Proposed Mathematical Model of the Cyclic Relationship Between Estradiol and Endometriosis Lesions

Camila Nunez Polanco* cnunezpolanc@umass.edu
Russell J. Martinez† russman@caltech.edu
McKenzie L. Skrastins‡ mskrast1@binghamton.edu

*Department of Mathematics and Statistics, University of Massachusetts, Amherst, Massachusetts, United States
†Division of Physics, Mathematics, and Astronomy, California Institute of Technology, Pasadena, California, United States
‡Department of Mathematics and Statistics, The State University of New York at Binghamton, Binghamton, New York, United States

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Endometriosis is a disorder in which endometrial tissue grows on or outside the uterus. While endometriosis affects roughly 190 million females around the world, little research exists exploring both the causes of endometriosis and preventative treatment of progressive factors. One theory for endometriosis is an imbalance of estradiol, E2, and progesterone, P4, in the body. An elevated ratio of E2 to P4 can indicate the growth of endometriosis lesions, which are another source of E2 production. Such lesions disrupt regular E2 levels throughout the menstrual cycle, resulting in continuous endometrium growth. The relationship between E2 levels and lesion growth – and an increased ratio of E2 to P4 – was demonstrated using Margolskee et al.'s 2013 model of the menstrual cycle and Arbeláz-Gómez et al.'s 2022 model of endometrium growth. Periodic exogenous E2 suppression was shown to be an effective treatment for preventing excessive endometrial tissue volume in the presence of lesions.

Introduction

Endometriosis is a biological condition in which endometrial tissue continuously grows outside the endometrium, forming *endometriosis lesions*. Most cases of endometriosis result in lesions growing around the uterus, i.e., the fallopian tubes and the ovaries, but growth on the abdomen, lungs, and brain is also possible [1]. While endometriosis affects one in ten persons with uteri (roughly 190 million persons with uteri worldwide), little research has been conducted on contributing factors and preventative treatments [2]. Out of the many theories of the cause of endometriosis, an imbalance

‡Corresponding author.

of estradiol and progesterone and its relationship with endometrium and lesion growth will be analyzed throughout this paper.

Estradiol, E2, and progesterone, P4, are hormones that support the uterus throughout the menstrual cycle. During the first part of the menstrual cycle, the follicular phase, E2 communicates to the endometrium to grow and thicken in preparation for a fertilized egg. During the second part of the menstrual cycle, the luteal phase, P4 levels rise and inhibit E2 communication with the body. When a pregnancy fails to occur, E2 and P4 levels drop so the endometrium can shed, returning the uterus to homeostasis. When the ratio of estradiol to progesterone increases, E2 over-communicates with the body, resulting in uncontrollable endometrium growth [1]. Research shows that endometriosis lesions produce estradiol, contributing to a cycle of continuous estradiol and progesterone imbalance [12]. Thus, excess E2 can indicate the presence of lesions outside the endometrium.

A common treatment for endometriosis is exogenous E2 suppression [2]. Although the aforementioned aids with lesion growth regulation, E2 suppression is not a cure nor is it effective without the consequence of major side effects.

In 2013, Margolskee et al. modeled the menstrual cycle by plotting the fluctuations of several hormones, including E2 and P4, over several cycle days [3]. In 2022, Arbeláez-Gómez et al. took the outputs of estradiol and progesterone from Margolskee et al.'s model as inputs for their model of endometrium growth over several cycle days [4]. The proposed model expanded on Arbeláez-Gómez et al.'s model to incorporate endometriosis lesions and the estradiol they produce, producing a new model of endometriosis lesion growth over several menstrual cycles.

Biological Background

Endometriosis Lesions

Although the exact pathogenesis of endometriosis remains unknown, many theories exist. One theory, raised by Dr. John Sampson, a gynecologist from the 1920s, states that endometriosis is caused by *retrograde menstruation*. This is when the menstrual blood flows backward through the fallopian tubes and into the abdomen instead of exiting through the uterus [6]. This menstrual blood is perceived to contain endometrial cells that get transported into the abdomen, which is a possible explanation for how these cells – and ultimately the lesions – end up outside the uterus. However, Sampson's theory is controversial: Retrograde menstruation is a normal occurrence, yet only a small number of people who experience it ever develop endometriosis. While the exact pathogenesis of endometriosis is not of concern to this paper, it is necessary to highlight Sampson's theory because it provides a possible explanation for why endometrial cells are misplaced.

