - (26):

$$LH^* = \left[\frac{V_{1,LH} + \dfrac{V_{2,LH}\left[Es(t)\right]^8}{\left[K_{nLH}\right]^8 + \left[Es(t)\right]^8}}{1+Pr(t)/K_{aLH,p}}\right]\left[\frac{1}{vA_{LH}}\right] \quad (14)$$

$$MP^*_{LH} = \left[\frac{V_{1,LH} + \dfrac{V_{2,LH}\left[Es(t)\right]^8}{\left[K_{nLH}\right]^8 + \left[E(t)\right]^8}}{1+Pr(t)/K_{aLH,p}}\right]\left[\frac{1+cl_{LH,E}Es(t)}{k_{LH}\left[1+cl_{LH,p}Pr(t)\right]}\right] \quad (15)$$

$$FSH^* = \left[\frac{1}{vA_{FSH}}\right]\left[\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}\right] \quad (16)$$

$$MP^*_{FSH} = \left[\frac{V_{FSH}}{1+Ac(t)/K_{aFSH,Ac}}\right]\left[\frac{1+cl_{FSH,E}\left[Es(t)\right]^2}{k_{FSH}\left[1+cl_{FSH,p}Pr(t)\right]}\right] \quad (17)$$

$$MMe^* = \frac{bFSH^*}{k_2(LH^*)^{\alpha} - k_1 FSH^*} \quad (18)$$

$$MSe^{*} = \frac{bFSH^{*}k_2(LH^{*})^{\alpha}}{\left(k_1FSH^{*}-k_2(LH^{*})^{\alpha}\right)\left(k_3(LH^{*})^{\beta}-k_4LH^{*}\right)} \tag{19}$$

$$MPe^{*} = \frac{k_4bFSH^{*}k_2(LH^{*})^{1+\alpha-\gamma}}{k_5\left(k_1FSH^{*}-k_2(LH^{*})^{\alpha}\right)\left(k_3(LH^{*})^{\beta}-k_4LH^{*}\right)} \tag{20}$$

$$MS^{*}_{1} = \frac{k_4bFSH^{*}k_2(LH^{*})^{1+\alpha}}{k_6\left(k_1FSH^{*}-k_2(LH^{*})^{\alpha}\right)\left(k_3(LH^{*})^{\beta}-k_4LH^{*}\right)} \tag{21}$$

$$MS^{*}_{2} = \frac{k_4bFSH^{*}k_2(LH^{*})^{1+\alpha}}{k_7\left(k_1FSH^{*}-k_2(LH^{*})^{\alpha}\right)\left(k_3(LH^{*})^{\beta}-k_4LH^{*}\right)} \tag{22}$$

$$MC^{*}_{1} = \frac{k_4bFSH^{*}k_2(LH^{*})^{1+\alpha}}{k_8\left(k_1FSH^{*}-k_2(LH^{*})^{\alpha}\right)\left(k_3(LH^{*})^{\beta}-k_4LH^{*}\right)} \tag{23}$$

$$MC^{*}_{2} = \frac{k_4bFSH^{*}k_2(LH^{*})^{1+\alpha}}{k_9\left(k_1FSH^{*}-k_2(LH^{*})^{\alpha}\right)\left(k_3(LH^{*})^{\beta}-k_4LH^{*}\right)} \tag{24}$$

$$MC^{*}_{3} = \frac{k_4bFSH^{*}k_2(LH^{*})^{1+\alpha}}{k_{10}\left(k_1FSH^{*}-k_2(LH^{*})^{\alpha}\right)\left(k_3(LH^{*})^{\beta}-k_4LH^{*}\right)} \tag{25}$$

$$MC^{*}_{4} = \frac{k_4bFSH^{*}k_2(LH^{*})^{1+\alpha}}{k_{11}\left(k_1FSH^{*}-k_2(LH^{*})^{\alpha}\right)\left(k_3(LH^{*})^{\beta}-k_4LH^{*}\right)} \tag{26}$$

5.3 Numerical Results

In this section, we analyze the model given by equations (1) - (13). We divide our analysis based on the degree of obesity, which is measured by the level of BMI.

1. BMI is between 18.5 to 23.4: a person’s weight is normal.
2. BMI is between 23.5 to 28.4: the weight is on the threshold of being higher than normal.
3. BMI is between 28.5 to 34.9: the weight of people who are obese step 1.
4. BMI is between 35.0 to 39.9: the weight of people who are obese step 2.
5. BMI of 40 and above: the weight of people with severe obesity.

The trajectories of the solutions when the parameter values lead to the equilibrium state are shown in the following figures.

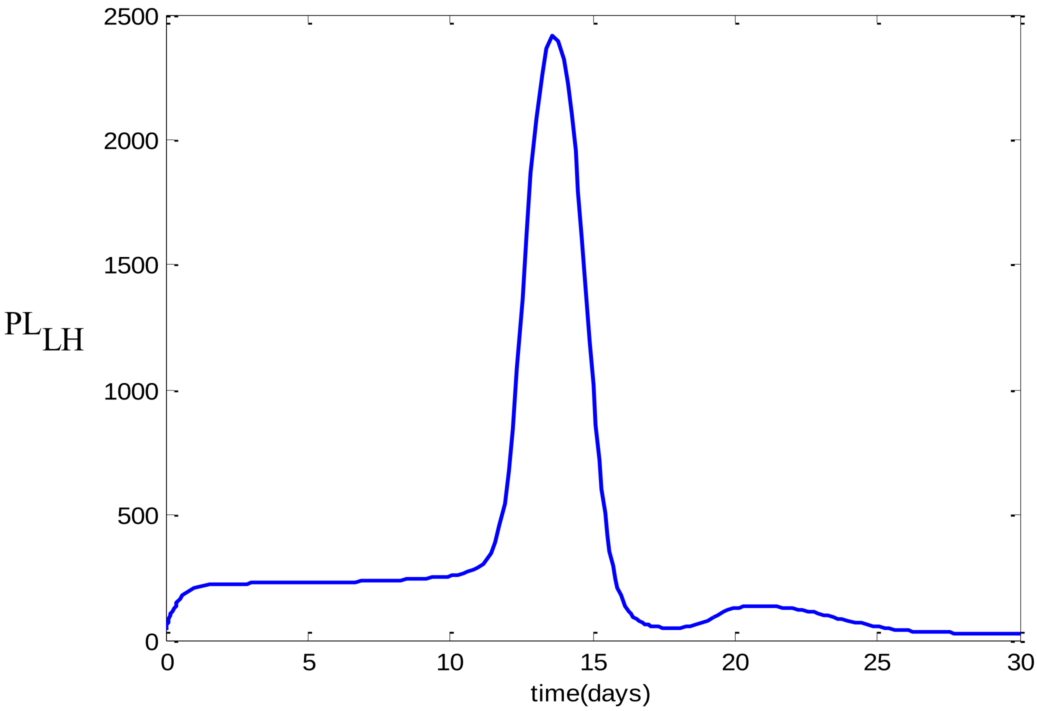


Figure 5.1: The graph shows the proportion of PL_{LH} with time. PL_{LH} is the highest volume on the 13th day of the menstrual cycle.

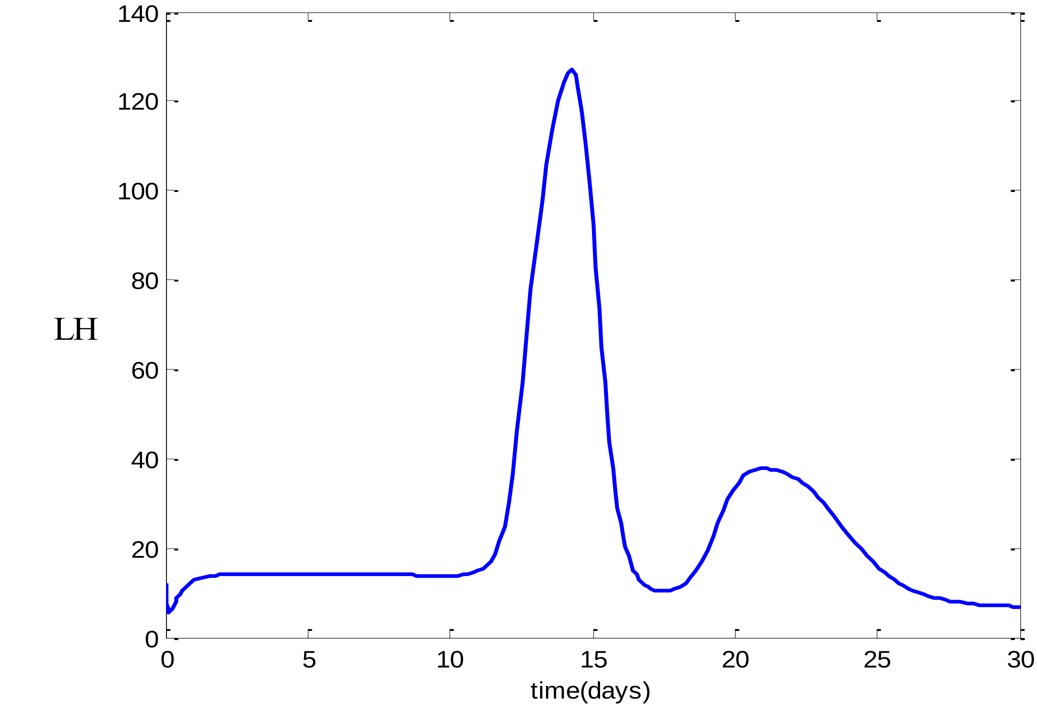


Figure 5.2: The graph shows the proportion of LH with time. LH is the highest volume on the 14th day, which is the stage of late follicular phase.

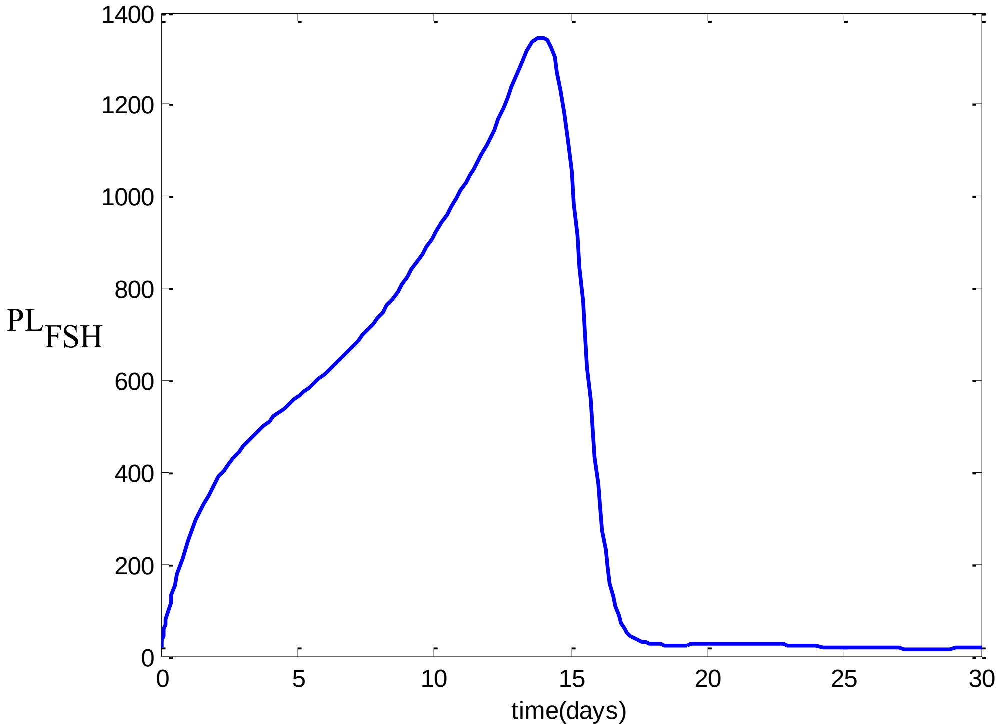


Figure 5.3: The graph shows the proportion of PL_{FSH} with time. PL_{FSH} is the highest volume on the 14th day of the menstrual cycle.

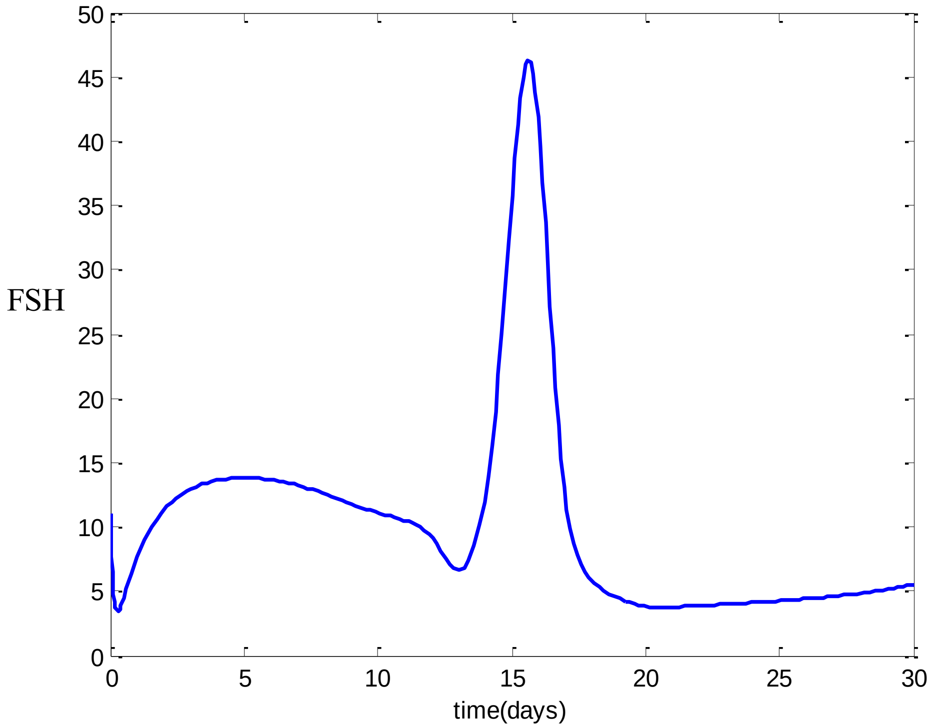


Figure 5.4: The graph shows the proportion of FSH with time. FSH is the highest volume on the 16th day, which is the stage of late follicular phase.

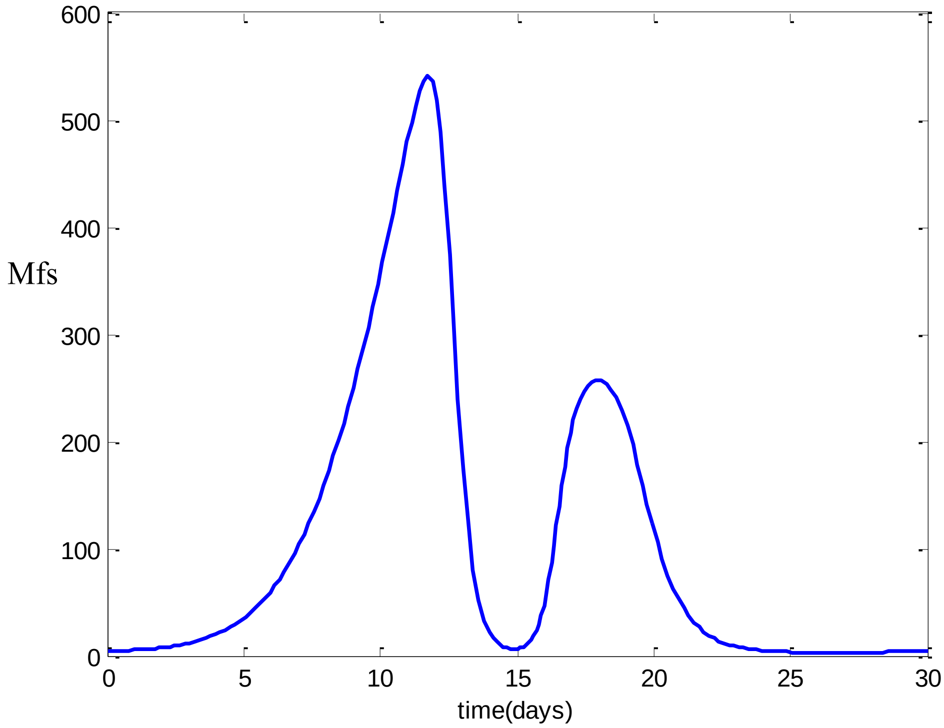


Figure 5.5: The graph shows the proportion of Mfs with time. Mfs is the highest volume on the 12^{th} day of the menstrual cycle.

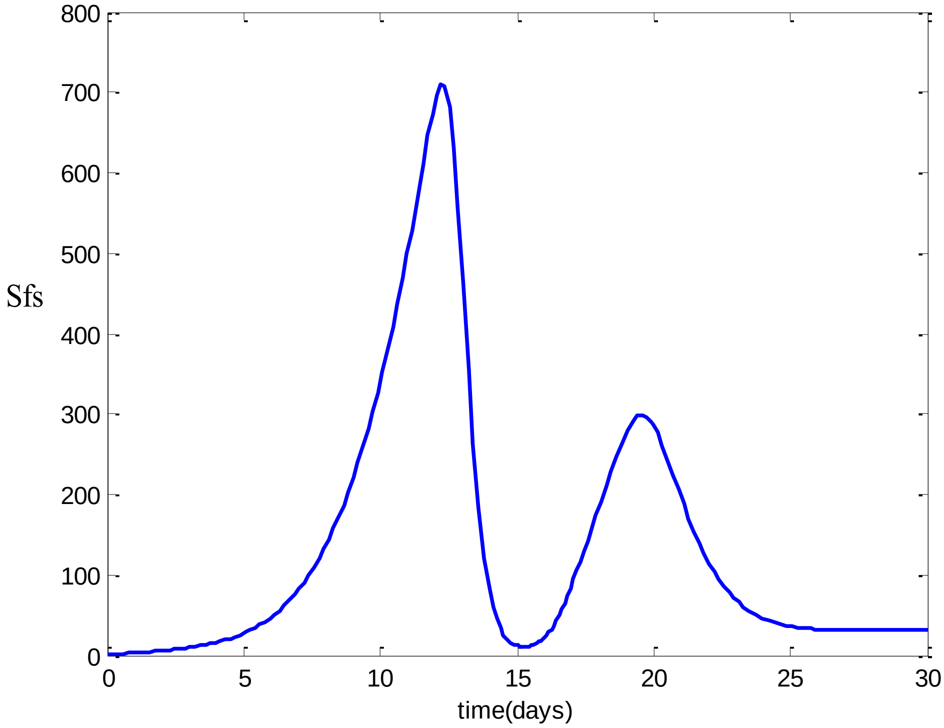


Figure 5.6: The graph shows the proportion of Sfs with time. Sfs is the highest volume on the 12^{th} day of the menstrual cycle.

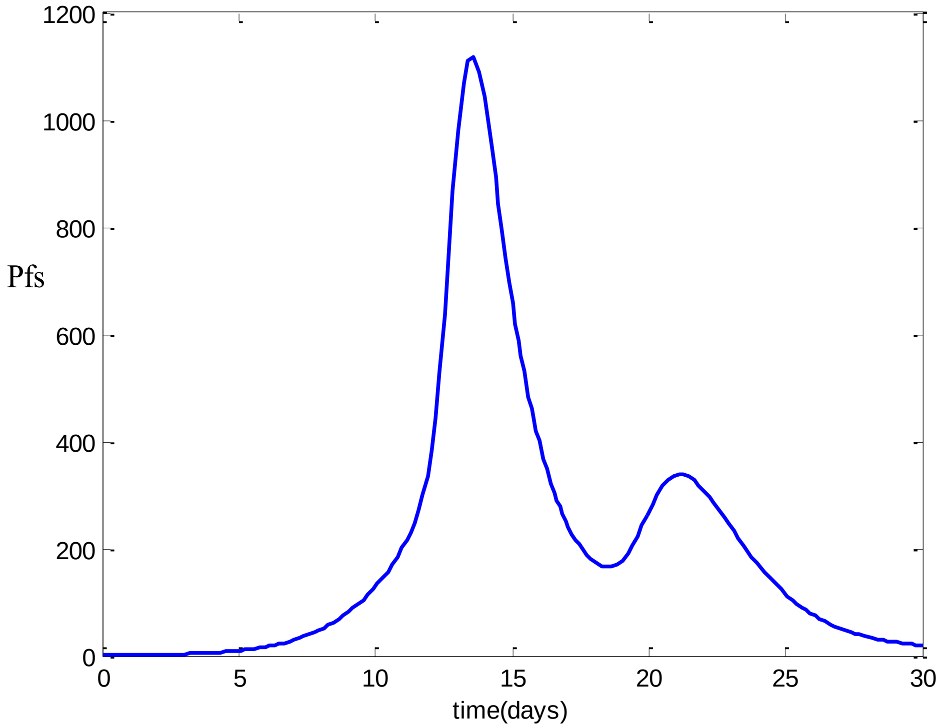


Figure 5.7: The graph shows the proportion of Pfs with time. Pfs is the highest volume on the 14th day of the menstrual cycle.

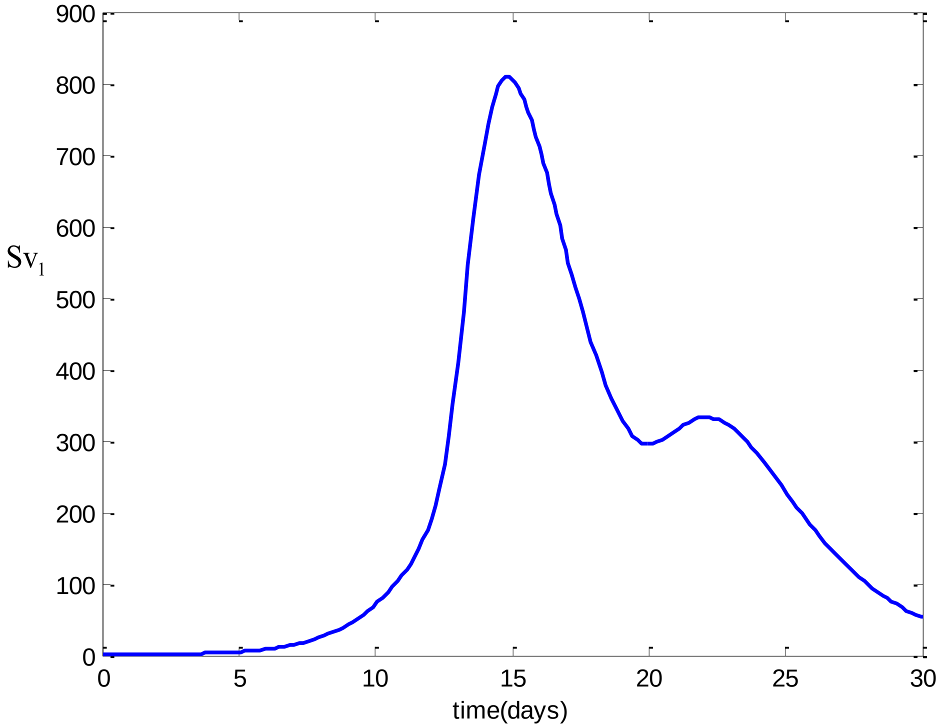


Figure 5.8: The graph shows the proportion of Sv_1 with time. Sv_1 is the highest volume on the 15th day of the menstrual cycle.