Regardless of how the cellular attachment and invasion of endometrial cells are established, the endometriosis lesions start growing with the help of mitogenesis and angiogenesis. Mitogenesis, a process where new mitochondria are produced by growth and division from existing ones, is promoted by mitogens [7]. These substances, which include growth factors, hormones, and other

signaling molecules, activate cell cycle pathways. Angiogenesis, the process by which new blood vessels form from pre-existing ones, not only supports the growth of these lesions but also facilitates the formation of nerves, activating peripheral pain pathways. Since endometrial cells are dislocated, the body's tissue injury repair (TIAR) mechanism activates local estrogen production, proliferation, and infiltrative growth. The continuation of the menstrual cycle promotes more growth by the influx of estrogen and other inflammatory mediators.

Once endometrial tissues settle in a new location they respond to the menstrual cycle hormones. While endometriosis lesions can be found on the ovaries and the fallopian tubes, they can also settle and grow on major organs, sometimes causing organs to "stick" together. The three types of lesions are characterized as follows: Superficial peritoneal lesions are the most common subtype and consist of lesions of various colors located on the surface of the peritoneum. Endometriomas are ovarian cysts that contain dark, blood-stained fluid (often called chocolate cysts). Deep endometriosis (previously called deep infiltrating endometriosis) is identified by lesions that extend beyond the peritoneum; these lesions are nodular and fibrotic, and have the capacity to invade adjacent pelvic organs such as the rectosigmoid, ureter, or bladder [9].

Types of Estrogen and Their Functions

Estrogen presents itself, in the body, in three forms; estrone (E1), estradiol (E2), and estriol (E3). E1 is most prominent during and after menopause, E2 during a person's reproductive years, and E3 during pregnancy [14]. For the remainder of the Biological Background section of this paper, the term *estrogen* was used, as the theories presented are applied to all forms of estrogen. For the Model Development, Results, Discussion, and Conclusion sections of this paper, the term *estradiol* was used, since the research was solely focused on people assigned female at birth's reproductive years.

The Menstrual Cycle with and without Endometriosis

The menstrual cycle is a natural process involving a complex hormone dynamic with four phases: menstruation, the follicular phase, the ovulation phase, and the luteal phase. The ultimate goal is to prepare the body for potential pregnancies each month by coordinated physiological processes designed to create an optimal environment for fertilization and implantation of an embryo [10]. Throughout these phases of the menstrual cycle, the levels of the hormones involved, such as estrogen and progesterone, fluctuate accordingly.

Menstruation marks the first day of the cycle; during this phase, the uterus lining sheds a layer and flows out of the vagina. The hypothalamus, a brain region below the thalamus and above the pituitary gland, releases signaling hormones like gonadotropin-releasing hormone (GnRH). This hormone stimulates the pituitary gland in the brain to release LH, the luteinizing hormone, and FSH, the follicle-stimulating hormone. During the follicular phase, levels of FSH slowly begin to increase, which stimulates the ovaries to produce follicles on their surface. The ovaries contain the female gamete cell, called the oocyte, also known as the "egg." Follicles are fluid-filled structures

in which the egg matures [11]. These follicles secrete estrogen, a naturally occurring hormone that promotes the growth and maturation of these follicles while also stimulating the proliferation of the endometrial lining of the uterus. Rising estrogen levels also help the body slow FSH production and trigger LH to start surging throughout the ovaries. LH plays a crucial role in the final stages of the menstrual cycle, triggering ovulation and the subsequent transformation of the follicle into the corpus luteum.

The ovulation phase marks the end of the follicular phase and the beginning of the luteal phase. The surge of LH (caused by high estrogen levels) triggers the release of the matured egg previously stored in the dominant follicle. After ovulation, follicles on the ovaries transform into the corpus luteum, a temporary collection of cells. The presence of the corpus luteum is another sign that the luteal phase is beginning. The corpus luteum begins secreting progesterone – another naturally occurring hormone – and small amounts of estrogen that cause the endometrium to thicken and make the uterus a healthy place for a fetus to grow. If an egg fails to fertilize, the endometrium breaks down, and the corpus luteum degenerates, decreasing progesterone and estrogen levels. This triggers menstruation and the start of a new cycle.