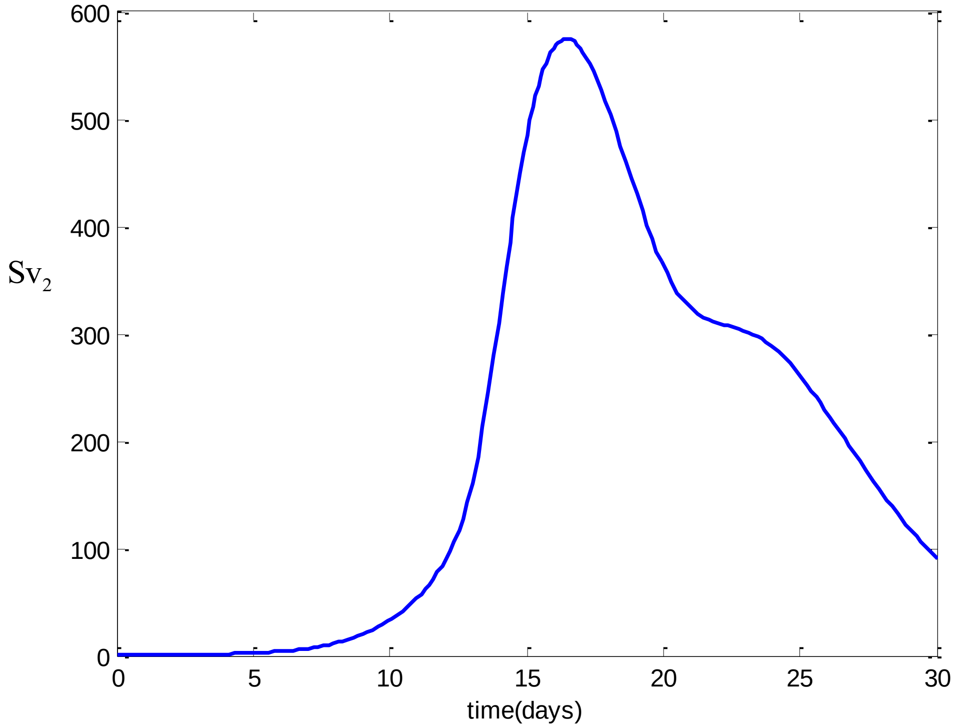


Figure 5.9: The graph shows the proportion of Sv_2 with time. Sv_2 is the highest volume on the 17^{th} day of the menstrual cycle.

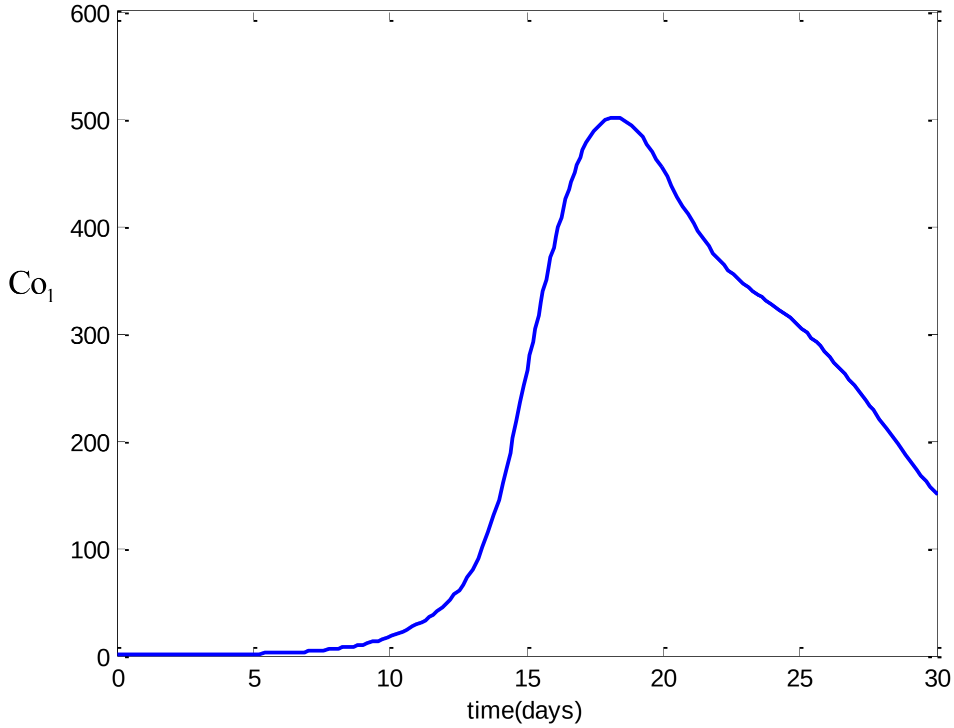


Figure 5.10: The graph shows the proportion of Co_1 with time. Co_1 is the highest volume on the 18^{th} day of the menstrual cycle.

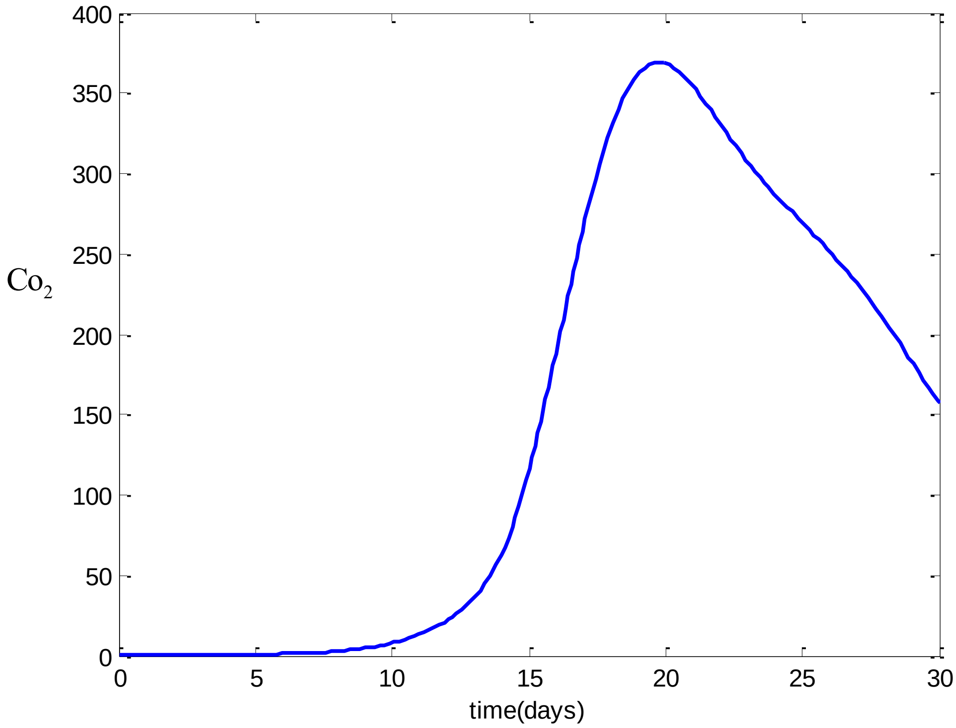


Figure 5.11: The graph shows the proportion of Co_2 with time. Co_2 is the highest volume on the 19th day of the menstrual cycle.

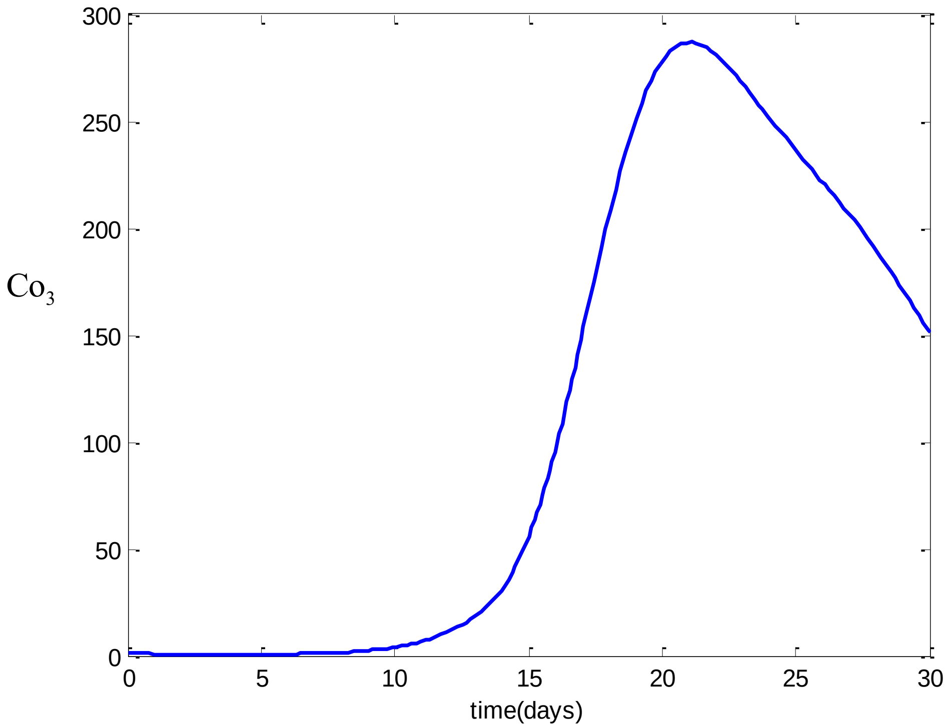


Figure 5.12: The graph shows the proportion of Co_3 with time. Co_3 is the highest volume on the 21st day of the menstrual cycle.

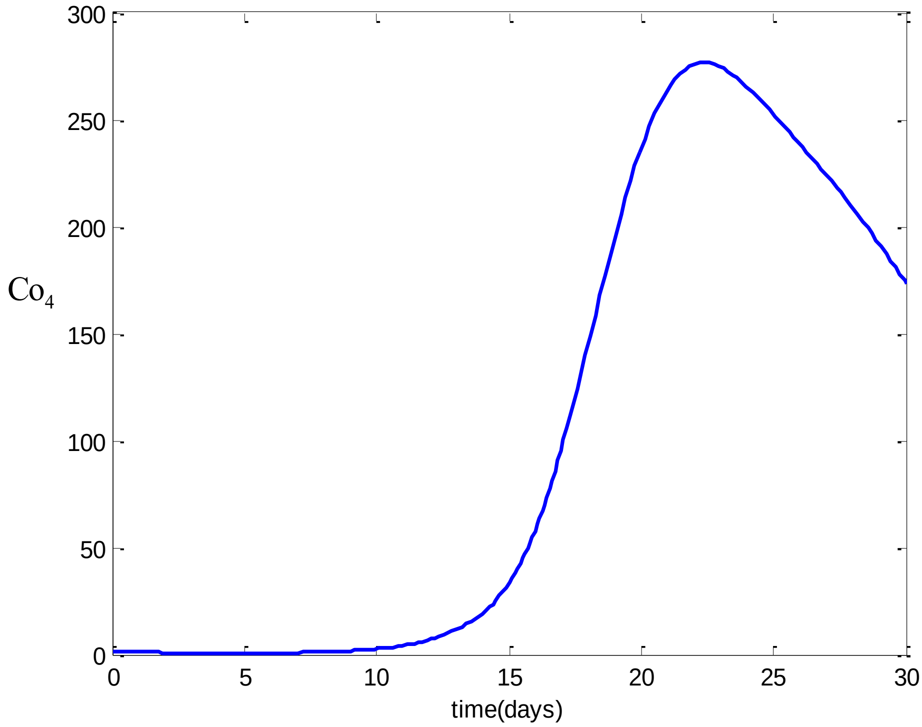


Figure 5.13: The graph shows the proportion of Co_4 with time. Co_4 is the highest volume on 22[nd] day of the menstrual cycle.

Figures 5.1-5.13 For normal weight, it was found that the LH hormone is the highest volume on day 14 and the FSH hormone is the highest volume on day 16. The values of the parameters are:

$K_{aLH,p} = 31.22\,\text{ng/mL}$, $k_{LH} = 2.49\ \text{day}^{-1}$, $V_{1,LH} = 1263.4\ \text{IU/day}$, $cl_{LH,p} = 0.07\,\text{mL/ng}$, $cl_{LH,E} = 0.0049\ \text{mL/pg}$, $A_{LH} = 14\ \text{day}^{-1}$, $A_{FSH} = 8.21\ \text{day}^{-1}$, $V_{FSH} = 5700\ \text{IU/day}$, $K_{aFSH,Ac} = 641\ \text{IU/mL}$, $k_{FSH} = 7.29\ \text{day}^{-1}$, $cl_{FSH,p} = 644\text{mL/ng}$, $\gamma = 0.0202$, $\alpha = 0.7736$, $cl_{FSH,E} = 0.16\ \text{mL/pg}$, $K_{nLH} = 360\text{pg/mL}$, $V_{2,LH} = 91000\ \text{IU/day}$, $\beta = 0.1566$, $LH[0]=40$, $MP_{LH}[0]=12$, $FSH[0]=20$, $MP_{FSH}[0]=11$, $MMe[0]=1$, $MSe[0]=5$, $MPe[0]=1$, $MS_1[0]=1$, $MS_2[0]=1$, $MC_1[0]=1$, $MC_2[0]=1$, $MC_3[0]=1$, $MC_4[0]=1$.

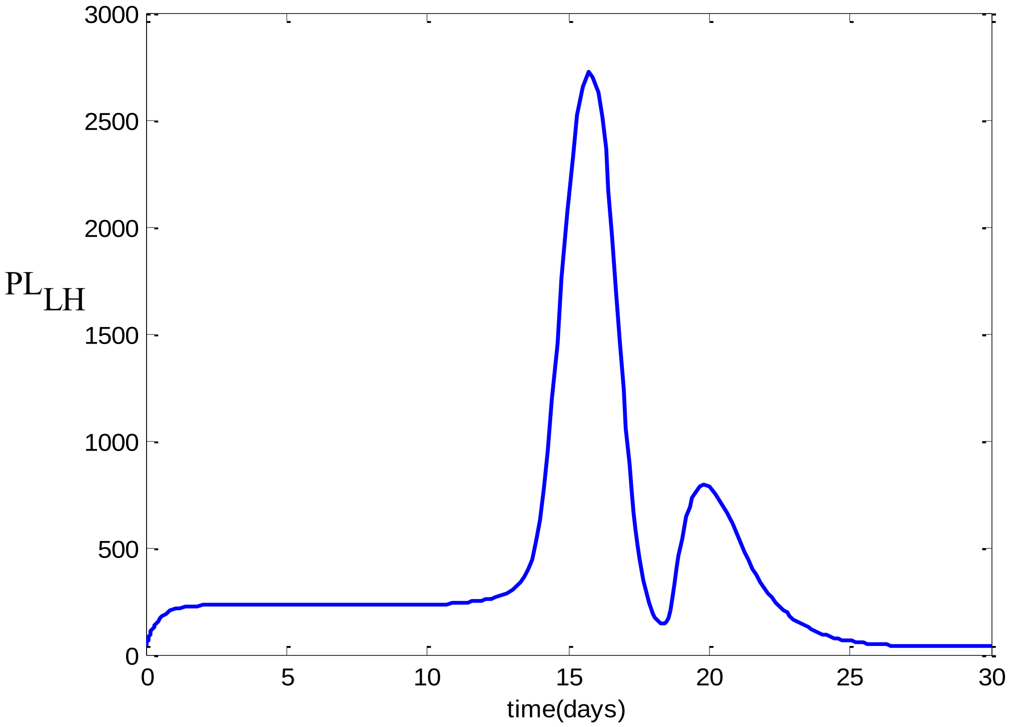


Figure 5.14: The graph shows the proportion of PL_{LH} with time. PL_{LH} is the highest volume on the 16th day of the menstrual cycle.

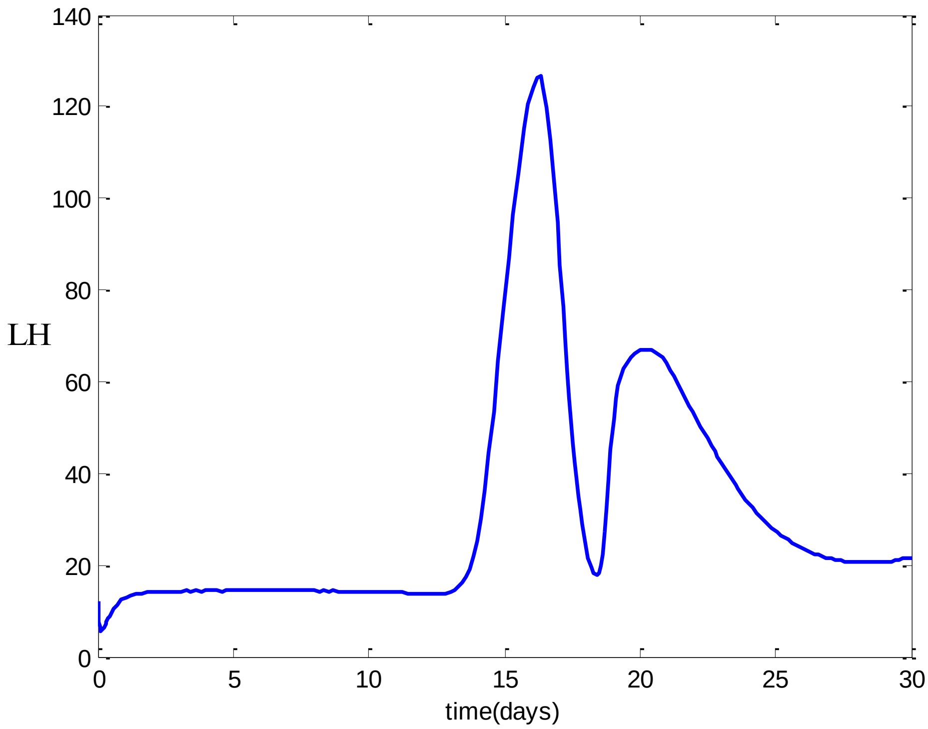


Figure 5.15: The graph shows the proportion of LH with time. LH is the highest volume on the 16th day, which is the stage of late follicular phase.

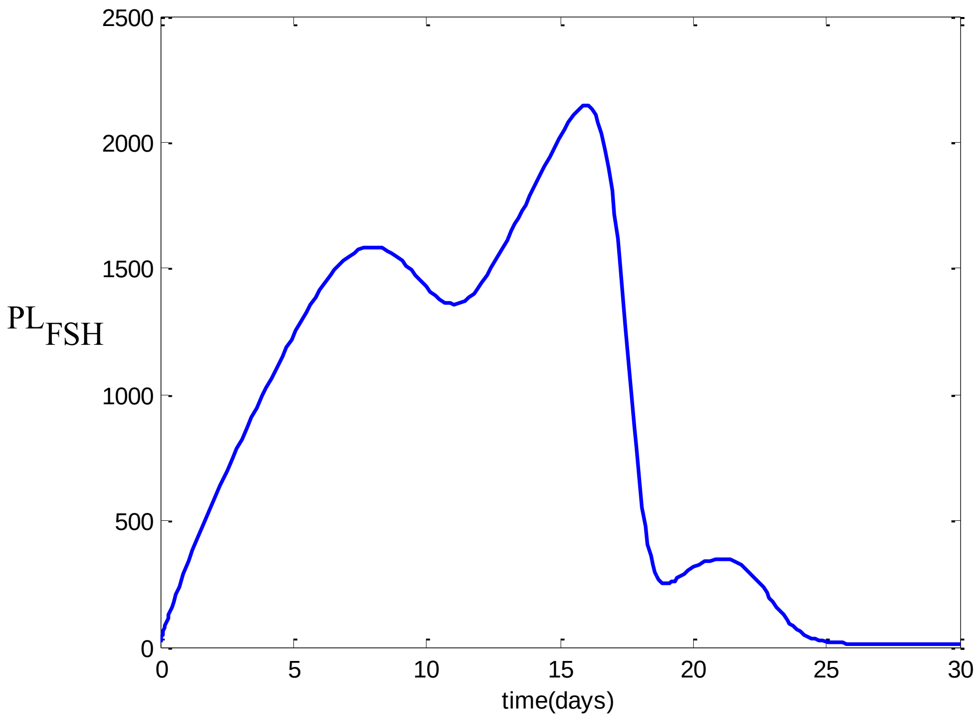


Figure 5.16: The graph shows the proportion of PL_{FSH} with time. PL_{FSH} is the highest volume on 16th day of the menstrual cycle.

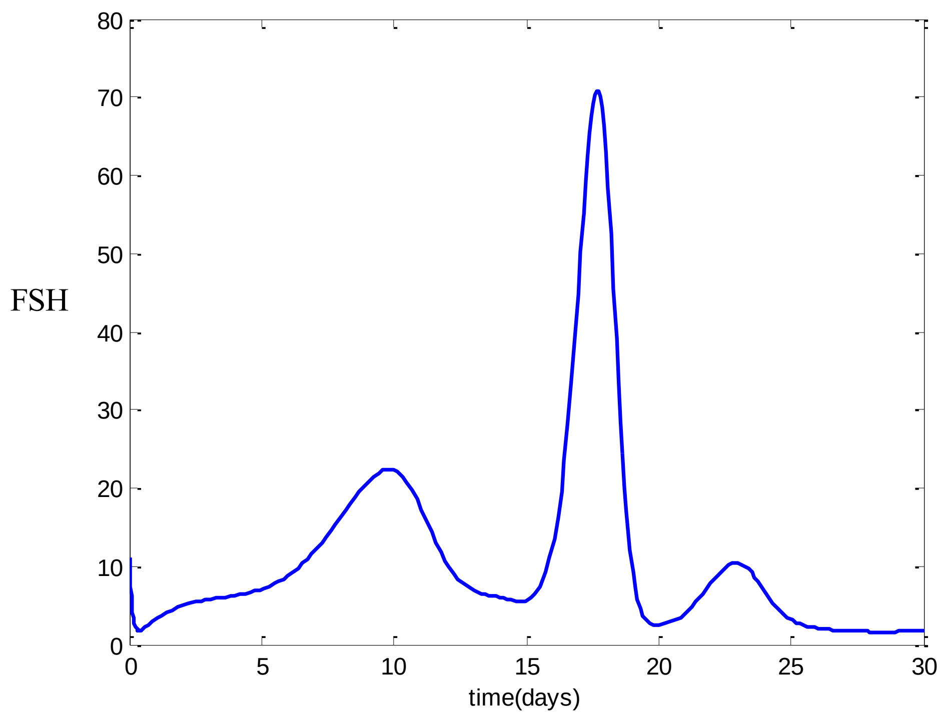


Figure 5.17: The graph shows the proportion of FSH with time. FSH is the highest volume on the 17th day, which is the stage of late follicular phase.

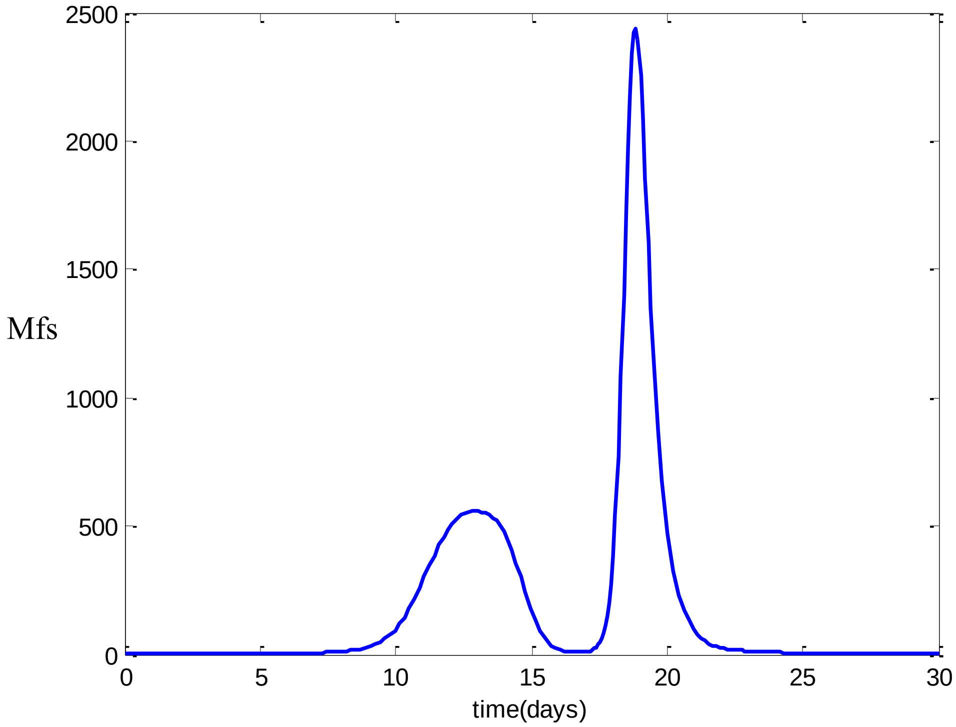


Figure 5.18: The graph shows the proportion of Mfs with time. Mfs is the highest volume on the 19th day of the menstrual cycle.