The menstrual cycle behaves differently with endometriosis. Menstrual cramps, heavy bleeding, and pelvic pain are more intense with endometriosis, severely affecting a person's quality of life [13]. During the follicular phase, hormone changes, particularly the increased estrogen levels, facilitate the endometrial lining's thickening and cause lesions to grow and thicken; the lesions may also bleed during the period as well. Unlike the uterine lining that sheds during menstruation, lesions have no proper way to exit the body and lead to local inflammation and pain. Over repeated menstrual cycles, the lesions eventually scar and adhere to significant organs. Thickened lesions can interfere with the normal function of the reproductive organs, leading to challenges with fertility. During the luteal phase, endometriosis lesions are less responsive to progesterone secreted by the corpus luteum due to progesterone resistance.

Hormonal Imbalances in Endometriosis Lesions

Hormone imbalance is a direct result of endometriosis: Endometriosis is also classified as an estrogen-dependent chronic inflammatory disease that causes *estrogen dominance*, an excess of estrogen compared to progesterone in the body [8]. Higher estrogen levels can stimulate the proliferation of endometriosis lesions and ultimately lead to the persistence and worsening of the condition. This is because endometriosis lesions respond to the menstrual cycle hormones similarly to the normal endometrial lining inside the uterus.

In addition to estrogen dominance, evidence points to *progesterone resistance* as a common feature in endometriosis. This resistance could be due to an insufficient progesterone-mediated transition from the late proliferative to the early secretory phase, leading to a reduction in the inhibitory effects of progesterone on endometrial tissue and the menstrual cycle. In combination with estrogen dominance, progesterone resistance contributes to hormonal imbalances in endometriosis lesions. While this imbalance doesn't fully explain endometriosis, it remains a crucial area for

future research and understanding.

Local Estrogen Production in Endometriosis Lesions

One factor of estrogen dominance is local estrogen production in endometriosis lesions. The biological effects of estrogen are mediated by estrogen receptors (ERs), which deal with the effects of estrogen on a cellular level. Estrogen Receptor Alpha (ERα) and Estrogen Receptor Beta (ERβ) are two main types of estrogen receptors. The main activity of ERα is thought to be to promote cell proliferation, whereas ERβ is believed to have anti-proliferative effects and can modulate the activity of ERα. In the normal endometrium, the expression of ERα is significantly higher than the ERβ expression. However, endometriosis lesions may have higher levels of ERs that can make them more responsive to levels of circulating estrogen; a recent study demonstrated that ERβ mediated ectopic proliferation, survival, and inflammatory activity of endometrial tissues [12].

Another way local estrogen production occurs in the lesions is by aromatase inhibitors. An aromatase is an enzyme that converts testosterone and androstenedione to estradiol and estrone, thereby increasing the local concentration of estrogen. This process significantly contributes to the estrogen dominance observed in endometriosis lesions. The same study showed that the mRNA level of aromatase was significantly more abundant in the proliferative/secretory menstrual phase of ovarian endometrioma and the proliferative phase of deep endometriosis [12]. These findings suggest that aromatase plays a critical role in local estrogen production, especially in ovarian endometriosis, and indicate the existence of autocrine and paracrine sources of estrogens in local lesions.

Model Development

Methodology

A thorough review of literature was conducted on Google Scholar using the keywords and phrases, “endometriosis”, “mathematical modeling of endometriosis”, “hormone levels and endometriosis”, and “estrogen and progesterone relationship with endometriosis;” all biases, including a restricted database of papers due to using a search engine and limited knowledge of the topic before the literature review, were accounted for. Margolskee et al.’s model was then able to be recreated using MATLAB. Arbeláez-Gómez et al.’s model was first reproduced using a similar approach as with Margolskee et al.’s model. However, the combination of delay differential equations and stiff differential equations resulted in an absurd computation time (roughly 9 hours of run time for only 10 days of the menstrual cycle). After troubleshooting for 2 weeks, an email was sent to Dr. Gómez-Echavarría, an author of Arbeláez-Gómez et al., to inquire about the code. The author responded and provided the original Simulink blueprint, from which the necessary modifications could be made to account for lesion volume and E2 suppression.