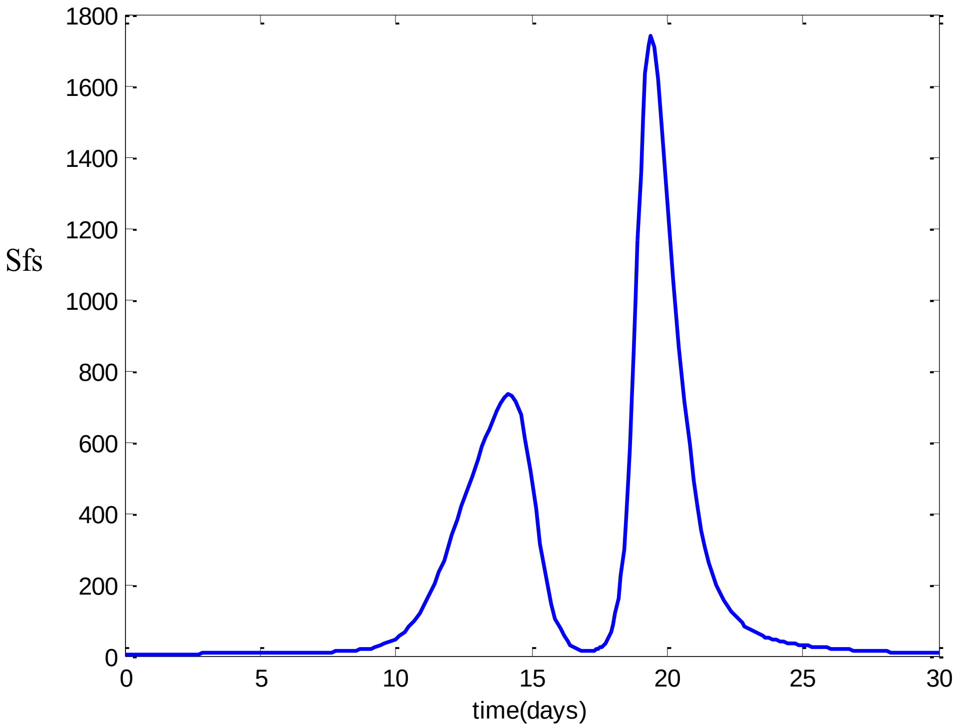


Figure 5.19: The graph shows the proportion of Sfs with time. Sfs is the highest volume on the 19th day of the menstrual cycle.

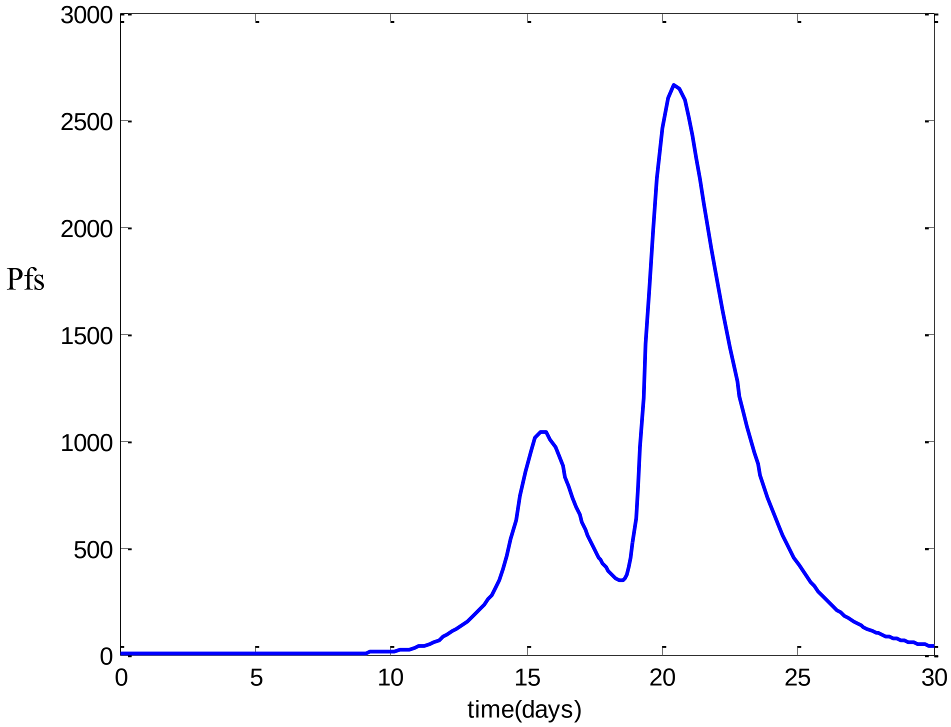


Figure 5.20: The graph shows the proportion of Pfs with time. Pfs is the highest volume on 21st day of the menstrual cycle.

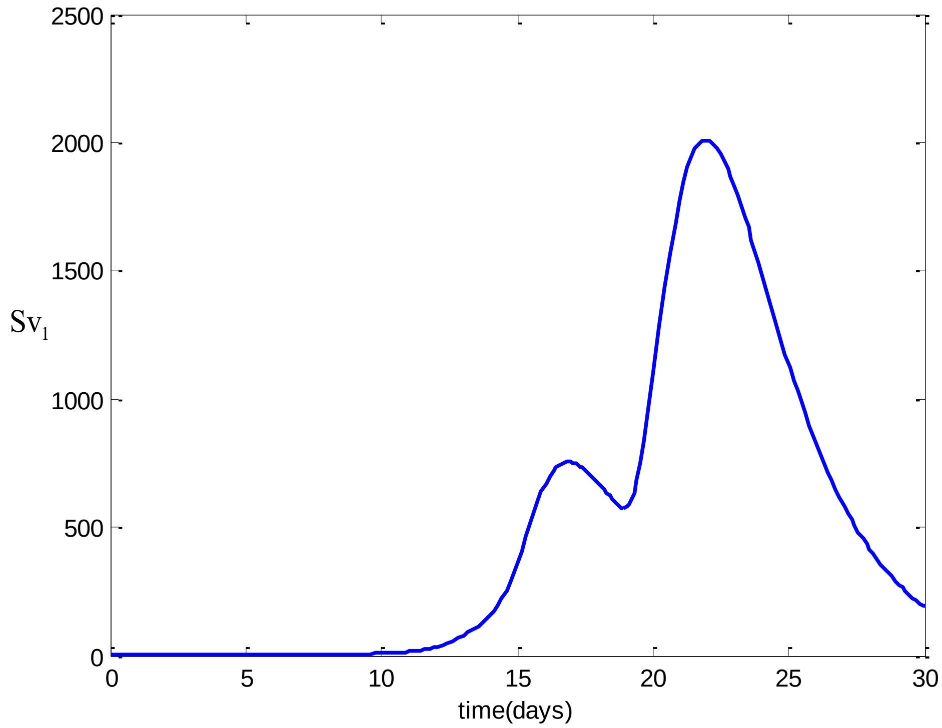


Figure 5.21: The graph shows the proportion of Sv_1 with time. Sv_1 is the highest volume on 22nd day of the menstrual cycle.

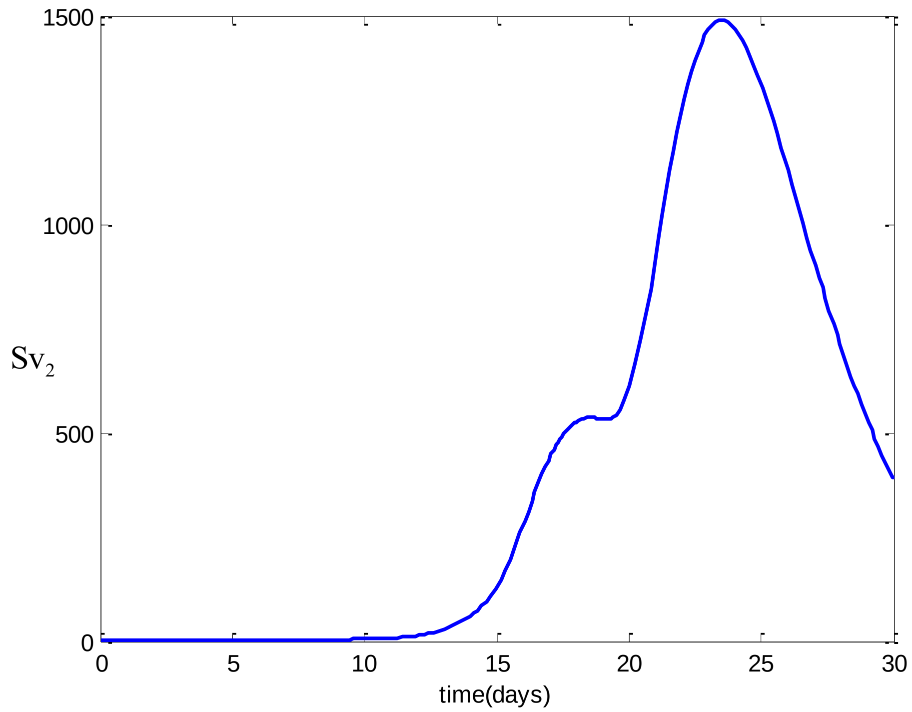


Figure 5.22: The graph shows the proportion of Sv_2 with time. Sv_2 is the highest volume on 23rd day of the menstrual cycle.

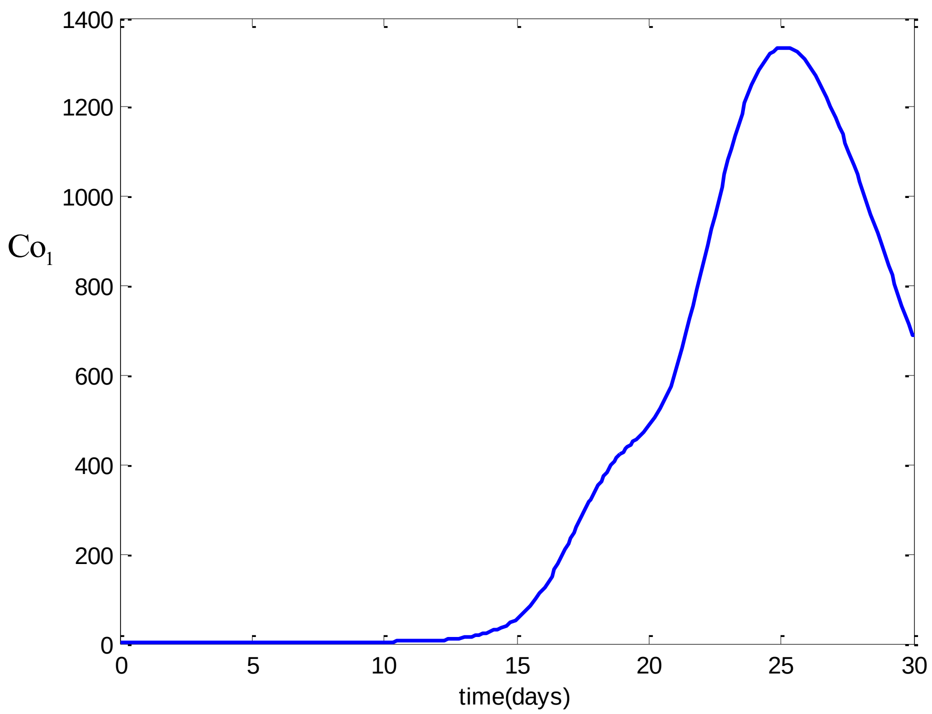


Figure 5.23: The graph shows the proportion of Co_1 with time. Co_1 is the highest volume on the 25th day of the menstrual cycle.

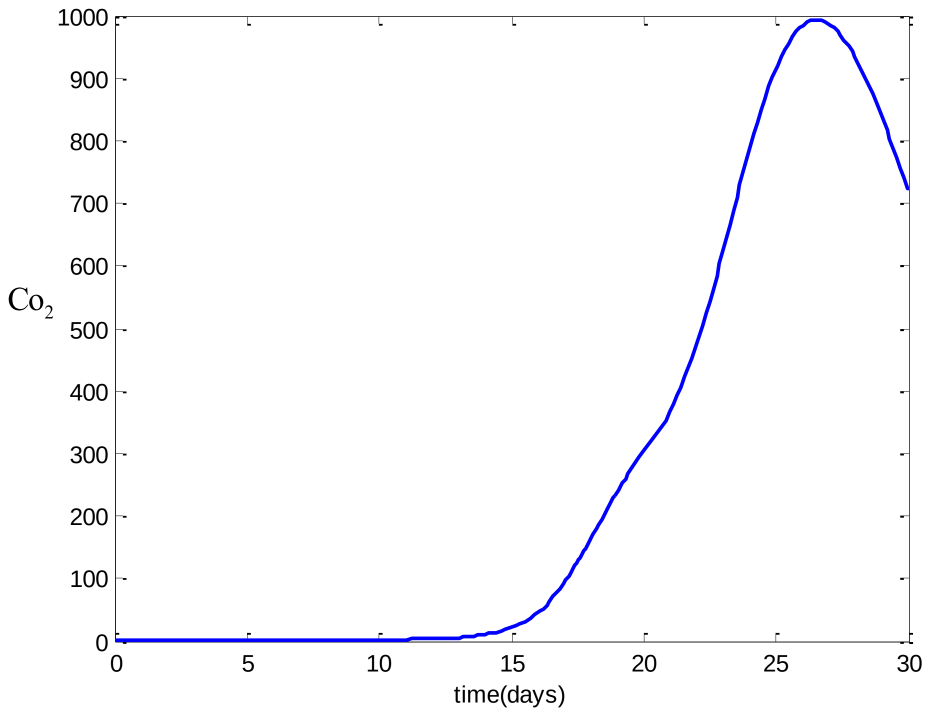


Figure 5.24: The graph shows the proportion of Co_2 with time. Co_2 is the highest volume on the 26th day of the menstrual cycle.

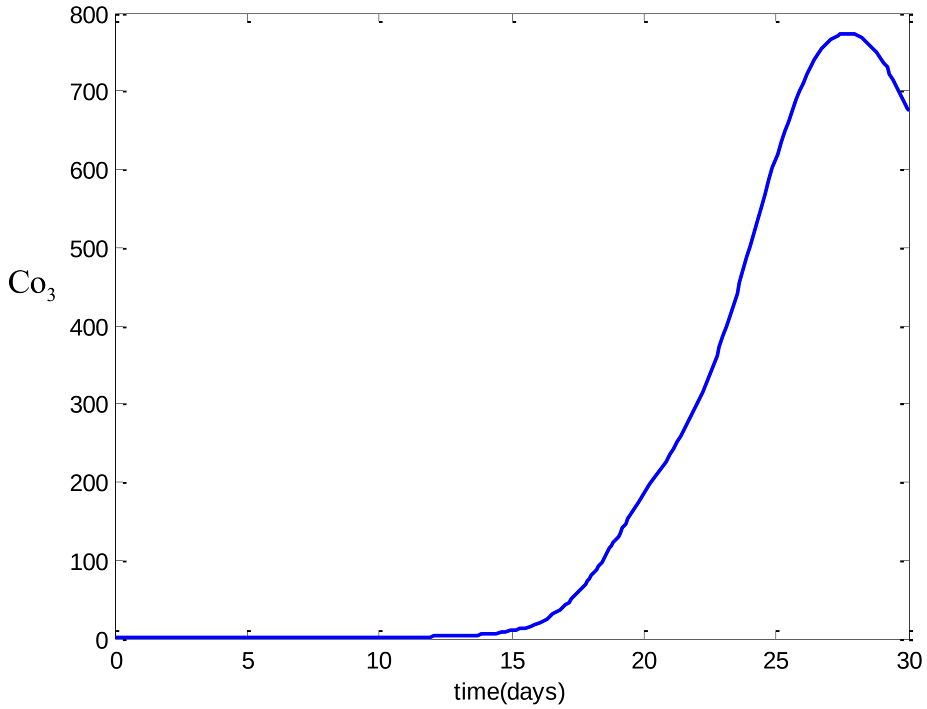


Figure 5.25: The graph shows the proportion of Co_3 with time. Co_3 is the highest volume on the 27th day of the menstrual cycle.

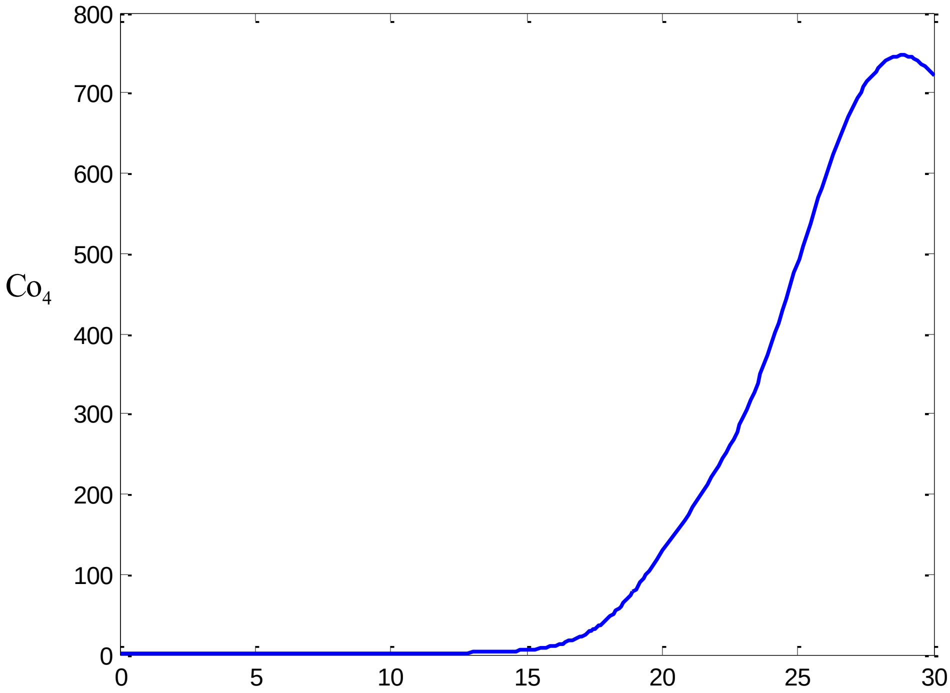


Figure 5.26: The graph shows the proportion of Co_4 with time. Co_4 is the highest volume on the 28th day of the menstrual cycle.

Figures 5.14-5.26 For weight on the threshold of obesity, it was found that the LH hormone is the highest volume on day 15 and the FSH hormone is the highest volume on day 17. The parameters are similar to those in Figures 5.1-5.13:

$K_{aLH,p} = 31.22$ ng/mL, $k_{LH} = 2.49$ day^{-1}, $V_{1,LH} = 1263.4$ IU/day, $cl_{LH,p} = 0.07$ mL/ng, $cl_{LH,E} = 0.0049$ mL/pg, $A_{LH} = 14$ day^{-1}, $A_{FSH} = 8.21$ day^{-1}, $V_{FSH} = 5700$ IU/day, $K_{aFSH,Ac} = 641$ IU/mL, $k_{FSH} = 7.29$ day^{-1}, $\gamma = 0.0202$, $cl_{FSH,p} = 644$mL/ng, $\alpha = 0.7736$, $cl_{FSH,E} = 0.16$ mL/pg, $K_{nLH} = 360$pg/mL, $V_{2,LH} = 91000$ IU/day, $\beta = 0.1566$, LH[0]=40, MP_{LH}[0]=12, FSH[0]=20, MP_{FSH}[0]=11, MMe[0]=1, MSe[0]=5, MPe[0]=1, MS_1[0]=1, MS_2[0]=1, MC_1[0]=1, MC_2[0]=1, MC_3[0]=1, MC_4[0]=1.

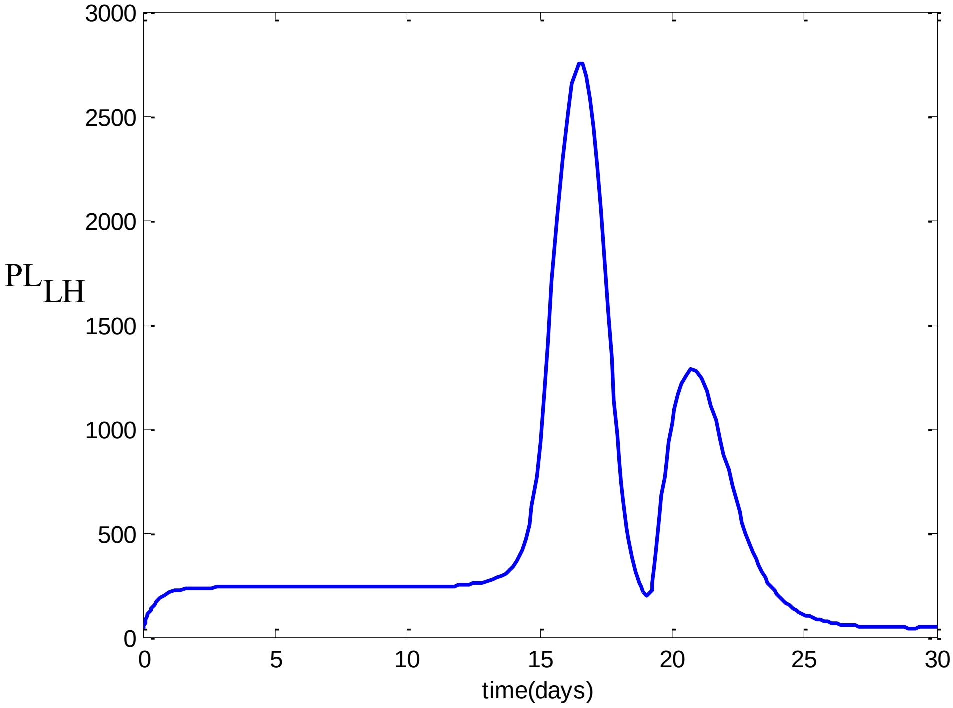


Figure 5.27: The graph shows the proportion of PL_{LH} with time. PL_{LH} is the highest volume on 16th day of the menstrual cycle.

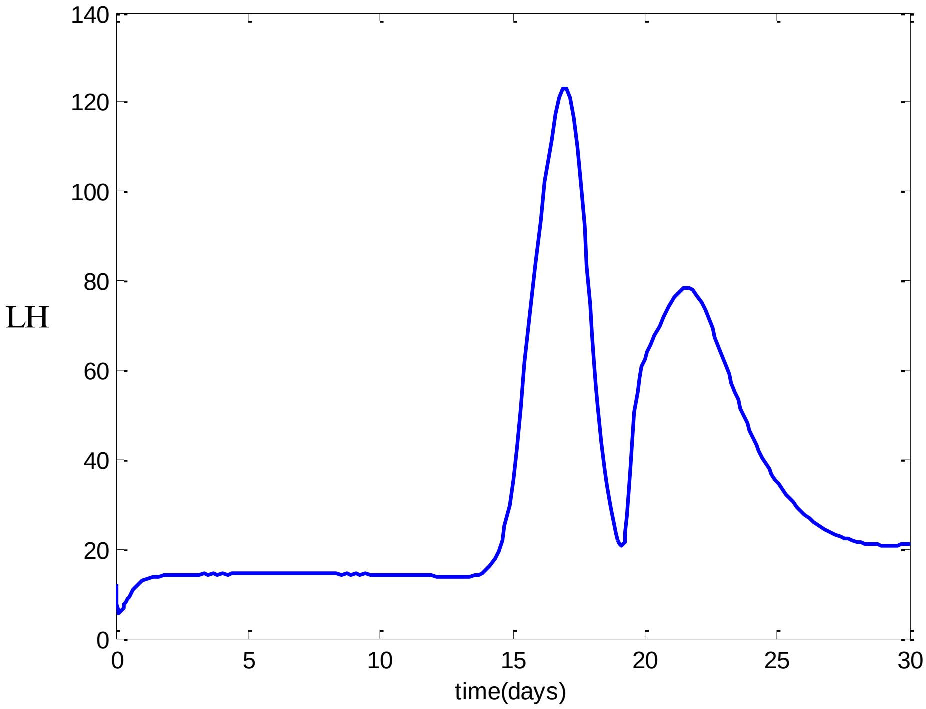


Figure 5.28: The graph shows the proportion of LH with time. LH is the highest volume on the 17th day, which is the stage of late follicular phase.

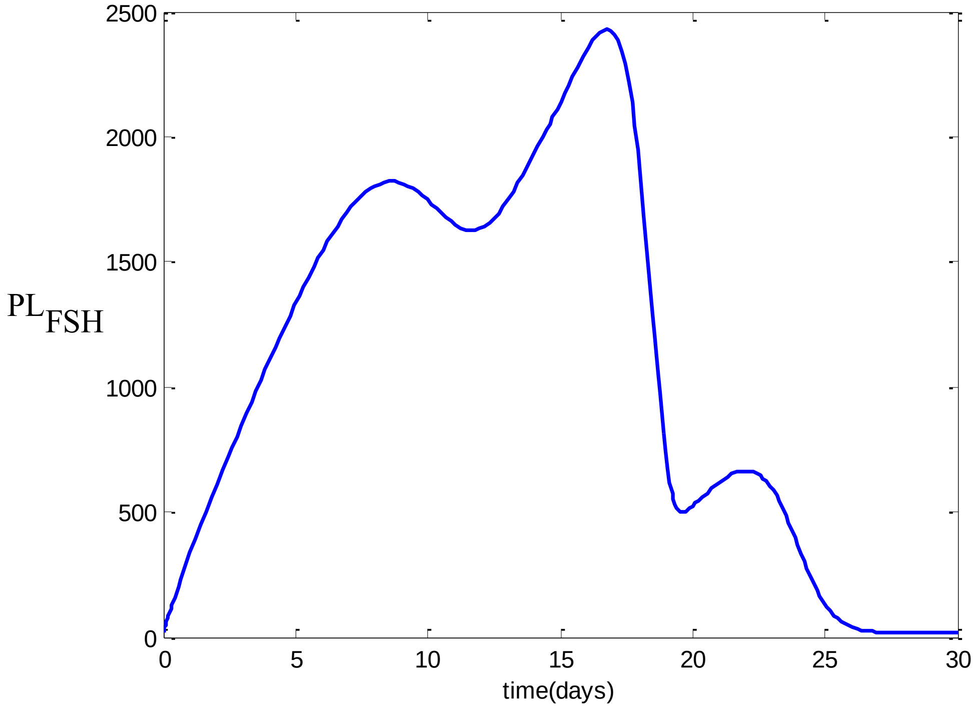


Figure 5.29: The graph shows the proportion of PL_{FSH} with time. PL_{FSH} is the highest volume on the 17th day of the menstrual cycle.

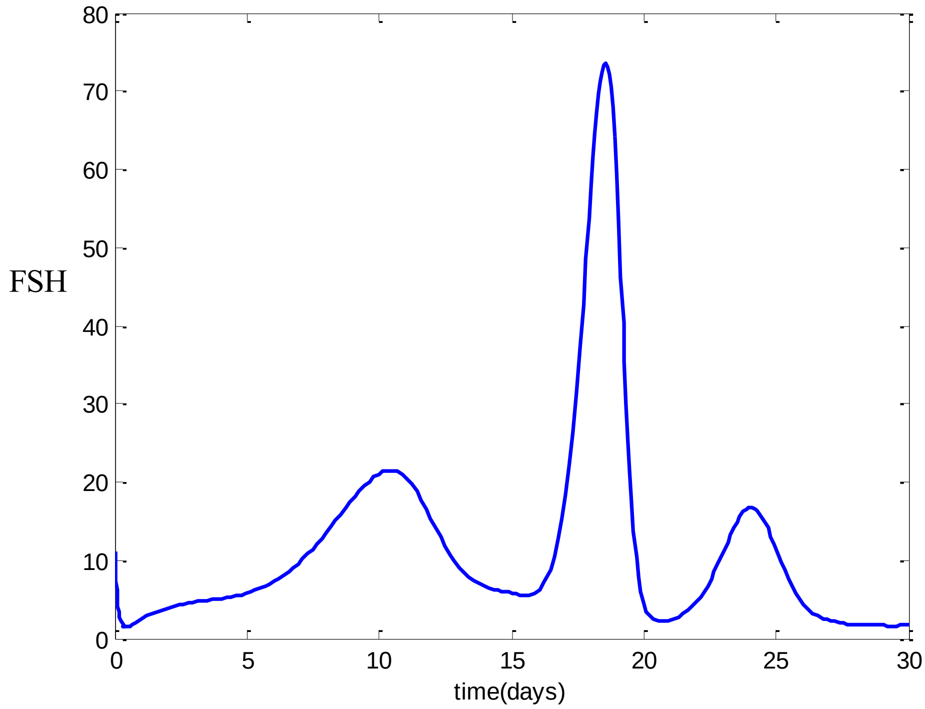


Figure 5.30: The graph shows the proportion of FSH with time. FSH is the highest volume on 18th day, which is the stage of late follicular phase.

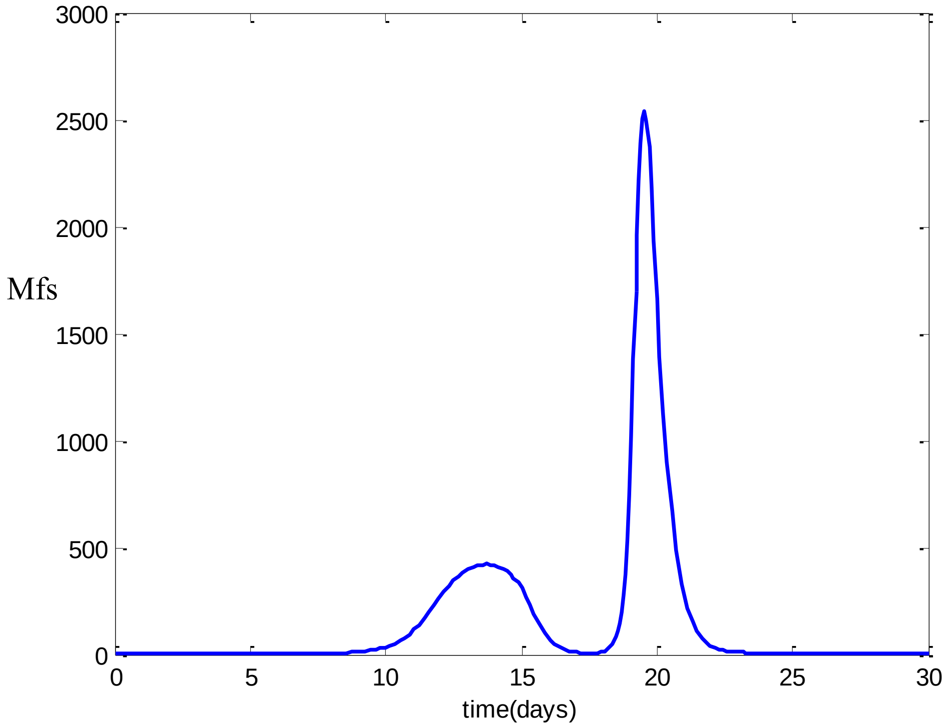


Figure 5.31: The graph shows the proportion of Mfs with time. Mfs is the highest volume on the 19th day of the menstrual cycle.

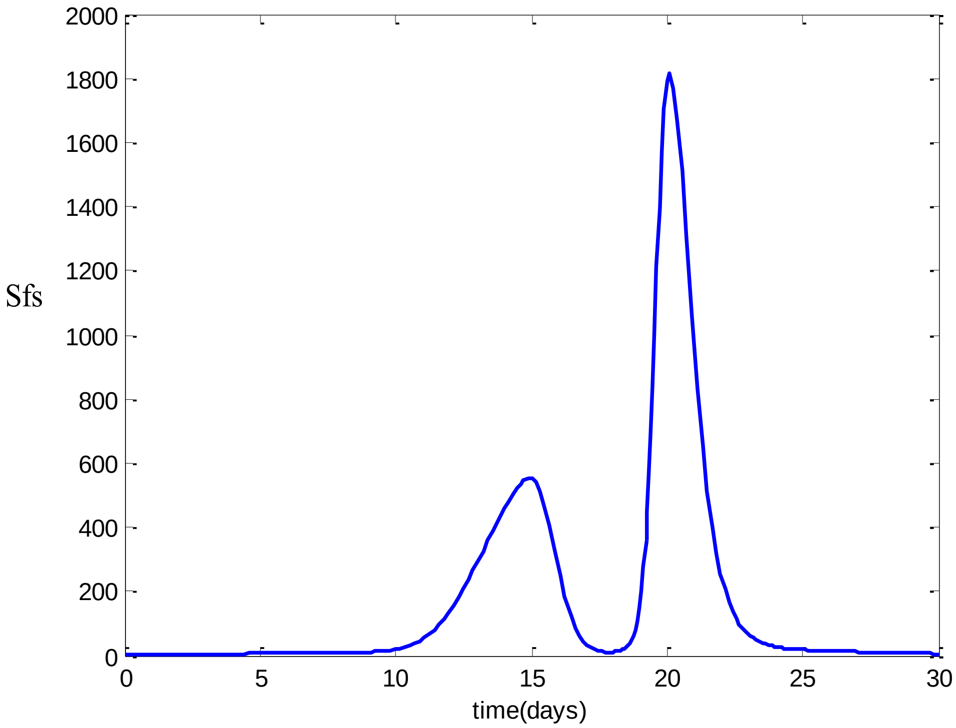


Figure 5.32: The graph shows the proportion of Sfs with time. Sfs is the highest volume on the 20th day of the menstrual cycle.

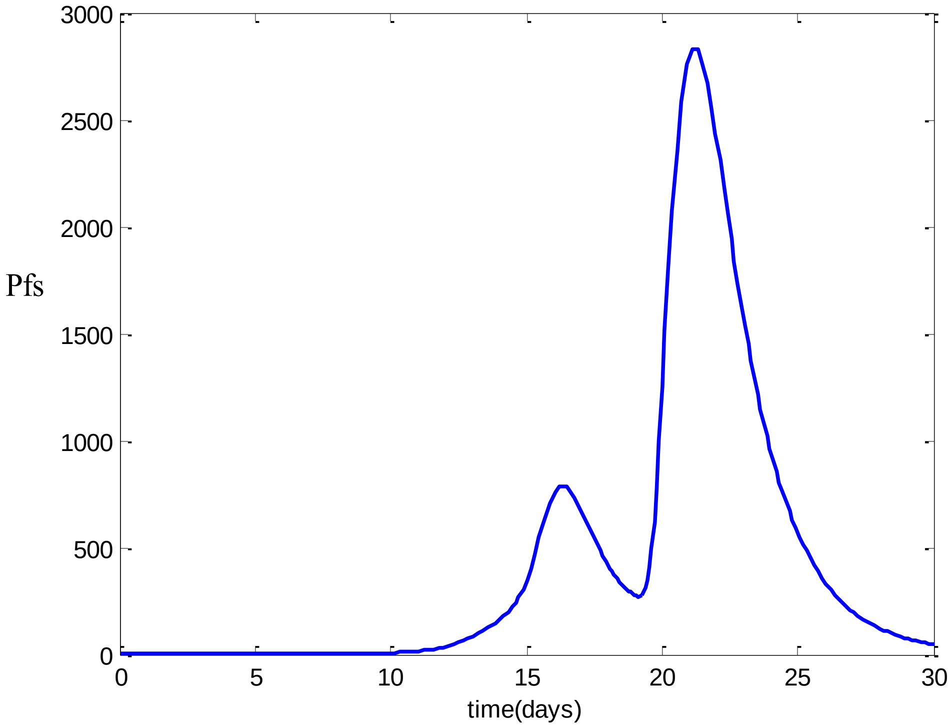


Figure 5.33: The graph shows the proportion of Pfs with time. Pfs is the highest volume on the 21st day of the menstrual cycle.

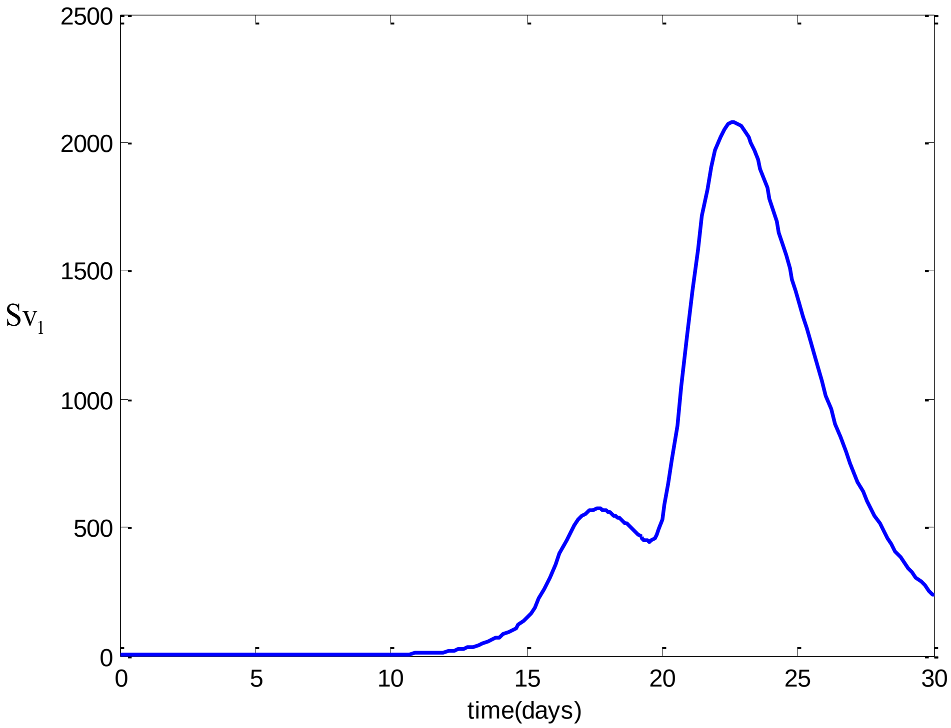


Figure 5.34: The graph shows the proportion of Sv_1 with time. Sv_1 is the highest volume on the 22nd day of the menstrual cycle.

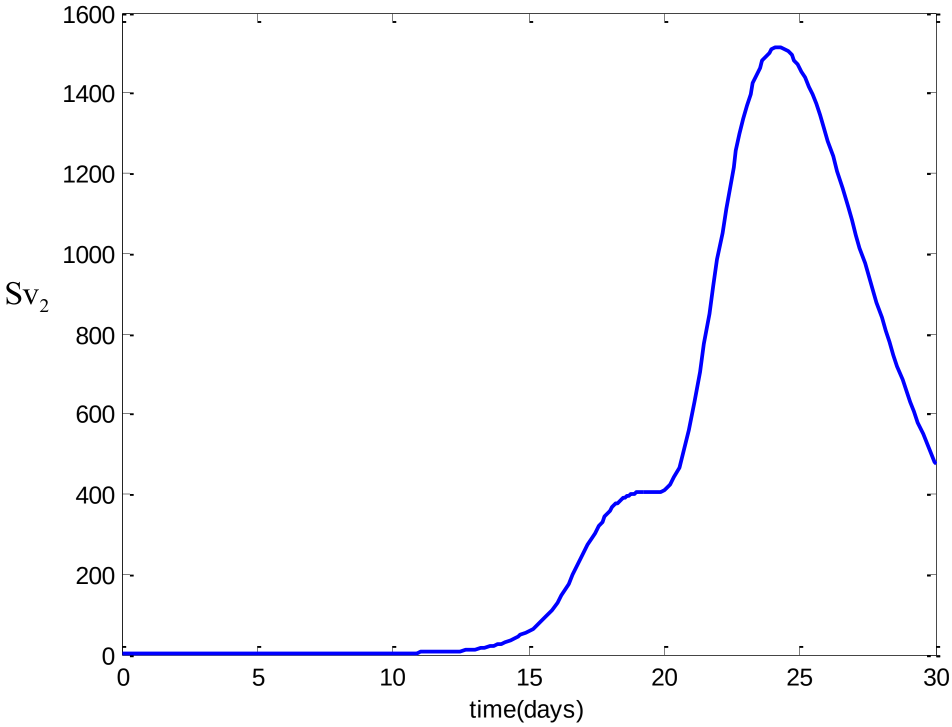


Figure 5.35: The graph shows the proportion of Sv_2 with time. Sv_2 is the highest volume on the 24th day of the menstrual cycle.

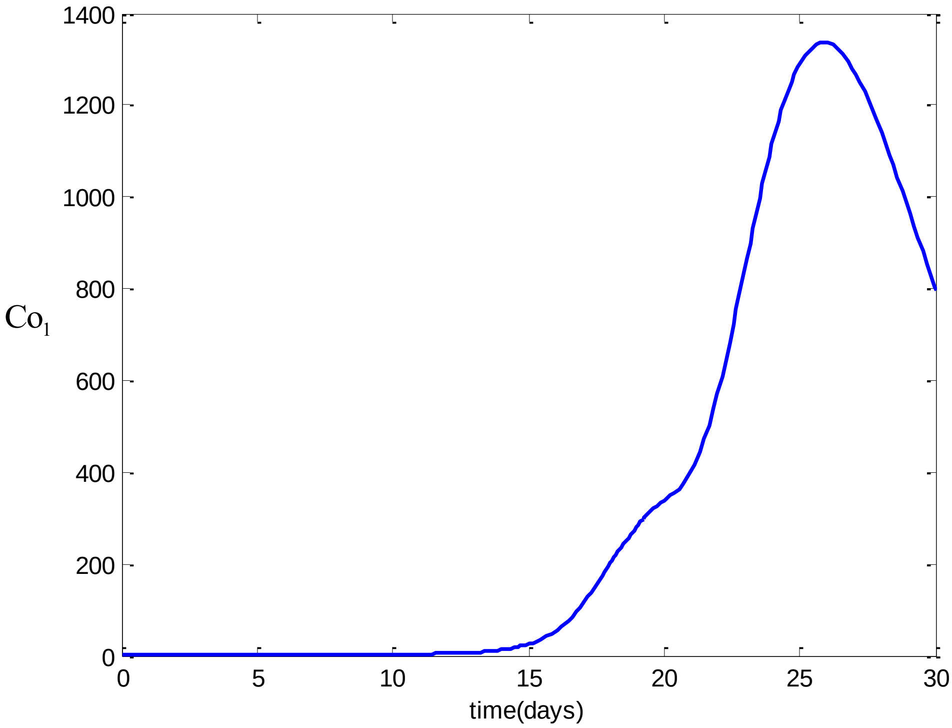


Figure 5.36: The graph shows the proportion of Co_1 with time. Co_1 is the highest volume on the 26th day of the menstrual cycle.

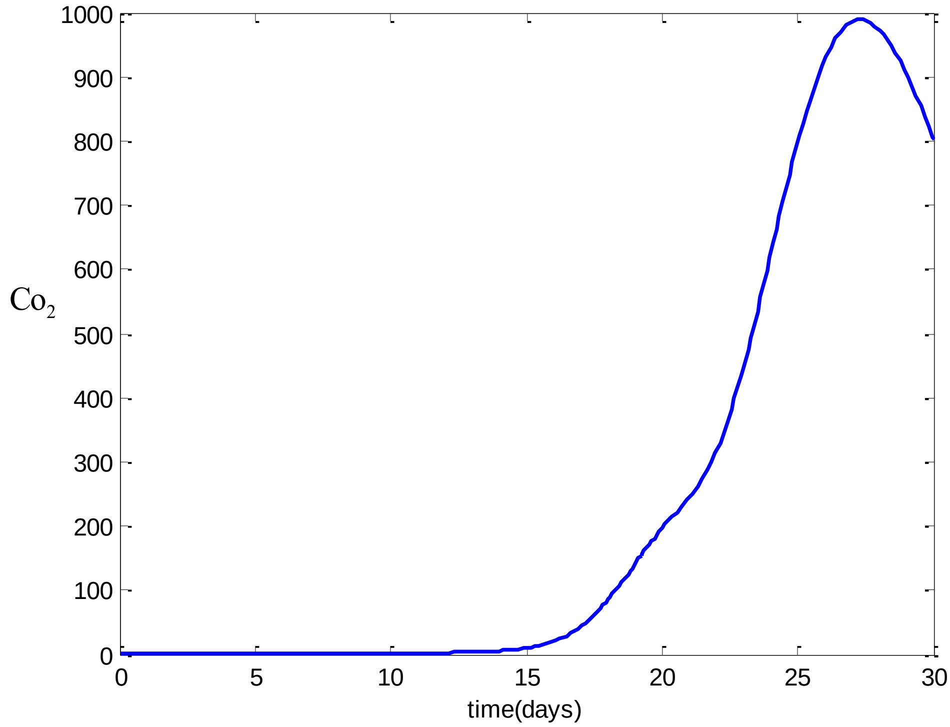


Figure 5.37: The graph shows the proportion of Co_2 with time. Co_2 is the highest volume on the 27th day of the menstrual cycle.

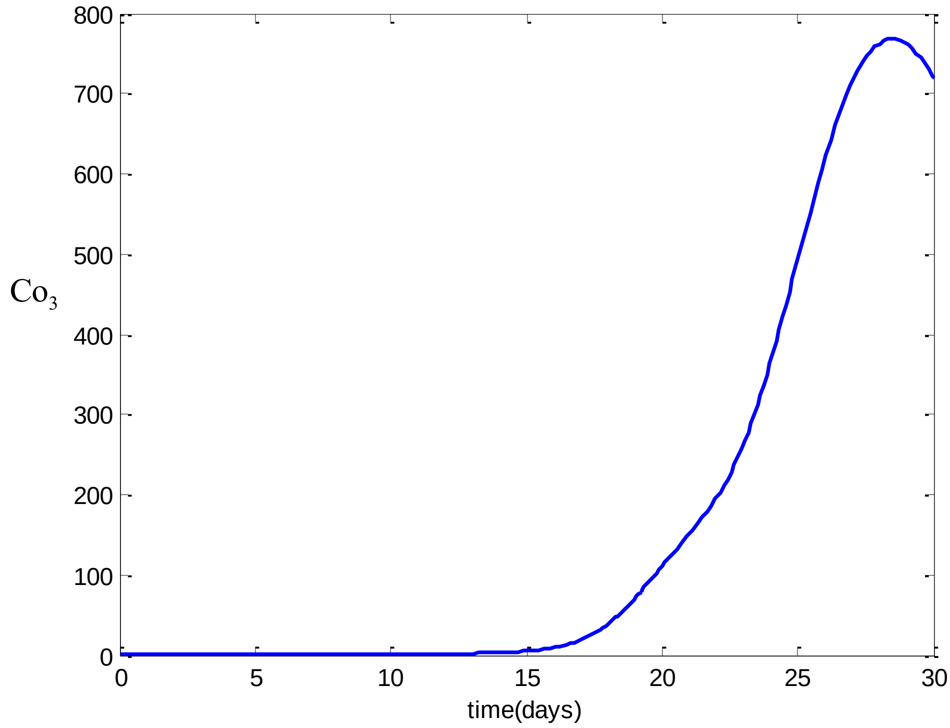


Figure 5.38: The graph shows the proportion of Co_3 with time. Co_3 is the highest volume on 28th day of the menstrual cycle.