Proposed Model

The proliferative cell growth of lesions, the secretory cell growth of lesions, and the cellular product secreted by lesions can be seen in Eq. (1), (2), and (3), respectively; see the Appendix for auxiliary algebraic and differential equations and parameter values. The interaction of this model with Margolskee et al.'s model and Arbeláez-Gómez et al.'s model can be seen in Figure 1.

$$\frac{dM_{\chi_{\text{pro}_L}}}{dt} = \mu_{\text{pro}_L} M_{\chi_{\text{pro}_L}} - \mu_{\text{sec}_L} M_{\chi_{\text{pro}_L}} \tag{1}$$

$$\frac{dM_{\chi_{\text{sec}_L}}}{dt} = Y_{\chi_{\text{sec}}\chi_{\text{pro}_L}} \mu_{\text{sec}_L} M_{\chi_{\text{pro}_L}} - \dot{m}_{6_L} w_{\chi_{\text{sec}},6_L} \tag{2}$$

$$\frac{dM_{\chi_{p_L}}}{dt} = q_{p_L} M_{\chi_{\text{sec}_L}} - \dot{m}_{6_L} w_{p,6_L} \tag{3}$$

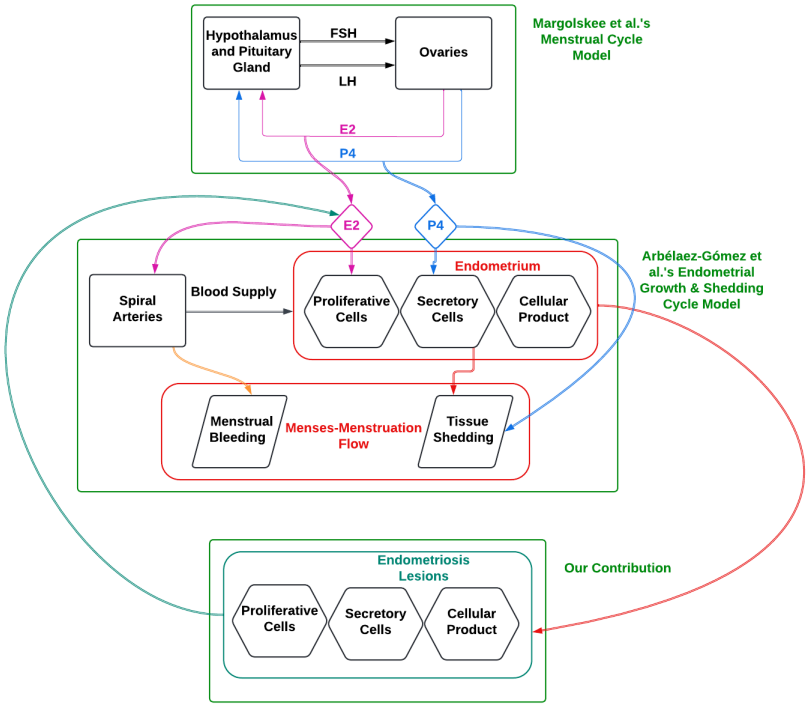

Figure 1: Flowchart of the interaction of Margolskee et al.'s model, Arbeláez-Gómez et al.'s model, and the proposed model.

The lesion volume in the body can then be calculated as in Eq. (4).

$$V_{T_L} = \frac{M_{\chi_{\text{pro}_L}}}{\rho_{\chi_{\text{pro}_L}}} + \frac{M_{\chi_{\text{sec}_L}}}{\rho_{\chi_{\text{sec}_L}}} + \frac{M_{\chi_{p_L}}}{\rho_{\chi_{p_L}}} \tag{4}$$

Eq. (4) feeds into Margolskee et al.'s model so that the equation of E2 becomes

$$\mathrm{E2} = e_0 + e_1\mathrm{GrF} + e_2\mathrm{DomF} + e_3\mathrm{Lut4} + e_4 V_{T_L} + e_5$$

where e_4 is the rate of E2 secretion for the lesions and e_5 is an exogenous E2 suppressor.