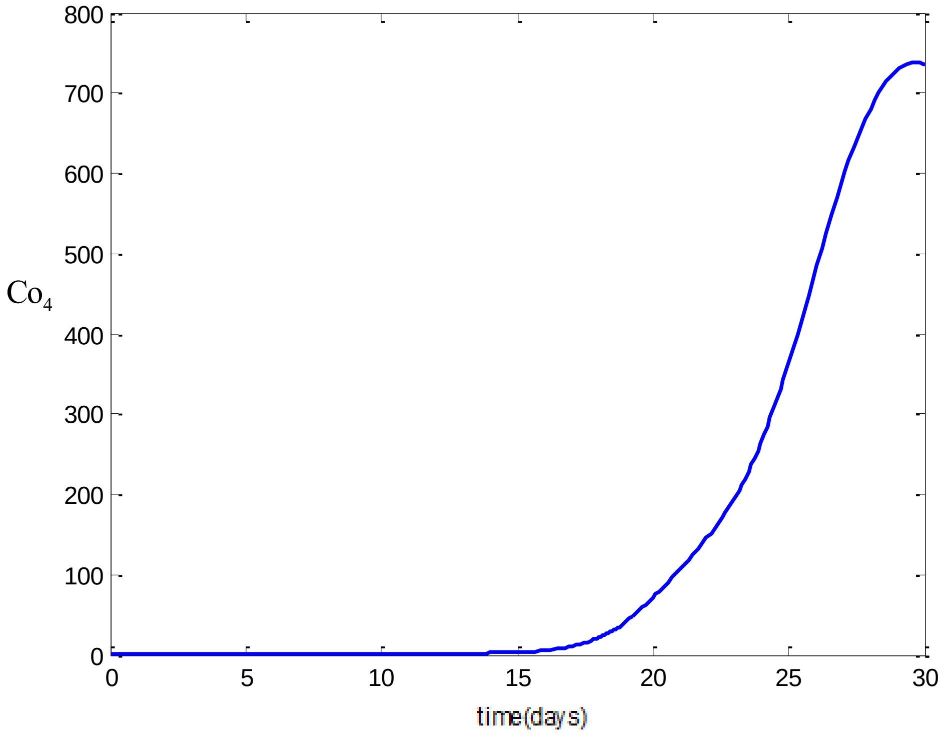


Figure 5.39: The graph shows the proportion of Co_4 with time. Co_4 is the highest volume on the 29th day of the menstrual cycle.

Figures 5.27-5.39 For Stage 1 obesity, it was found that the LH hormone is the highest volume on day 15 and the FSH hormone is the highest volume on day 17. The parameters are similar to those in Figures 5.1-5.13: $K_{aLH,p} = 31.22$ ng/mL, $k_{LH} = 2.49$ day^{-1}, $V_{1,LH} = 1263.4$ IU/day, $cl_{LH,p} = 0.07$ mL/ng, $cl_{LH,E} = 0.0049$ mL/pg, $A_{LH} = 14$ day^{-1}, $A_{FSH} = 8.21$ day^{-1}, $V_{FSH} = 5700$ IU/day, $K_{aFSH,Ac} = 641$ IU/mL, $k_{FSH} = 7.29$ day^{-1}, $\gamma = 0.0202$, $cl_{FSH,p} = 644$mL/ng, $\alpha = 0.7736$, $cl_{FSH,E} = 0.16$ mL/pg, $K_{nLH} = 360$pg/mL, $V_{2,LH} = 91000$ IU/day, $\beta = 0.1566$, LH[0]=40, MP_{LH}[0]=12, FSH[0]=20, MP_{FSH}[0]=11, MMe[0]=1, MSe[0]=5, MPe[0]=1, MS_1[0]=1, MS_2[0]=1, MC_1[0]=1, MC_2[0]=1, MC_3[0]=1, MC_4[0]=1.

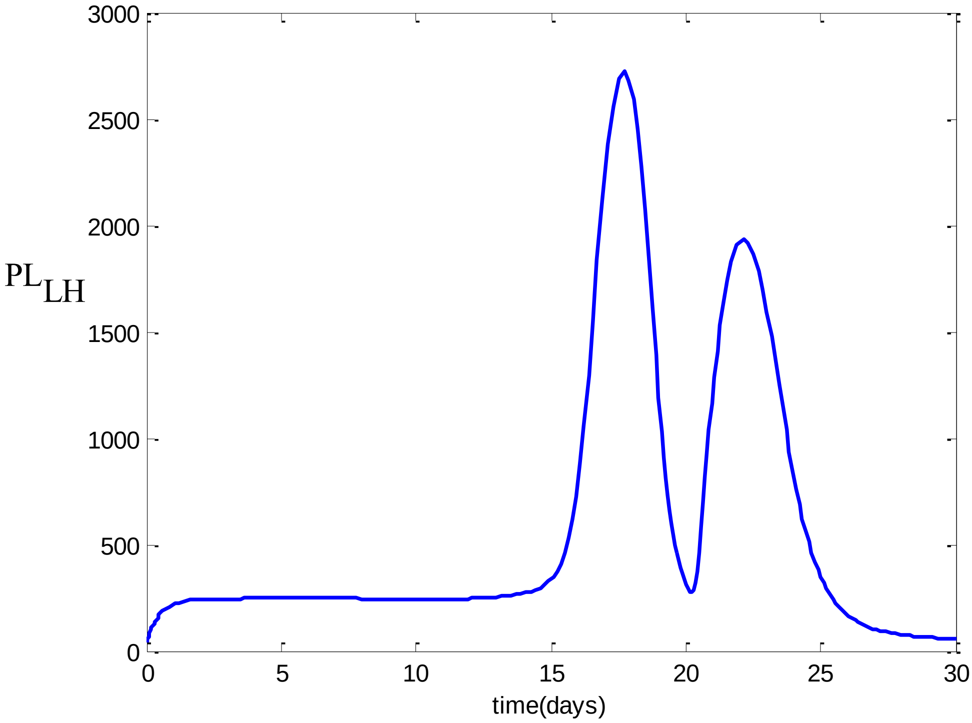


Figure 5.40: The graph shows the proportion of PL_{LH} with time. PL_{LH} is the highest volume on the 18th day of the menstrual cycle.

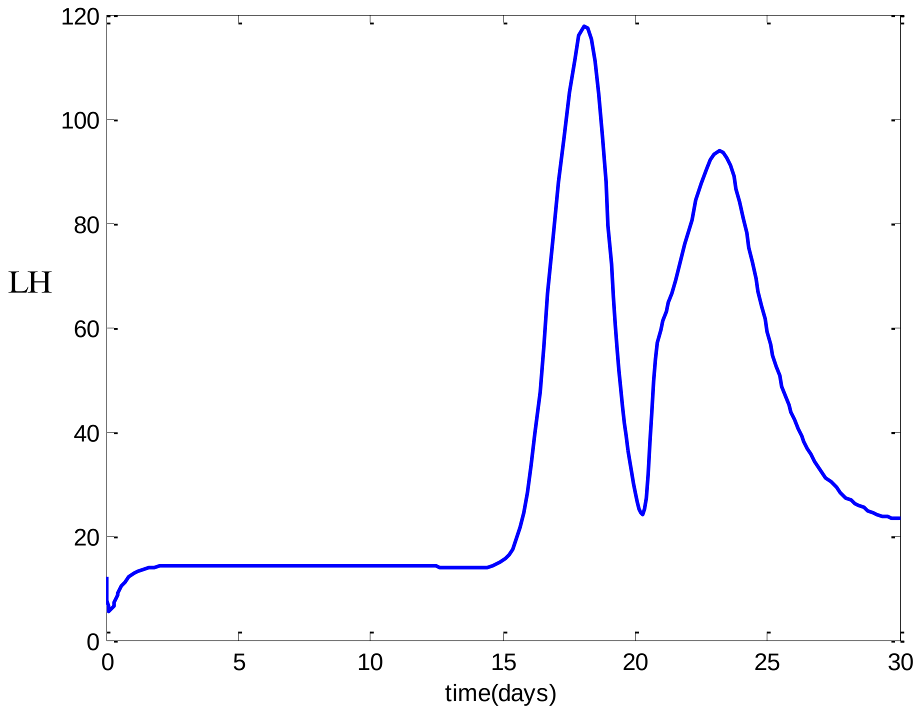


Figure 5.41: The graph shows the proportion of LH with time. LH is the highest volume on the 18th day, which is the stage of late follicular phase.

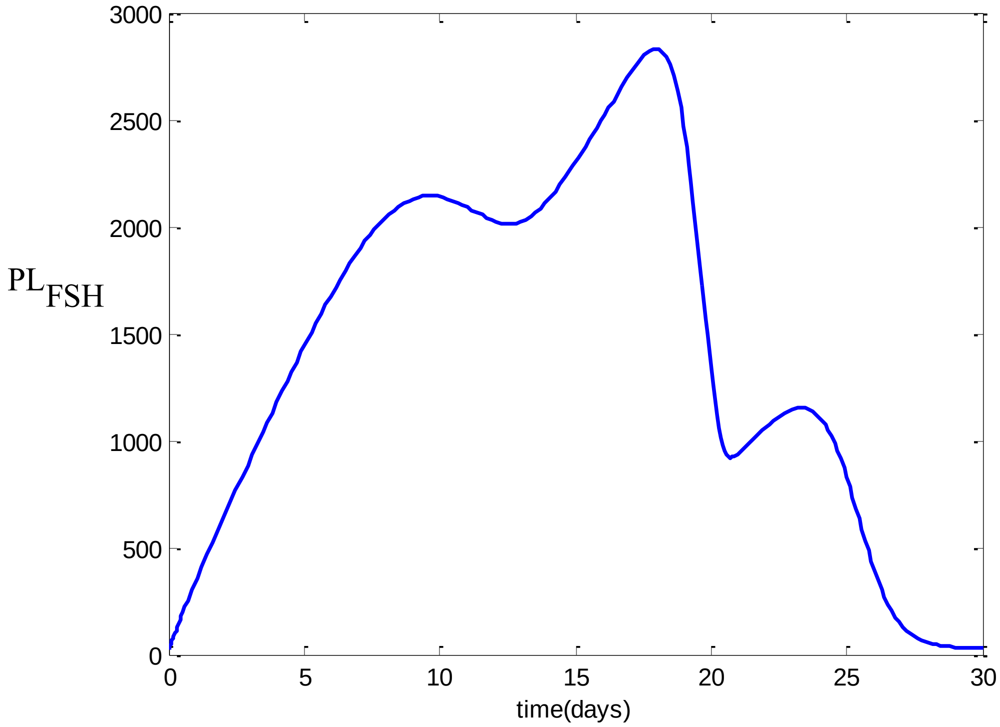


Figure 5.42: The graph shows the proportion of PL_{FSH} with time. PL_{FSH} is the highest volume on the 18th day of the menstrual cycle.

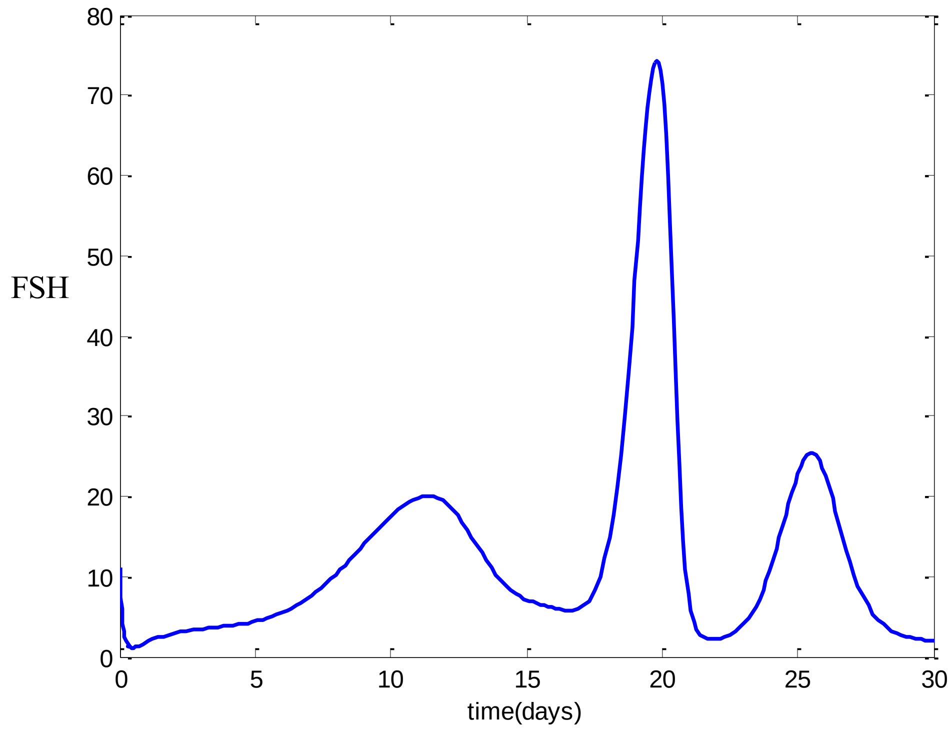


Figure 5.43: The graph shows the proportion of FSH with time. FSH is the highest volume on the 20th day, which is the stage of late follicular phase.

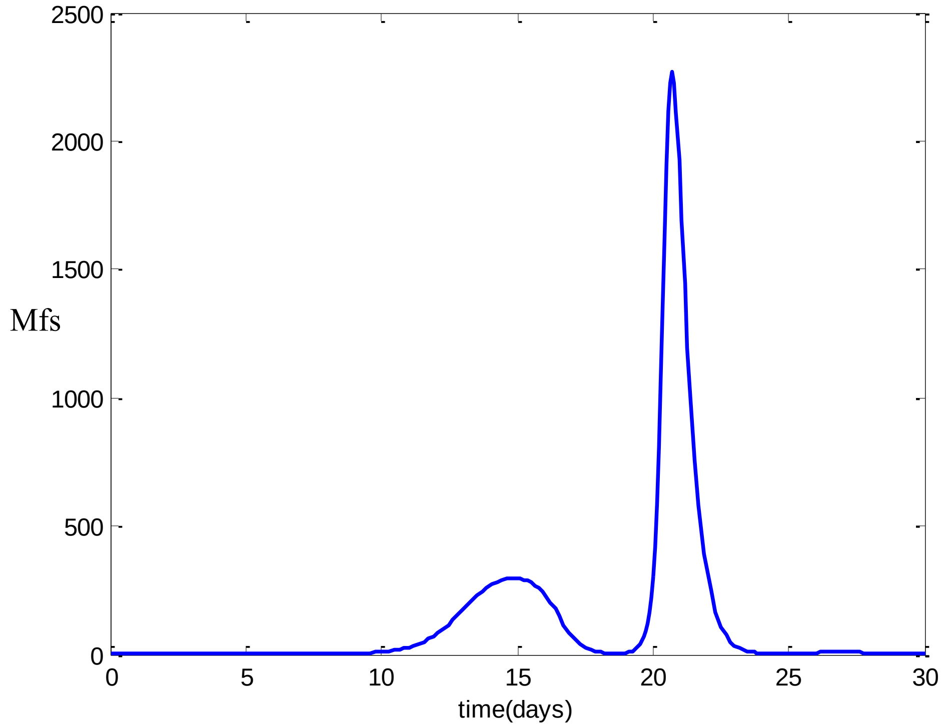


Figure 5.44: The graph shows the proportion of Mfs with time. Mfs is the highest volume on the 21st day of the menstrual cycle.

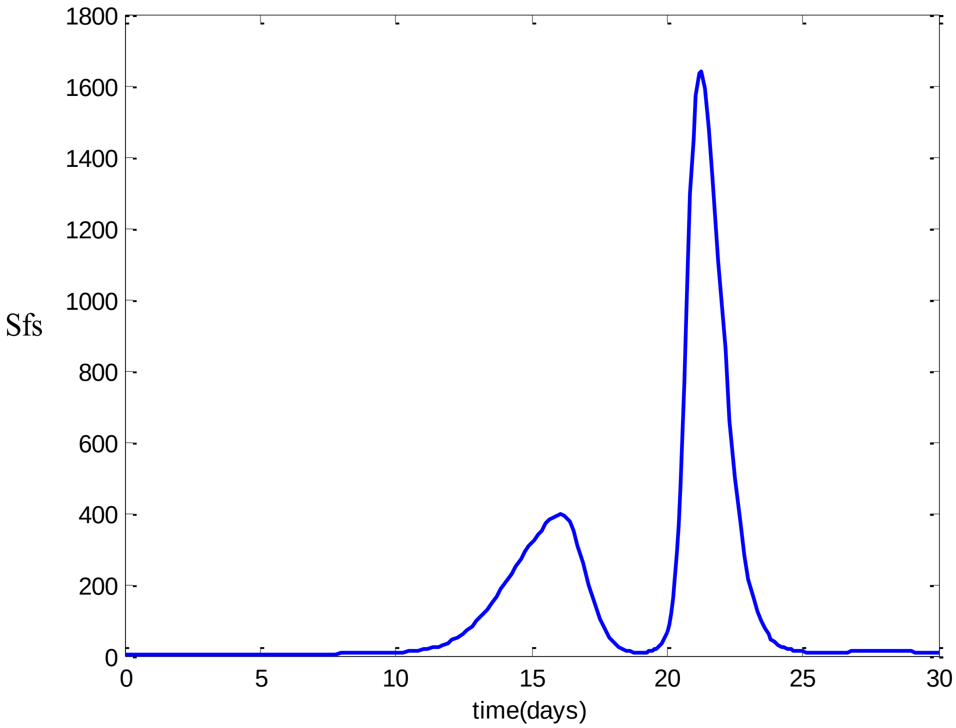


Figure 5.45: The graph shows the proportion of Sfs with time. Sfs is the highest volume on the 21st day of the menstrual cycle.

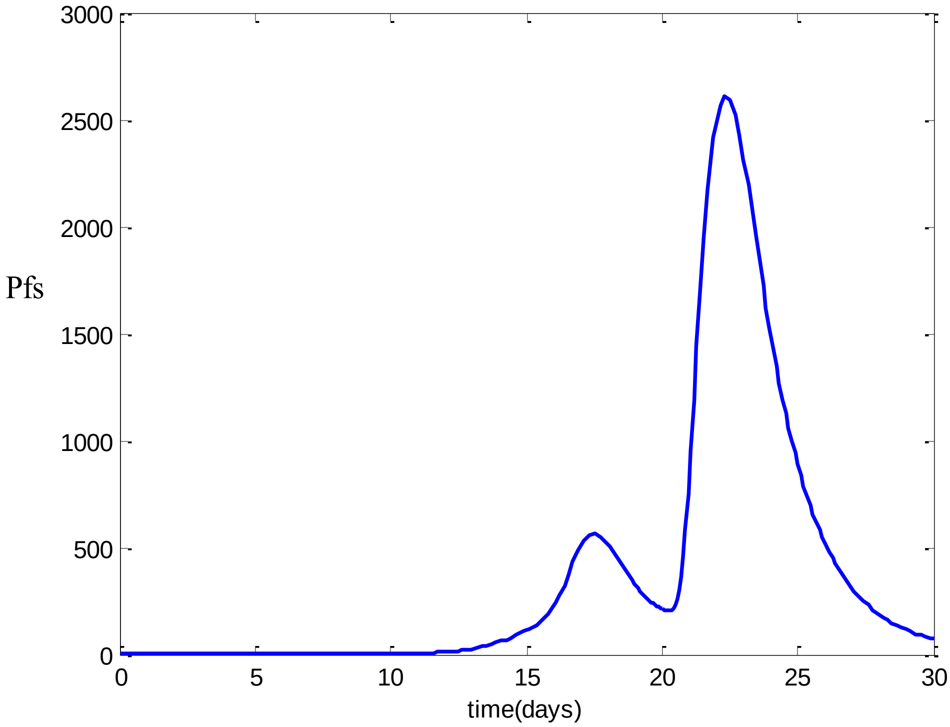


Figure 5.46: The graph shows the proportion of Pfs with time. Pfs is the highest volume on the 23rd day of the menstrual cycle.

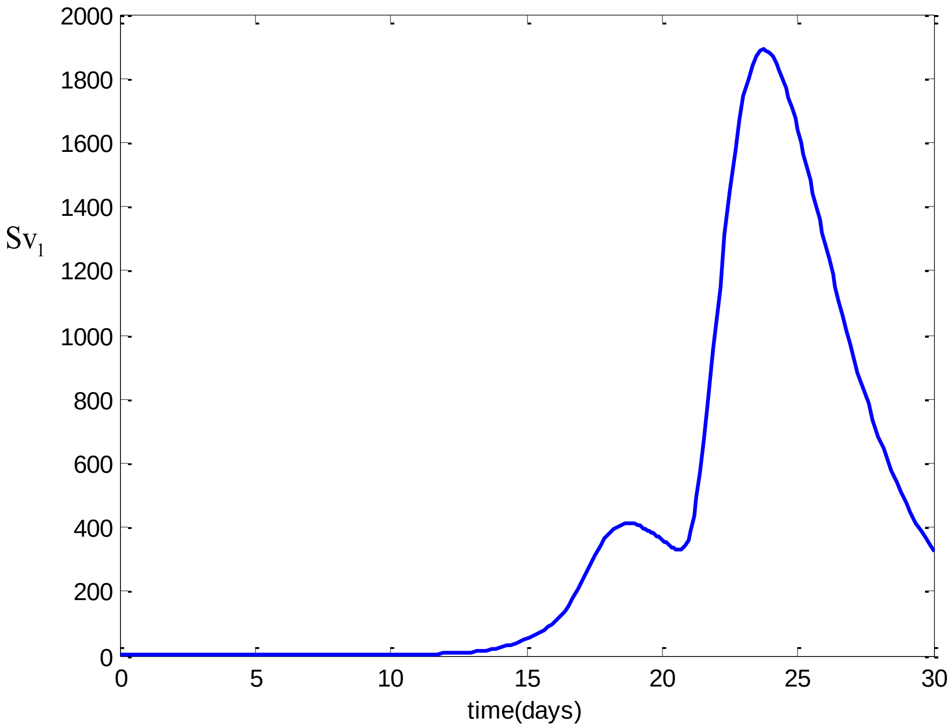


Figure 5.47: The graph shows the proportion of Sv_1 with time. Sv_1 is the highest volume on the 24th day of the menstrual cycle.

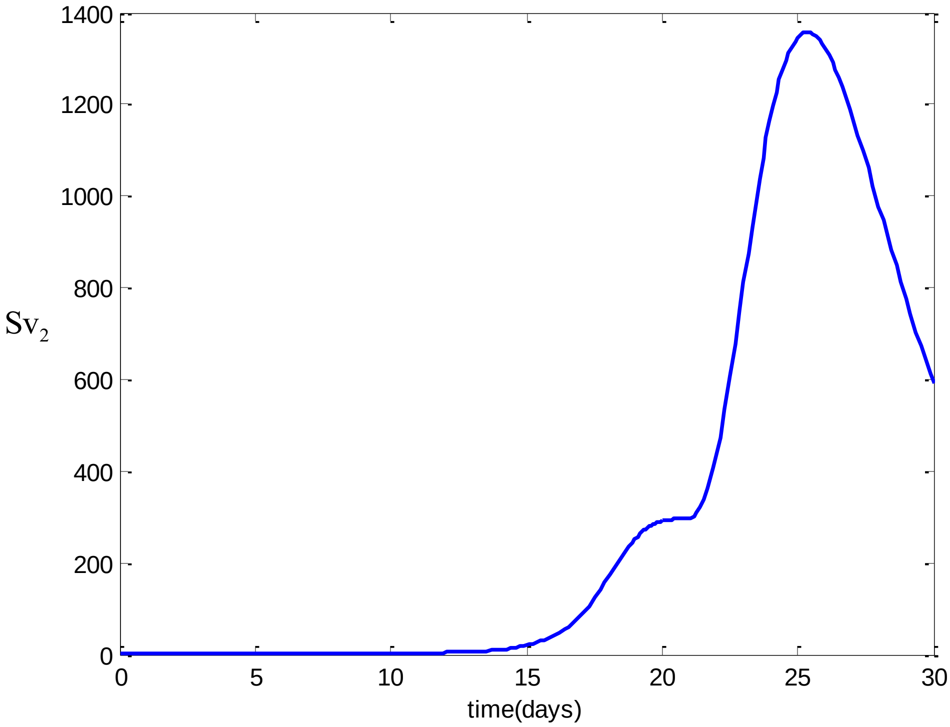


Figure 5.48: The graph shows the proportion of Sv_2 with time. Sv_2 is the highest volume on the 25th day of the menstrual cycle.

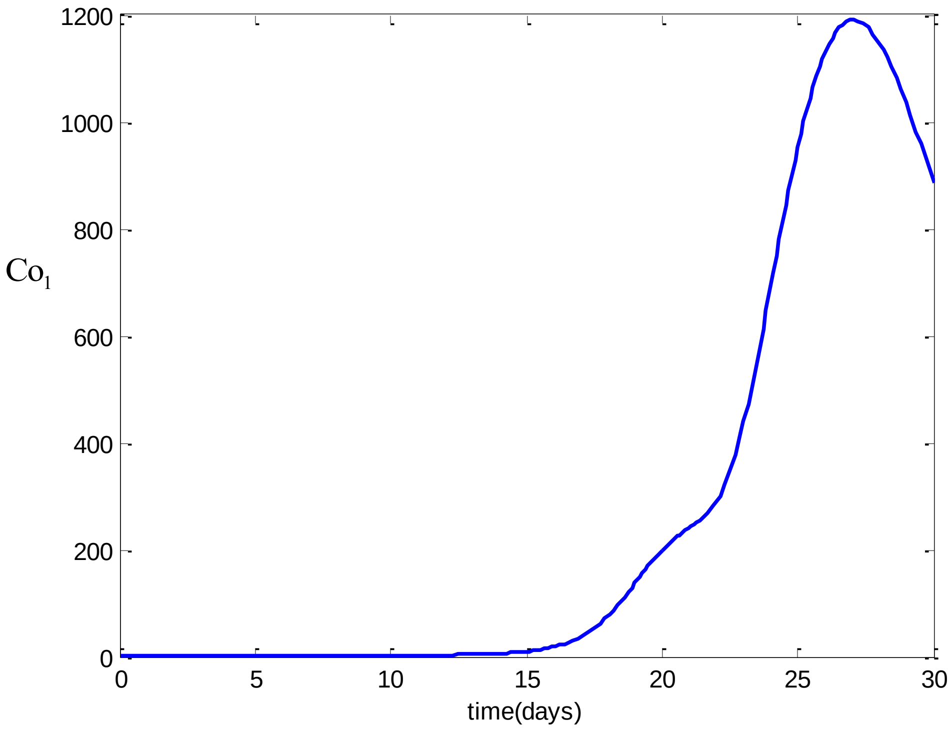


Figure 5.49: The graph shows the proportion of Co_1 with time., Co_1 is the highest volume on the 27th day of the menstrual cycle.

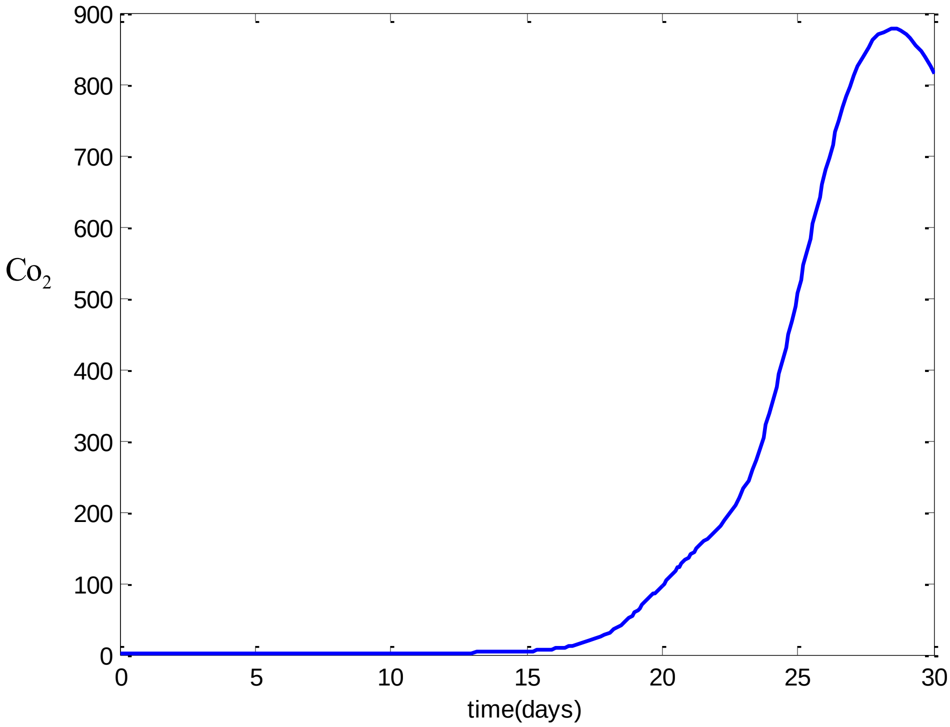


Figure 5.50: The graph shows the proportion of Co_2 with time. Co_2 is the highest volume on the 28th day of the menstrual cycle.

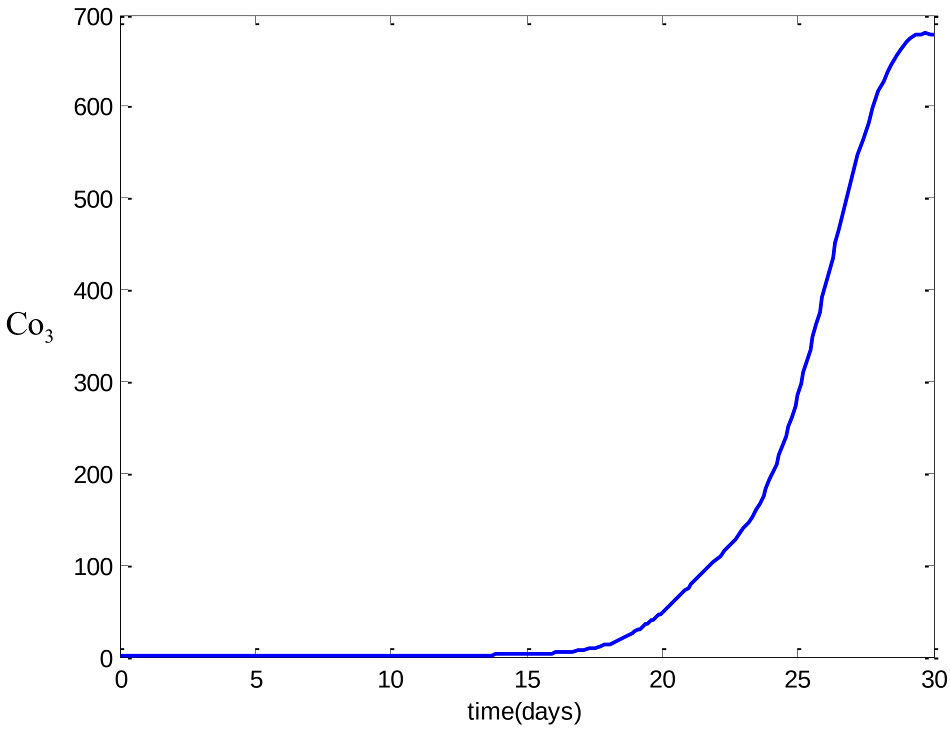


Figure 5.51: The graph shows the proportion of Co_3 with time. Co_3 is the highest volume on 29th day of the menstrual cycle.

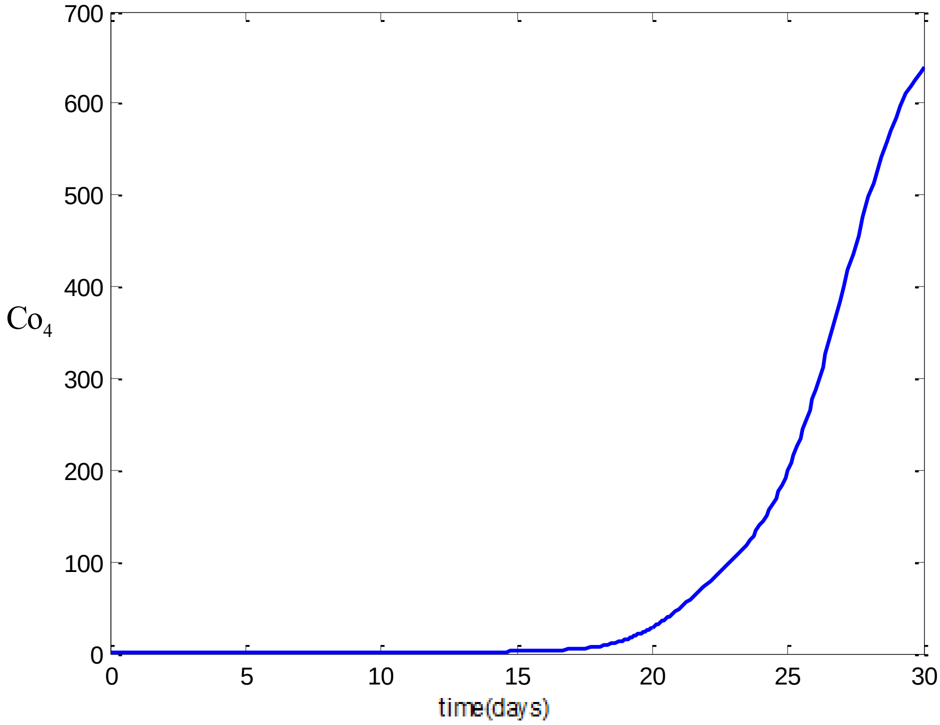


Figure 5.52: The graph shows the proportion of Co_4 with time. Co_4 is the highest volume on the 30th day of the menstrual cycle.

For Stage 2 obesity, it was found that the LH hormone is the highest volume on day 15 and the FSH hormone is the highest volume on day 18. It can be seen in figures 5.40-5.52. The parameters are similar to those in Figures 5.1-5.13:

$K_{aLH,p} = 31.22$ ng/mL, $k_{LH} = 2.49$ day^{-1}, $V_{1,LH} = 1263.4$ IU/day, $cl_{LH,p} = 0.07$ mL/ng, $cl_{LH,E} = 0.0049$ mL/pg, $A_{LH} = 14$ day^{-1}, $A_{FSH} = 8.21$ day^{-1}, $V_{FSH} = 5700$ IU/day, $K_{aFSH,Ac} = 641$ IU/mL, $k_{FSH} = 7.29$ day^{-1}, $\gamma = 0.0202$, $cl_{FSH,p} = 644$mL/ng, $\alpha = 0.7736$, $cl_{FSH,E} = 0.16$ mL/pg, $K_{nLH} = 360$pg/mL, $V_{2,LH} = 91000$ IU/day, $\beta = 0.1566$, LH[0]=40, MP_{LH}[0]=12, FSH[0]=20, MP_{FSH}[0]=11, MMe[0]=1, MSe[0]=5, MPe[0]=1, MS_1[0]=1, MS_2[0]=1, MC_1[0]=1, MC_2[0]=1, MC_3[0]=1, MC_4[0]=1.

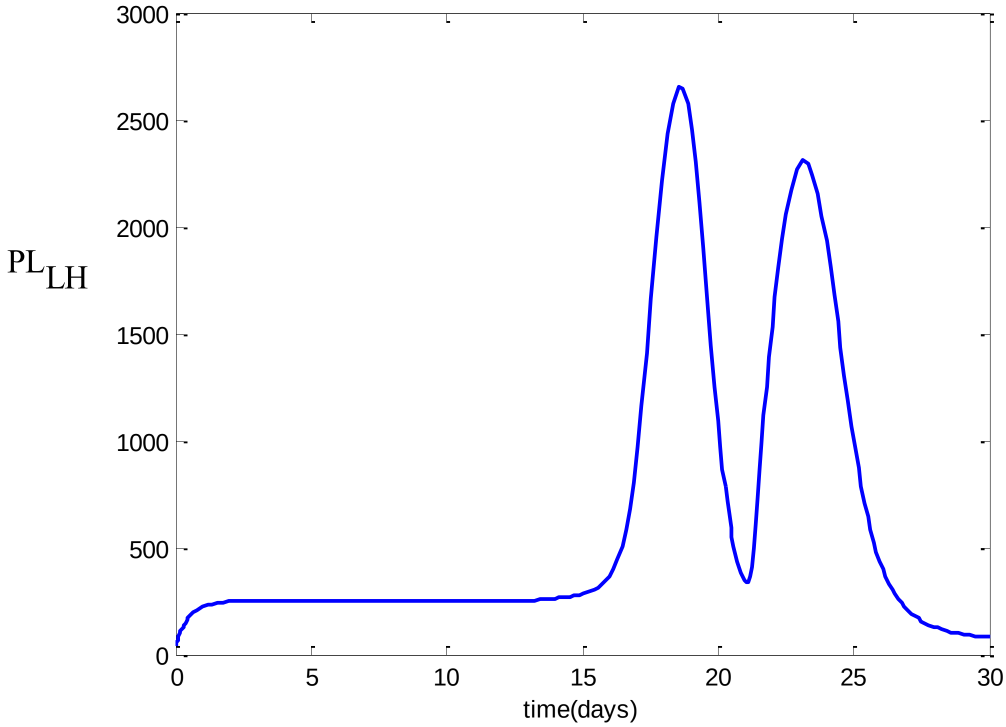


Figure 5.53: The graph shows the proportion of PL_{LH} with time. PL_{LH} is the highest volume on the 19th day of the menstrual cycle.

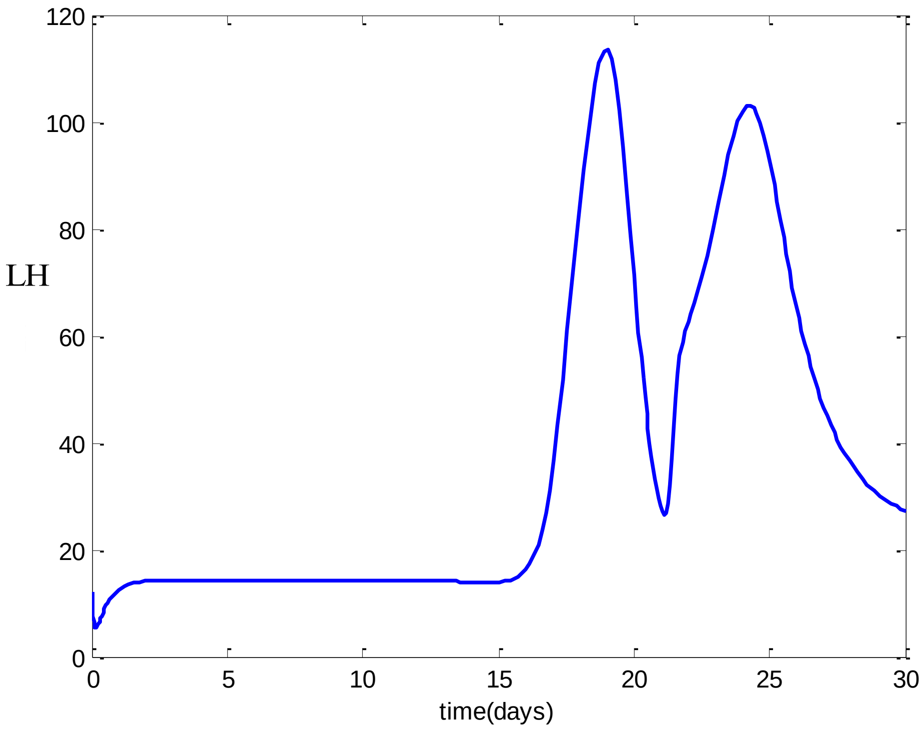


Figure 5.54: The graph shows the proportion of LH with time. LH is the highest volume on the 19th day, which is the stage of late follicular phase.

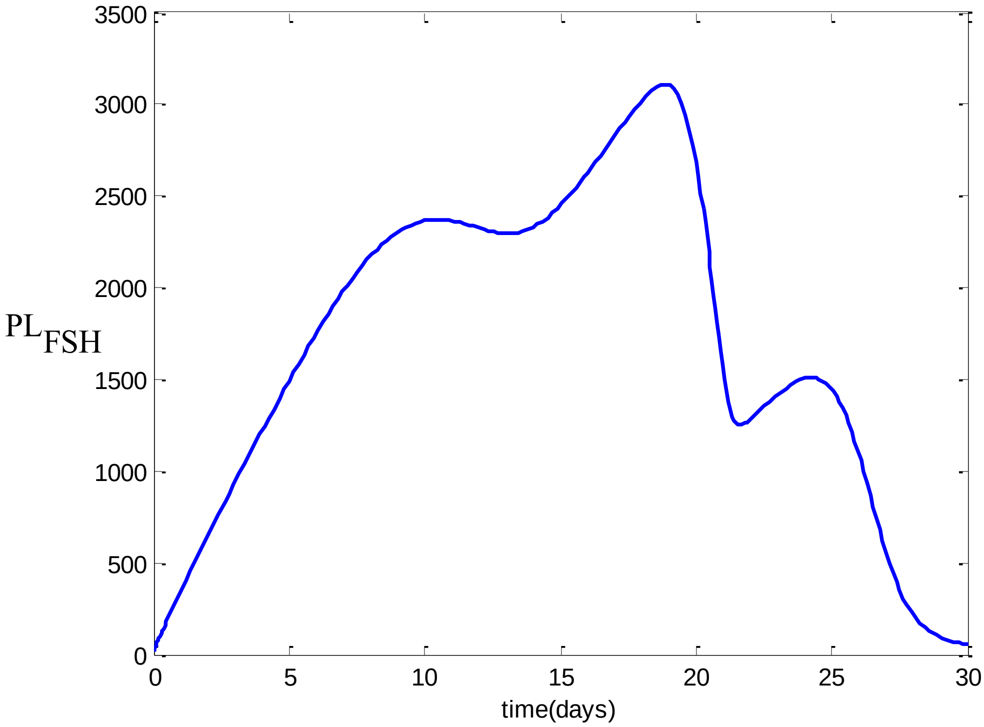


Figure 5.55: The graph shows the proportion of PL_{FSH} with time. PL_{FSH} is the highest volume on the 19th day of the menstrual cycle.

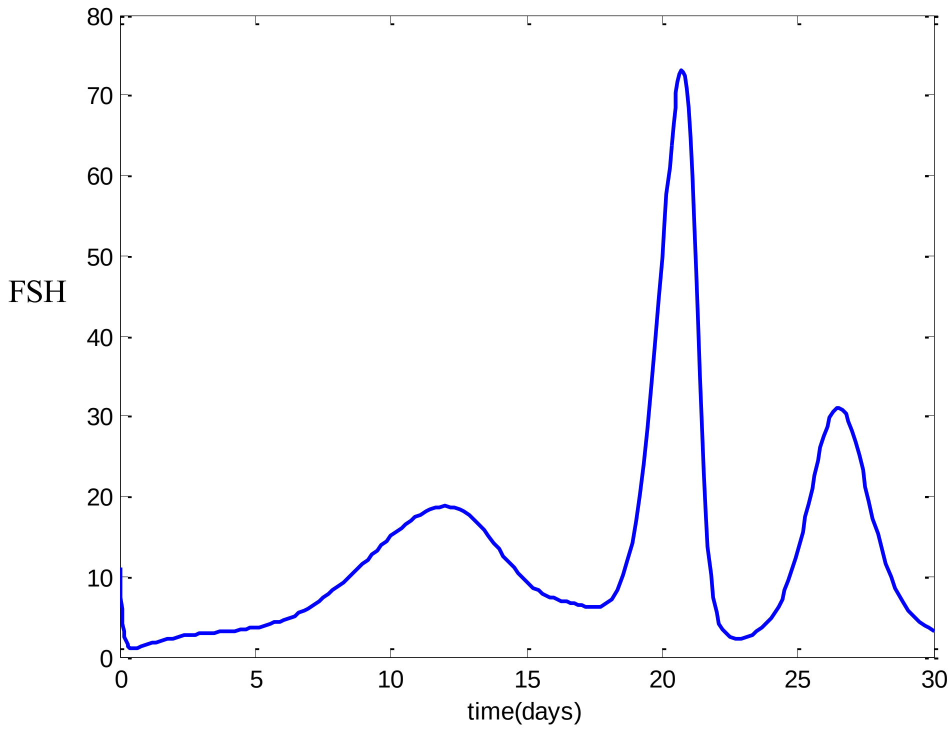


Figure 5.56: The graph shows the proportion of FSH with time. FSH is the highest volume on the 21st day, which is the stage of late follicular phase.

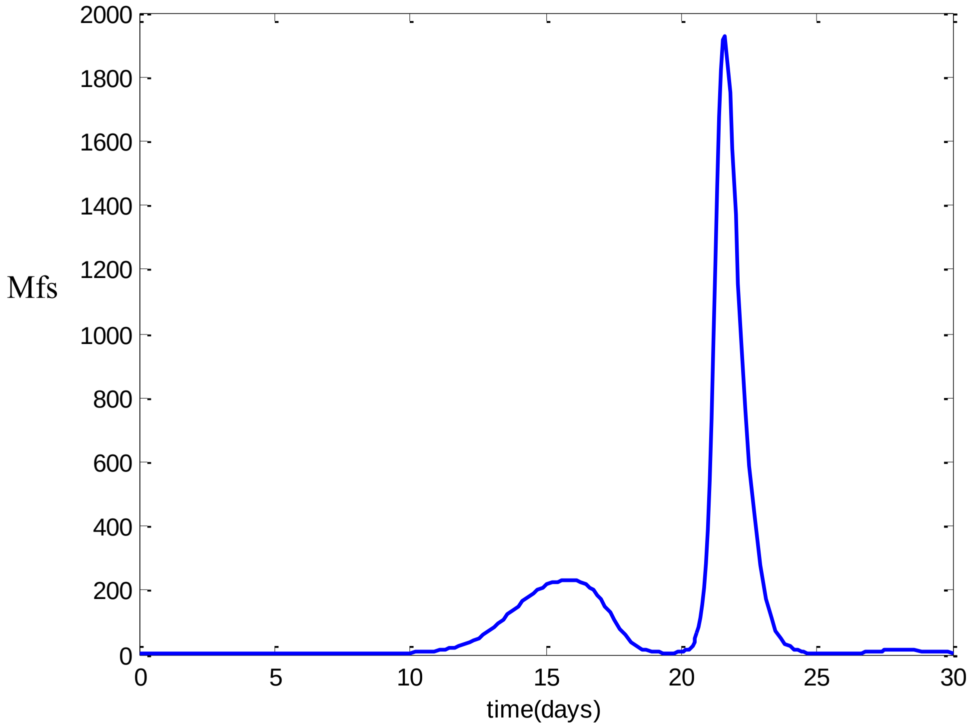


Figure 5.57: The graph shows the proportion of Mfs with time. Mfs is the highest volume on the 22nd day of the menstrual cycle.