Results

Once the proposed model was completed, a choice of parameters was made so that the endometriosis lesion volume roughly followed a logarithmic curve; see Figure (2).

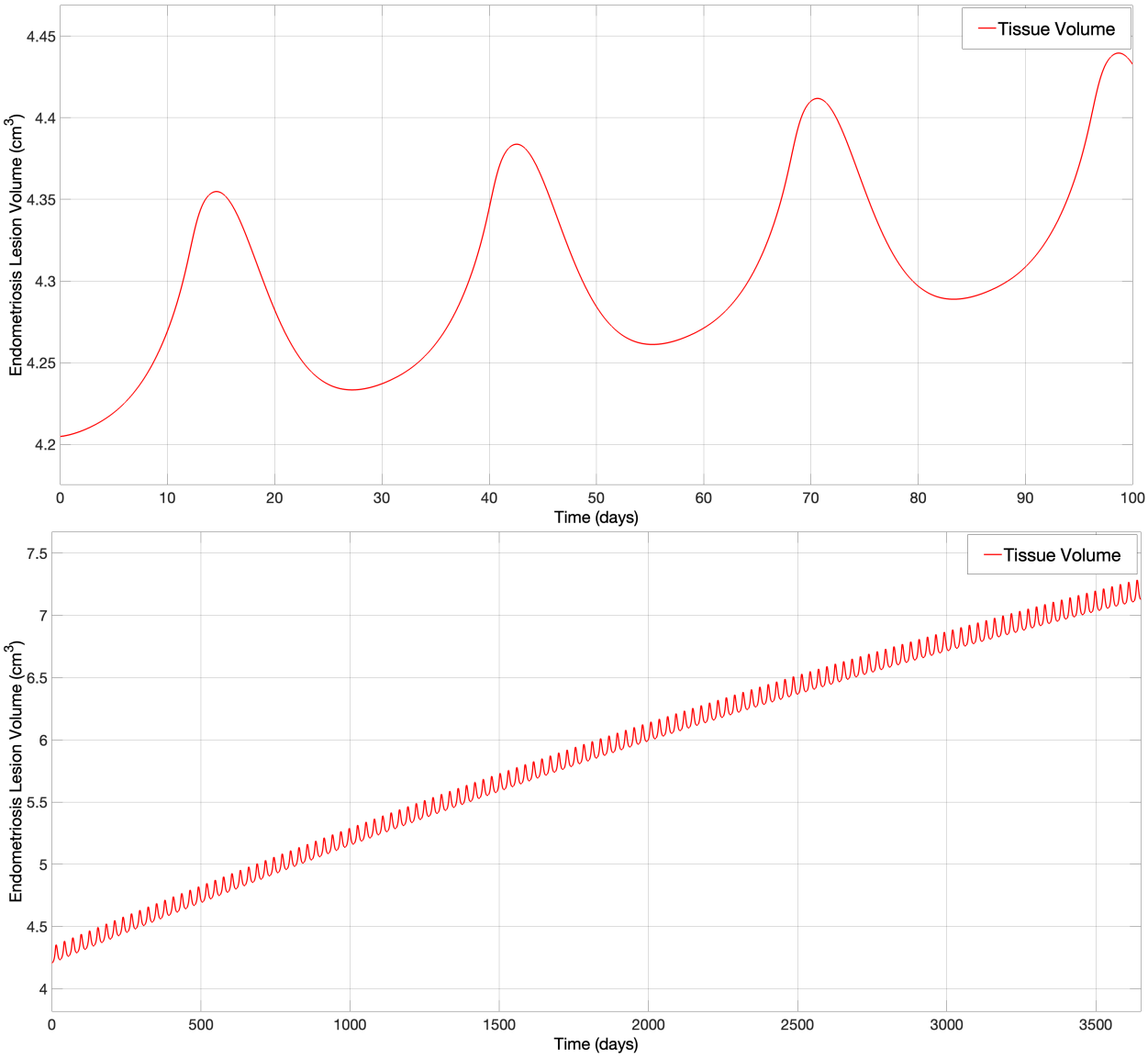

Figure 2: Endometriosis lesion volume over 100 days and 3650 days, respectively.

The endometrium volume over time can be seen in Figure (3).

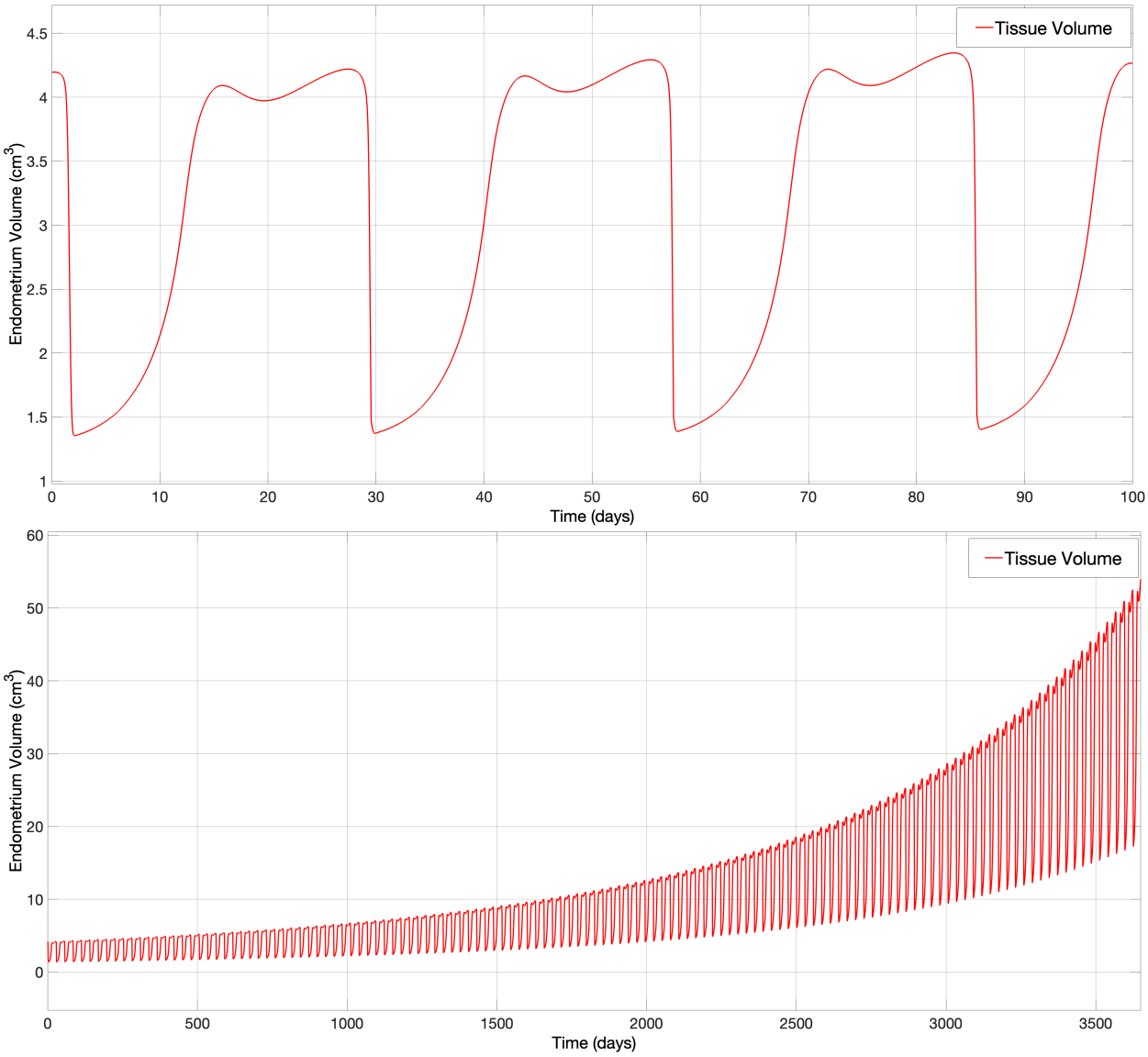

Figure 3: Endometrium volume over 100 days and 3650 days, respectively.