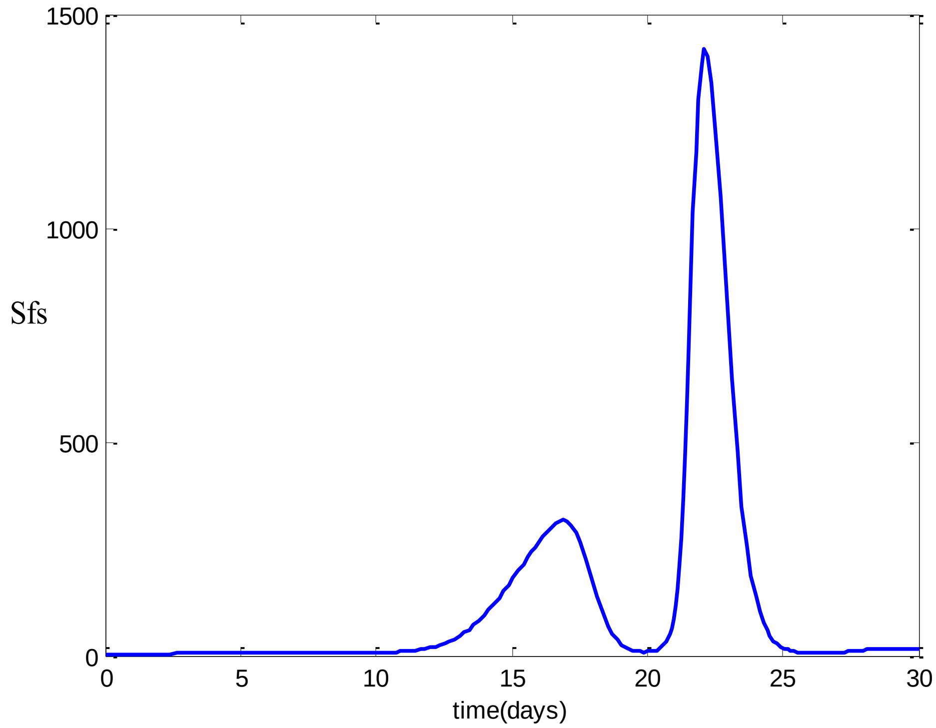


Figure 5.58: The graph shows the proportion of Sfs with time. Sfs is the highest volume on the 22nd day of the menstrual cycle.

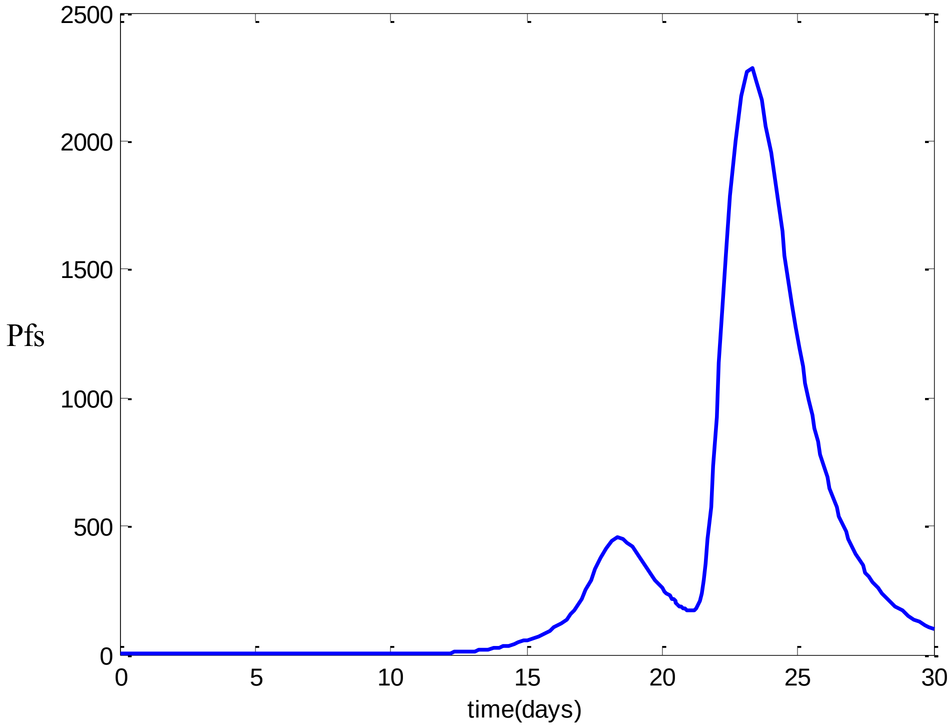


Figure 5.59: The graph shows the proportion of Pfs with time. Pfs is the highest volume on the 23rd day of the menstrual cycle.

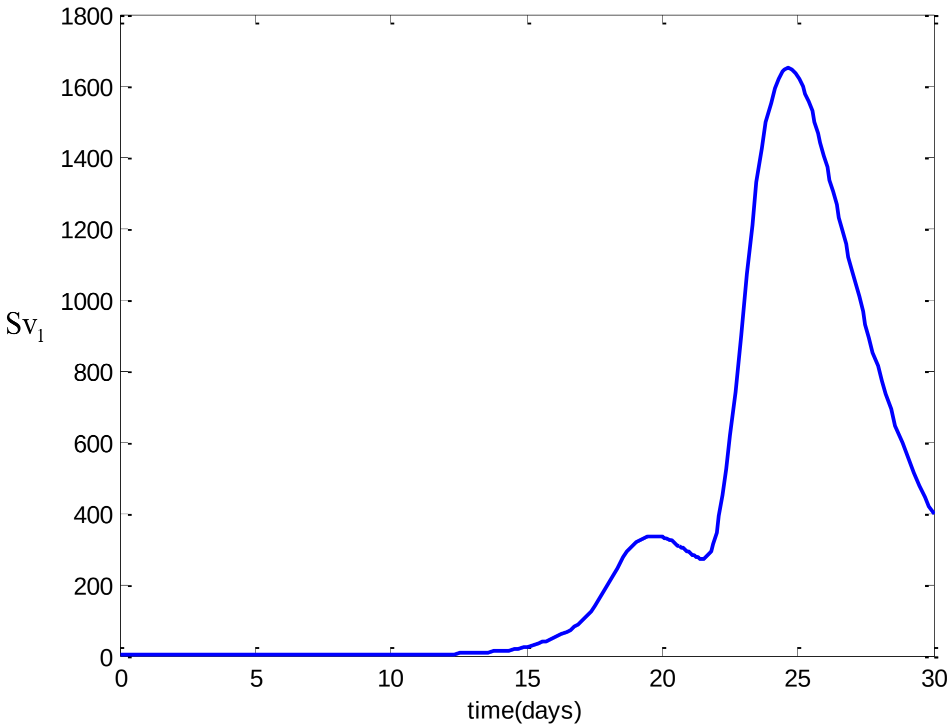


Figure 5.60: The graph shows the proportion of Sv_1 with time. Sv_1 is the highest volume on the 24th day of the menstrual cycle.

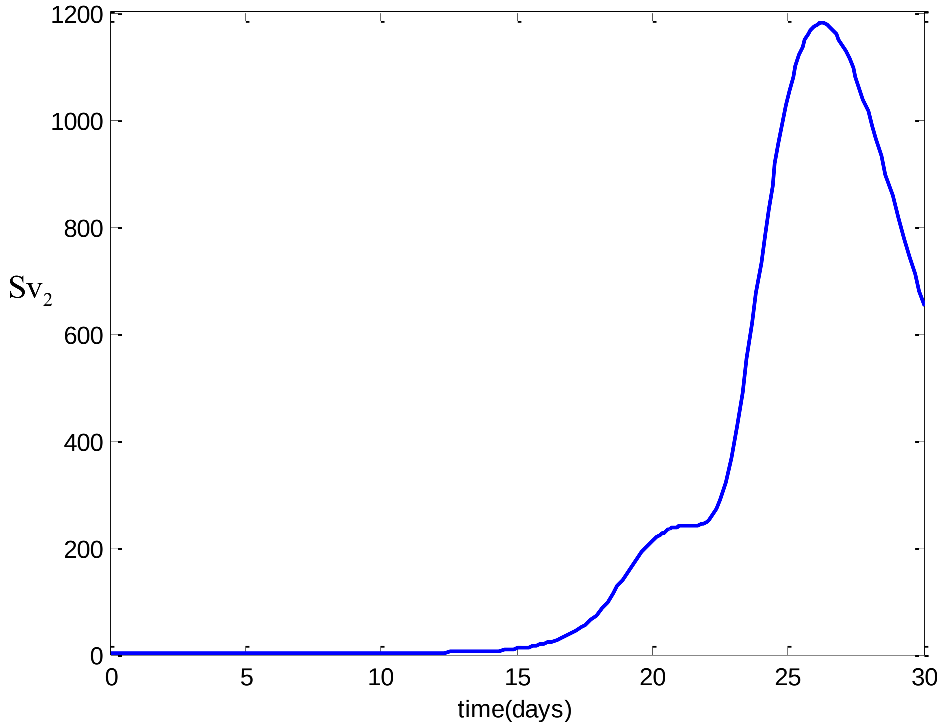


Figure 5.61: The graph shows the proportion of Sv_2 with time. Sv_2 is the highest volume on the 26th day of the menstrual cycle.

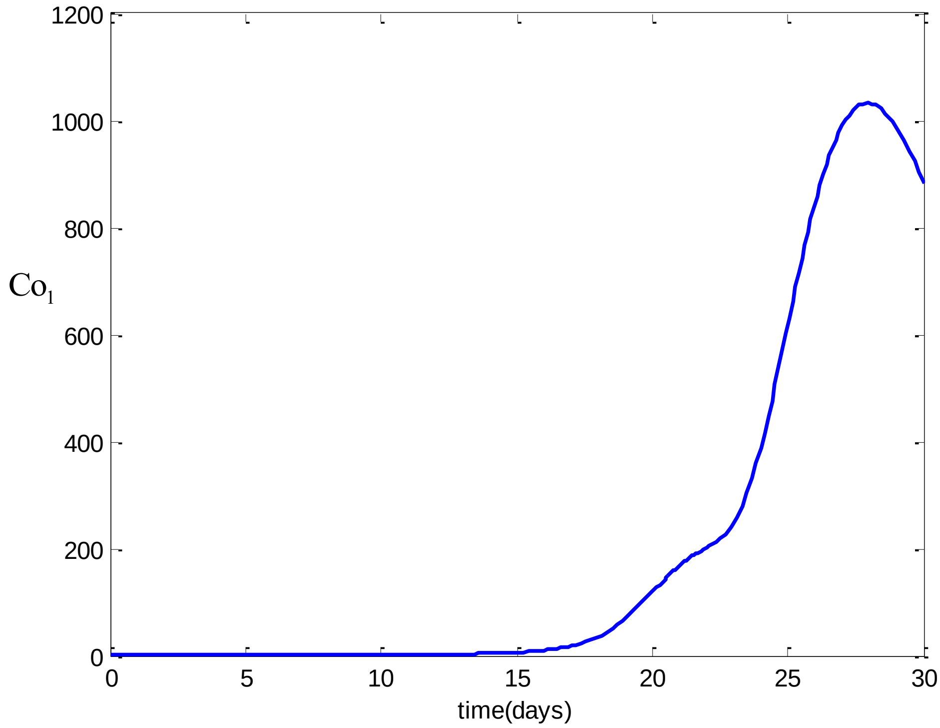


Figure 5.62: The graph shows the proportion of Co_1 with time. Co_1 is the highest volume on the 28th day of the menstrual cycle.

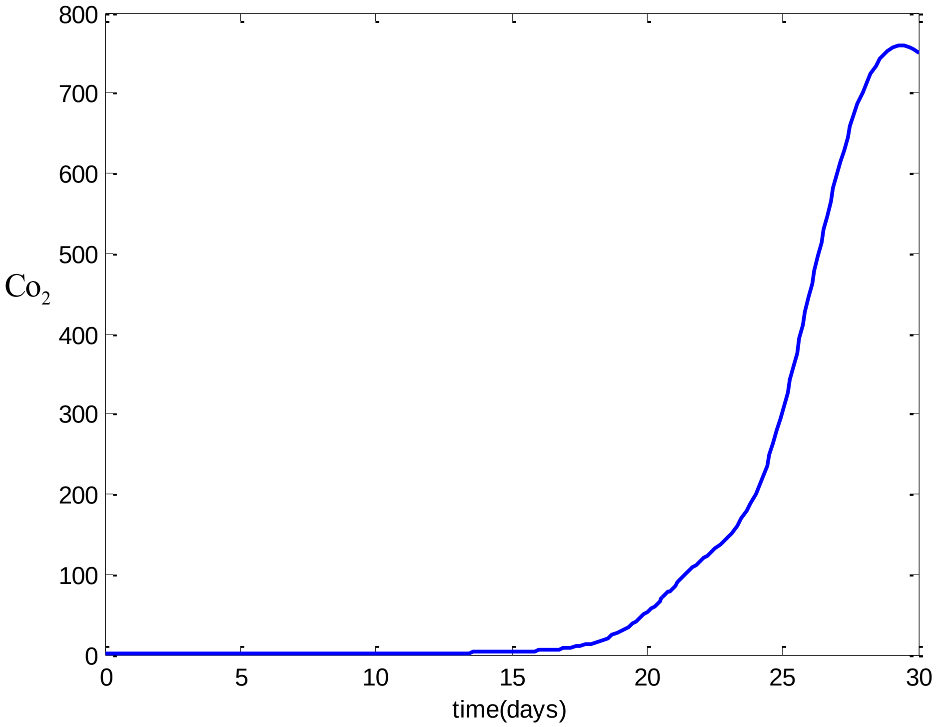


Figure 5.63: The graph shows the proportion of Co_2 with time. Co_2 is the highest volume on 29th day of the menstrual cycle.

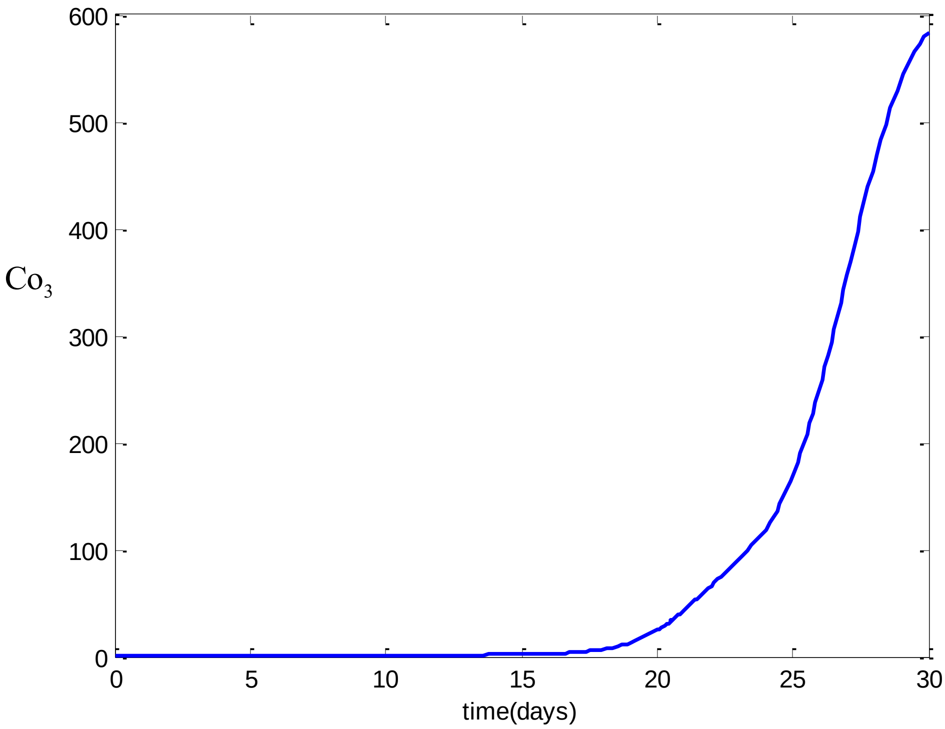


Figure 5.64: The graph shows the proportion of Co_3 with time. Co_3 is the highest volume on the 30th day of the menstrual cycle.

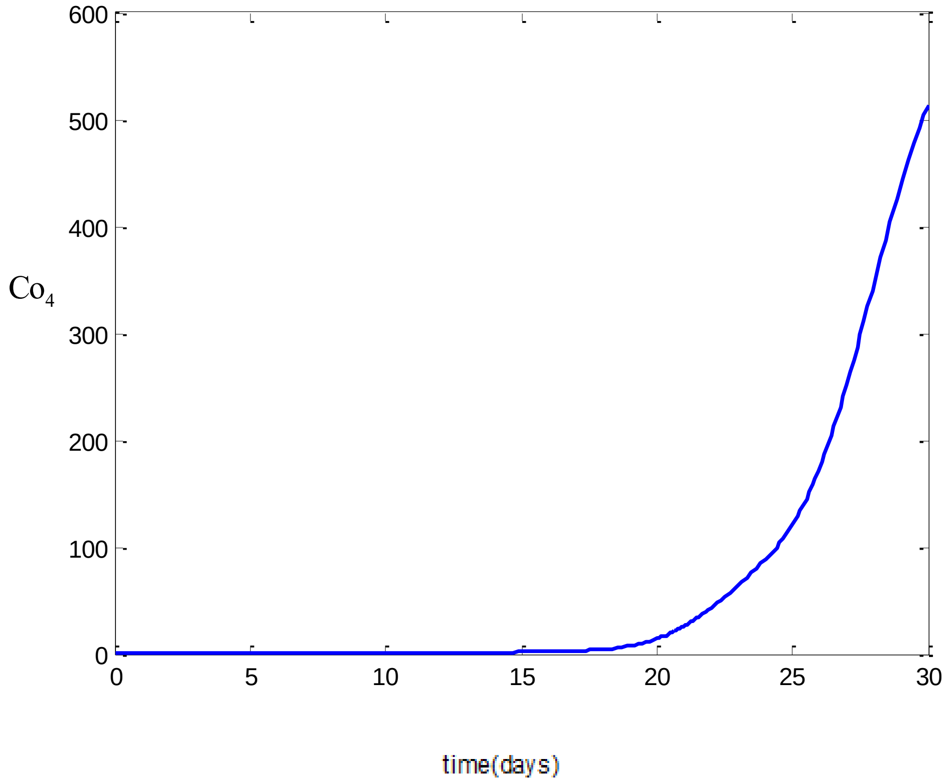


Figure 5.65: The graph shows the proportion of Co_4 with time. Co_4 is the highest volume on the 31[st] day of the menstrual cycle.

Figures 5.53-5.65 For Severe obesity, it was found that the LH hormone is the highest volume on day 16 and the FSH hormone is the highest volume on day 18. The parameters are similar to those in Figures 5.1-5.13: $K_{aLH,p} = 31.22\,\text{ng/mL}$, $k_{LH} = 2.49\ \text{day}^{-1}$, $V_{1,LH} = 1263.4\ \text{IU/day}$, $cl_{LH,p} = 0.07\,\text{mL/ng}$, $cl_{LH,E} = 0.0049\ \text{mL/pg}$, $A_{LH} = 14\ \text{day}^{-1}$, $A_{FSH} = 8.21\ \text{day}^{-1}$, $V_{FSH} = 5700\ \text{IU/day}$, $K_{aFSH,Ac} = 641\ \text{IU/mL}$, $k_{FSH} = 7.29\ \text{day}^{-1}$, $\gamma = 0.0202$, $cl_{FSH,p} = 644\text{mL/ng}$, $\alpha = 0.7736$, $cl_{FSH,E} = 0.16\ \text{mL/pg}$, $K_{nLH} = 360\text{pg/mL}$, $V_{2,LH} = 91000\ \text{IU/day}$, $\beta = 0.1566$, LH[0]=40, MP_{LH}[0]=12, FSH[0]=20, MP_{FSH}[0]=11, MMe[0]=1, MSe[0]=5, MPe[0]=1, MS_1[0]=1, MS_2[0]=1, MC_1[0]=1, MC_2[0]=1, MC_3[0]=1, MC_4[0]=1.

From the results above, any person who has a BMI between 18.5-23.4 is a person whose weight is normal. As shown in Figures 5.1-5.13, LH the hormone testosterone has the highest volume on the 14th day, FSH the amount of the hormone estrogen is highest volume on the 16th day, PL_{LH} has the highest volume on the 13th day, PL_{FSH} has the highest volume on the 14th day, Mfs has the highest volume on the 12th day, Sfs has the highest volume on the 12th day, Pfs has the highest volume on the 14th day. Meanwhile, Sv_1 has the highest volume on the 15th day, Sv_2 has the highest volume on the 17th day, Co_1 has the highest volume on the 18th day, Co_2 has the highest volume on the 19th day, and Co_3 has the highest volume on the 21st day. The highest volume of Co_4 occurs on the 22nd day.

If BMI is between 23.5-28.4, a person's weight exceeds the normal range, as shown in Figures 5.14-5.26, which show that LH the hormone estrogen is the highest volume on the 16th day, and FSH is the amount of the hormone estrogen peaks on the 17th day. Meanwhile, PL_{LH} has the highest volume on the 16th day, PL_{FSH} has the highest volume on the 16th day, Mfs has the highest volume on the 19th day, Sfs has the highest volume on the 19th day, Pfs has the highest volume on the 21st day. Meanwhile, Sv_1 has the highest volume is on day 22, Sv_2 has the highest volume is on the 23rd day, Co_1 has the highest volume on the 25th day, Co_2 has the highest volume on the 26th day, and Co_3 has the highest volume on the 27th day. The highest volume of Co_4 occurs on the 28th day.

If BMI is between 28.5-34.9, a person's weight is in a state of obesity, as shown in Figures 5.27-5.39. It can be seen that LH is the amount of the hormone estrogen peaks on the 17th day, FSH is the hormone testosterone which is highest volume on the 18th day. PL_{LH} has the highest volume on the 16th day, PL_{FSH} has the highest volume on the 17th day, with Mfs has the highest volume on the 19th day, Sfs has the highest volume on the 20th day, and Pfs has the highest volume on the 21st day. Meanwhile, Sv_1 has the highest volume on the 22th day, Sv_2 has the highest volume on the 24th day, Co_1 has the highest volume on the 26th day, Co_2 has the highest volume on the 27th day, and Co_3 has the highest volume on the 28th day. The highest volume of Co_4 occurs on the 29th day.

If BMI is between 35.0-39.9, a person's weight is in a state of obesity Step 2(see page 67). as shown in Figures 5.40-5.52, LH is the hormone testosterone which the has the highest volume on the 18^{th} day, FSH is the amount of the hormone estrogen which is highest volume on the 20^{th} day, PL_{LH} is the highest volume on 18^{th} day, PL_{FSH} is the highest volume on the 18^{th} day, Mfs has the highest volume on the 21^{st} day, Sfs has the highest volume on the 21^{st} day, and Pfs has the highest volume on the 23^{rd} day. Meanwhile, Sv_1 has the highest volume on 24^{th} day, Sv_2 has the highest volume on the 25^{th} day, Co_1 has the highest volume on the 27^{th} day, Co_2 has the highest volume on the 28^{th} day, with Co_3 has the highest volume on the last 29 days. The highest volume of Co_4 occurs on the 30^{th} day.

If BMI is 40 and above, the person's weight is of the highest volume obesity conditions. As shown in Figure 5.53-5.65, it was found that LH; the hormone estrogen is the highest volume on the 19^{th} day, the FSH hormones peak at day 21, PL_{LH} has the highest volume on the 19^{th} day, PL_{FSH} has the highest volume on the 19^{th} day, Mfs has the highest volume on the 22^{nd} day, Sfs has the highest volume on the 22^{nd} day. Pfs has the highest volume on the 23^{rd} days, Sv_1 has the highest volume on the 24^{th} day, Sv_2 has the highest volume on the 26^{th} day, Co_1 has the highest volume on the 28^{th} day, and Co_2 has the highest volume on the 29^{th} day. Meanwhile, Co_3 has the highest volume on 30^{th} day, and Co_4 has the highest volume on the 31^{st} day.

CHAPTER 6
Conclusions and Suggestions

This research created a mathematical model of the menstrual cycle and a mathematical model of a differential equation of hormones in the menstrual cycles and ovarian cycles accordingly. The equation has the correct balance of the system, which is an equilibrium point: is

$$E(LH^*, PL_{LH}^*, FSH^*, PL_{FSH}^*, Mfs^*, , Sfs^*, Pfs^*, Sv_1^*, Sv_2^*, Co_1^*, Co_2^*, Co_3^*, Co_4^*)$$

the stable equilibrium point when. $w_{01} > 1$ and $w_{02} > 1$.

The first day of menstruation cycle is the day that the dominant follicle is selected within 5-7 days of the menstrual cycle by FSH to stimulate the creation of follicle Estrogen (Estradiol) and the Estrogen level will increase significantly on the 7th day. When there is a high volume of Estradiol (about the 6th day of the cycle), it makes the Pituitary secretion of FSH decrease with negative feedback, and creating Progesterone is the key with the Granulosa cells. FSH will stimulate the production of Activin to the Granulosa cells. Activin enhances the operation of FSH, FSH receptor, expression, and Aromatization, creating activin and LH receptor expression Activin to accelerate LH to stimulate Androgen in Theca cells to form androgen compounds. Estrogen begins to build in the Granulosa cells by LH binding to LH Receptors. Cholesterol is a change to make the Theca Cell Androgen (Androstenedione and Testosterone), and then the second Androgen into Granulosa cells and change Estrogen (Estrone, Estradiol) by requiring FSH in the Aromatization. The amount of higher Estradiol Estrogen takes negative feedback on FSH, thus, reducing the minimum FSH (on the 12th day of the month), which is the lowest point of the period before ovulation. And that higher dose causes Estrogen Positive feedback to LH, which rises steadily during the late follicular phase. Encouraging the creation of Androgen (Progesterone) in Theca cells, Progesterone increases to a certain degree. FSH stimulates the secretion of FSH to rise as volume increases Progesterone (second rise on around 12th day) and Progesterone.

During Ovulation, it was found that Estrogen is increased until the Peak occurs about 13rd-14th day about 24 hours to come to Surge LH by LH Surge 48-50 hours, stretching over approximately 10th-12th day from LH Peak hours will make the egg fall. Around the 14th day, the LH Surge Luteinization stimulates the granulose cells, progesterone and prostaglandins within the follicle. The higher amount of progesterone induces negative feedback which stops making the LH Surge. Progesterone accelerates Proteolytic enzyme and prostaglandins. In order to digest the wall of follicles, prostagladins make FSH increase during mid-cycle and thus fall out of the oocyte and follicle replacement plasminogen. And the amount of a proteolytic enzyme plasmin and prostaglandin is enough for LH receptors to move into the luteal phase.

During the Luteal Phase after Ovulation, it was found that the Progesteron and Estrogen will continuous increase during the Luteal phase, by the level of FSH and LH are low. The amounts of Estrogen and Progesterone are high in the Luteal phase and are reduced about the 25^{th} day, when the Corpus luteum atrophies. Atrophy of the corpus luteum and luteolytic action is due to the creation of Estrogen combined with lower concentrations of Prostaglandin in the ovaries, when a woman is pregnant. In the early stages of pregnancy, HCG performs a luteal function. When the placenta is able to generate steroids, the corpus luteum atrophies around the 28^{th} day. Estradiol, Progesterone, and Activin in the blood reaches the end of the Activin drop which makes the pituitary to secrete FSH profusely. The amount of Estradiol and Progesterone is low and endometrial degrades itself. A period of decreasing of Estradiol and Progesterone makes GnRH pulsatile secretion increase and provides negative feedback to the pituitary. A decrease of Activin and Estradiol combined with an increase of the secretion of GnRH affects FSH. Compared with an increase of LH by increasing both the frequency of FSH secretion, an increase of FSH will help other non-Dominant Follicles, follicles from Atresia is causing the dominant follicle.

To understand how body weight affect the menstrual cycle, it is the first task to review the hormonal control of the normal functioning cycle. The menstrual cycle is influenced by body fat, and obesity can lead to irregularities in the menstrual cycle. Past studies have indicated that 30 - 47% of obese women have irregular cycles, although the incidence of infertility among obese women is not too high. Infertility in this population seems to be related to ovulatory dysfunction. A large case controlled study that compared obesity and ovulatory women with fertility controls found a relationship between BMI at age 18 and subsequent an ovulatory infertility.

The model includes factors that affect the balance of hormones that control the ovulation period. Such factors of obesity are medical criteria used to measure obesity. This is called the Body Mass Index (BMI), which is a popular scale used for the diagnosis of obesity. Any person who is obese has a BMI between 18.5-23.4. When a person's weight is normal, as shown in Fig. 5.1-5.13, it has been found that the LH hormones peak on the 14^{th} day and the FSH hormones are highest volume during the 16^{th} day. BMI of 23.5-28.4 indicates that a person's weight exceeds the normal range, as shown in Fig. 5.14-5.26. It was found that the LH hormones has the highest volume during the 15^{th} day and the FSH hormone has the highest volume during the 17th day. BMI of 28.5-34.9 indicates that a person's weight is in a state of obesity. 1, as shown in Figure 5.27-5.39. It was found that the LH hormone peaks on the 15th day and the FSH hormones are highest volume on the 17th day. If BMI is between 35.0-39.9, a person's weight is in a state of obesity Step 2 (see page 67). As shown in Figure 5.40-5.52, it was found that the LH hormone peaks on the 15th day and the FSH hormone is the highest volume on the 18th day. BMI 40 and above indicate that the person's weight is at the highest volume level of obesity conditions. As shown in Figure 5.53-5.65, it was found that levels of the LH hormones are highest volume during the 16th day and hormone FSH is at the maximum amount during 18th day of the cycle. Obesity affects the balance of LH and FSH hormones that control the menstrual cycle and ovulation. It was found that these hormones produce disorders which cause menstruation to be abnormal.

A considerable problem with a study of the menstrual cycle is to find the menstrual abnormalities that are caused by an imbalance of the hormones that are the most common. The cause of hormonal imbalance is the cause of diabetes. The normal sugar level in the blood is 80-100 mg/dl. LH and FSH hormone relationship in balance. Those people who are susceptible to diabetes or groups with the amount of 100-180 mg/dl of sugar in the blood were found in this group, the hormones LH and FSH. Incipient imbalance and in patients with diabetes is the amount of sugar in the blood of 180 mg/dl or more, making the amount of LH and FSH hormone imbalanced. As a result, the irregular menstruation occurs. The levels of sugar quantity in the blood is associated with the hormones. We can conclude that diabetes has an effect on disorders of hormones. There are many factors that cause stress and hormonal imbalance. These factors cause menstrual irregularities and each factor can occur with different groups of people. The study found that force has exceeded the weight and a condition of diabetes contributes to a malfunction of the menstrual period. In diabetes, it is for the people who are not overweight, the risk criterion of the month. The development of this model studies the relation of age and diabetes to analyze the time period of the next menstrual cycle.

To analyze the factors that affect menstruation and factors that lead to menstrual disorders, a mathematical model based on clinical neurology has been created. The model can provide efficient and practical data. We have the Matlab program to help in the analysis of mathematical models that are consistent with the terms of the menstrual cycle. The program indicates the rate of change of hormones in the menstrual cycle over time.

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Appendix

A.1 Theory

Definition A.1.1 Jacobian Matrix

Let $f(x)=[f_1(x),......,f_m(x)]^T$ be a vector valued function, differentiable at $x=[x_1,x_2......,x_n]$. The **Jacobian matrix** of f at x is defined to be the matrix of partial derivatives:

$$J_f = \begin{bmatrix} \frac{\partial f_1(x)}{\partial x_1} & \cdots & \frac{\partial f_1(x)}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_m(x)}{\partial x_1} & \cdots & \frac{\partial f_m(x)}{\partial x_n} \end{bmatrix}$$

Definition A.1.2 Characteristic polynomial

Let J be a square matrix and I be the identity matrix of identical dimension. The characteristic polynomial is $\det(J-\lambda I_n)$ and the characteristic equation is defined as:

$$\det(J-\lambda I_n)=0.$$

Definition A.1.3 Eigenvalue and Eigenvector

Let J be a linear transformation represented by a matrix J. If there is a vector $X \in \mathbb{R}^n \neq 0$ so that:

$$JX=\lambda X$$

for some scalar λ , then λ is called the eigenvalue of J with a corresponding (right) eigenvector X.

Definition A.1.4 **Equilibrium point**

A point $X_e \in R^n$ is called an equilibrium point of $X' = f(t,X)$ (at time $t^* \in R^+$) if:

$$f(t,X_e) = 0 \quad \text{for all } t \geq t^*$$

Theorem A.1.1 **Stability**

The equilibrium $X = 0$ of $X' = JX$, $t \geq 0$ is stable if all eigenvalues of J have nonpositive real parts and every eigenvalue of J which has a zero real part is a simple zero of the characteristic polynomial of J. The stability properties of ordinary differential equation systems are given by:

$$X_1' = a_{11}X_1 + a_{12}X_2$$
$$X_2' = a_{21}X_1 + a_{22}X_2$$

or in a matrix from:

$$X' = JX$$

where:

$$J = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \dfrac{\partial f_1(x)}{\partial x_1} & \dfrac{\partial f_1(x)}{\partial x_2} \\ \dfrac{\partial f_2(x)}{\partial x_1} & \dfrac{\partial f_2(x)}{\partial x_2} \end{bmatrix}.$$

The characteristic equation is:

$$\begin{vmatrix} a_{11} - \lambda & a_{12} \\ a_{21} & a_{22} - \lambda \end{vmatrix} = 0$$
$$(a_{11} - \lambda)(a_{22} - \lambda) - a_{21}a_{12} = 0$$
$$\lambda^2 - (a_{11} + a_{22})\lambda + a_{11}a_{22} - a_{21}a_{12} = 0$$

The eigenvalues are:

$$\lambda_{1,2} = \frac{(a_{11} + a_{22}) \pm \sqrt{(a_{11} + a_{22})^2 - 4(a_{11}a_{22} - a_{21}a_{12})}}{2}$$

Recall that when $\det J \neq 0$ we classify this equilibrium point according to the following cases which have the eigenvalues λ_1, λ_2 of J, it can be assumed that:

1. λ_1, λ_2 are real and $\lambda_1 < 0, \lambda_2 < 0 : x = 0$ is a stable node.

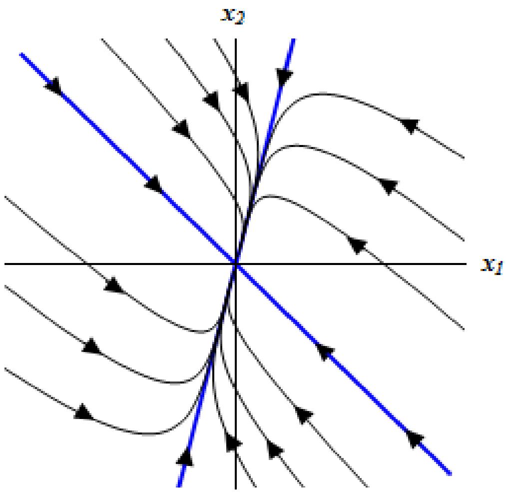

Figure A.1: A stable node.

2. λ_1, λ_2 are real and $\lambda_1 > 0, \lambda_2 > 0 : x = 0$ is an unstable node.

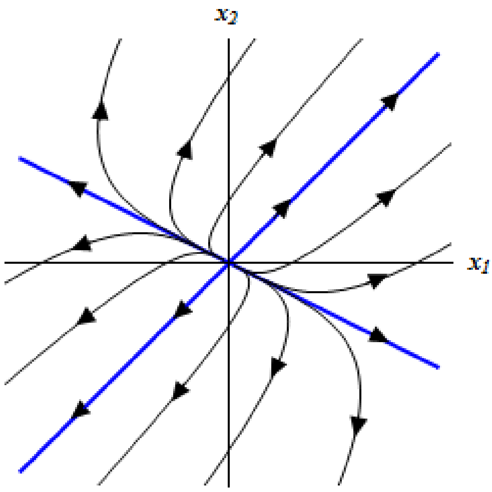

Figure A.2: An unstable node.

3. λ_1, λ_2 are real and $\lambda_1 \lambda_2 < 0 : x = 0$ is a saddle.

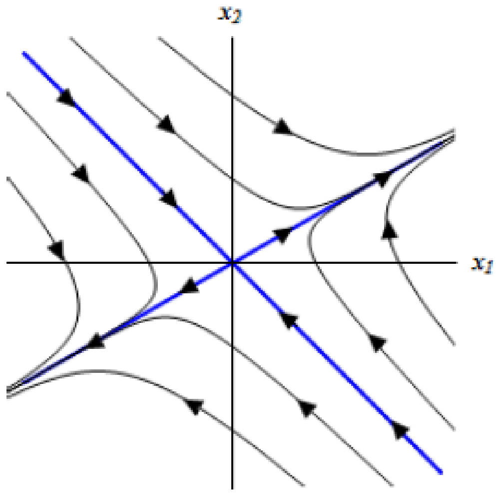

Figure A.3: A saddle point.

4. λ_1, λ_2 are complex conjugates and $\mathrm{Re}\,\lambda_1 = \mathrm{Re}\,\lambda_2 < 0 : x = 0$ is a stable focus (stable spiral node).

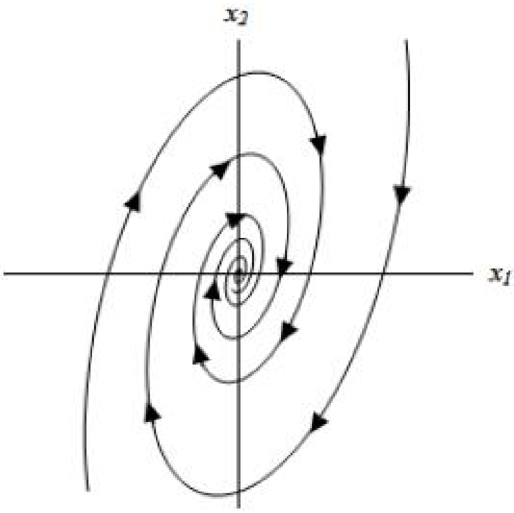

Figure A.4: A stable focus (stable spiral node).

5. λ_1, λ_2 are complex conjugates and $\text{Re}\,\lambda_1 = \text{Re}\,\lambda_2 > 0 : x = 0$ is an unstable focus (unstable spiral node).

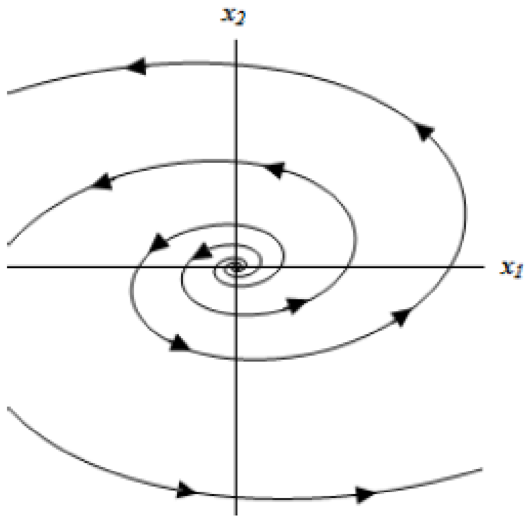

Figure A.5: An unstable focus (unstable spiral node).

6. λ_1, λ_2 are complex conjugates and $\text{Re}\,\lambda_1 = \text{Re}\,\lambda_2 = 0 : x = 0$ is a center.

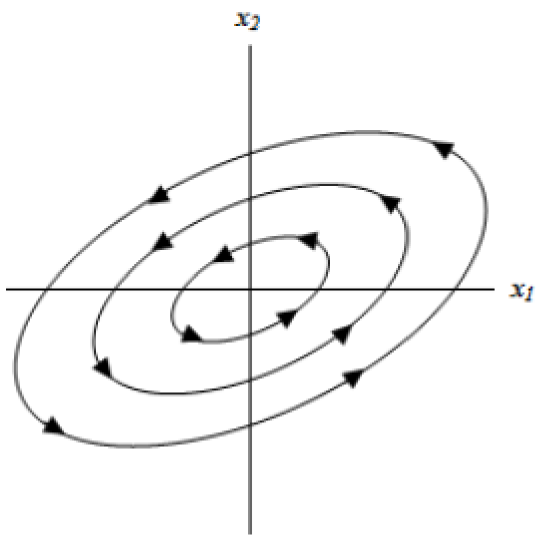

Figure A.6: A center.

Theorem A.1.2 *Poincarė – Bendixson*

Lemma A.2.1 If ξ_0 is an interior point of a transversal L, then for any $\in > 0$ there is a $\delta > 0$ so that any orbit passing through the ball $B(\xi_0, \delta)$ at $t = 0$ must cross L at some point in time $t \in (-\varepsilon, \varepsilon)$.

Lemma A.2.2 A transversal L cannot intersect a positive limit set $\Omega(\phi)$ of a bounded solution ϕ at more than one point.

Corollary A.2.1 Let ϕ be a bounded nonconstant solution of $X' = f(t, X)$ with $\phi(0) = \xi$ and $C^+(\xi) = \{\phi(t) : t \geq 0\}$.

(a) If $\Omega(\phi)$ and $C^+(\xi)$ intersect, then ϕ is a periodic solution.

(b) If $\Omega(\phi)$ contains a nonconstant periodic orbit C, then $\Omega(\phi) = C$.

Let ϕ be a bounded solution of $X' = f(t, X)$ with $\phi(0) = \xi$ if $\Omega(\phi)$ contains no critical points, then either:

(a) ϕ is a periodic solution $[\text{and } \Omega(\phi) = C^+(\xi)]$, or

(b) $\Omega(\phi)$ is a periodic orbit.

If (b) is true, but not (a), then $\Omega(\phi)$ is called a limit cycle.

Proof: If ϕ is periodic, then clearly $\Omega(\phi)$ is the orbit determined by ϕ. So, let us assume that ϕ is not periodic. Since $\Omega(\phi)$ is nonempty, invariant, and free of singular points, it contains a nonconstant and bounded semi-orbit C^+. Hence, there is a point $\xi \in \Omega(\psi)$ where ψ is the solution which generates C^+. Since $\Omega(\phi)$ is closed, it follows that $\xi \in \Omega(\psi) \subset \Omega(\phi)$.

Let L be a transversal through ξ. In Lemma A.2.1, we see that points of C^+ must meet L. Lemma A.2.2 states that C^+, is a subset of $\Omega(\phi)$, and can meet L only once, thus, it follows that $\xi \in C^+$. By Corollary A.2.1, we see that C^+ is the orbit of a periodic solution. Again applying Corollary A.2.1, we see that since $\Omega(\phi)$ contains a periodic orbit C, it follows that $\Omega(\phi) = C$.

If the trajectories are close to the limit cycle, they are spirals that approach the limit cycle as $t \to \infty$ as shown in the following figures.

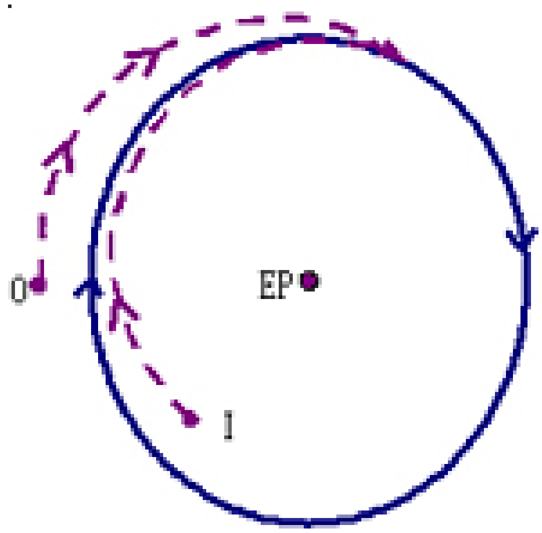

Figure A.7: A stable limit cycle.

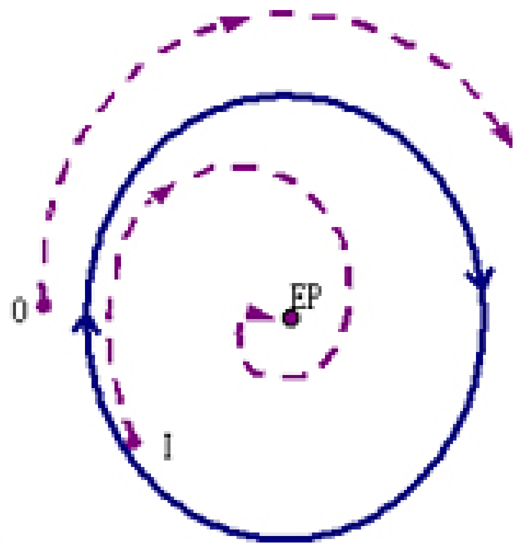

Figure A.8: An unstable limit cycle.

Theorem A.1.3 Lyapunov's First or Direct Method

Let $X=0$ be an equilibrium point for $x'=f(x)$ and $D \subset R^n$ be a continuously differentiable function so that:

(a) $V(0)=0$ and $V(x)>0 \ \forall x \in D \setminus \{0\}$

(b) $V'(x) \le 0 \ \forall x \in D$. Then, $x=0$ is stable.

(c) $V'(x)<0 \ \forall x \in D \setminus \{0\}$. Then, $x=0$ is asymptotically stable [47]-[48].

Definition A.1.5 Globally asymptotically stable equilibrium

If the Lyapunov-candidate-function V is globally positive definite, radially unbounded and the time derivative of the Lyapunov-candidate-function is globally negative definite: $V'(x)<0 \ \forall x \in R^n \setminus \{0\}$, then the equilibrium is proven to be globally asymptotically stable. The Lyapunov-candidate-function $V(x)$ is radially unbounded if $\|x\| \to \infty \Rightarrow V(x) \to \infty$ [49]-[50].

A.2 Accepted Papers for publications and presentations

For publications:

1. W. Mumtong and P. Pongsumpun.“ Studying Menstrual Cycle by using Mathematical Model”, Far East Journal of Mathematical Sciences (FJMS), Volume 85, Number1, 2014, Pages 1-22

2. W. Mumtong and P. Pongsumpun.“ Analysis of Model for Menstrual Cycle with the effect of Body Mass Index”, Far East Journal of Mathematical Sciences (FJMS), Volume 93, Number2, 2014, Pages 243-266

For presentations:

1. W. Mumtong and P. Pongsumpun.“ Local Stability Analysis of the Mathematical Model for Menstrual Cycle”, 1 Mae Fah Luang University International Conference 2012, 29 November - 1 December 2012 Mae Fah Luang University, Chiang Rai, Thailand

2. W. Mumtong and P. Pongsumpun.“ Limit Cycle behaviour of Menstrual Cycle Model”, Burapha University International Conference 2014 ,Burapha University, Thailand ,July 3-4, 2014

3. W. Mumtong and P. Pongsumpun.“ Numerical Analysis of Menstrual Cycle Model with the effect of Diabetes”, 2015 International Conference on Food, Ecological and Life Sciences (FELS-2015) June 15-16, 2015 Bangkok (Thailand)

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