The estradiol levels over time can be seen in Figure (4).

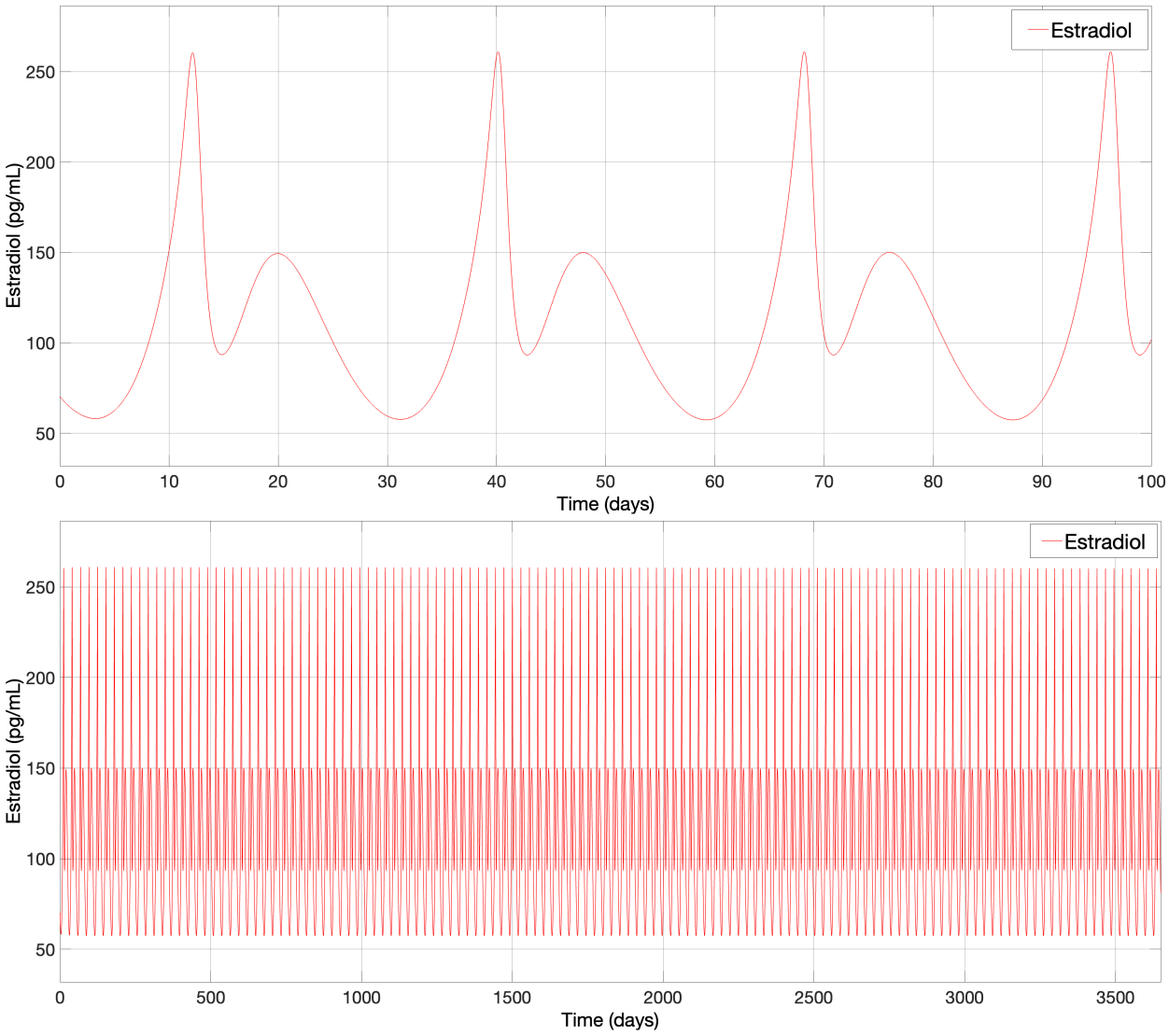

Figure 4: Estradiol levels over 100 days and 3650 days, respectively.

The progesterone levels over time can be seen in Figure (5).

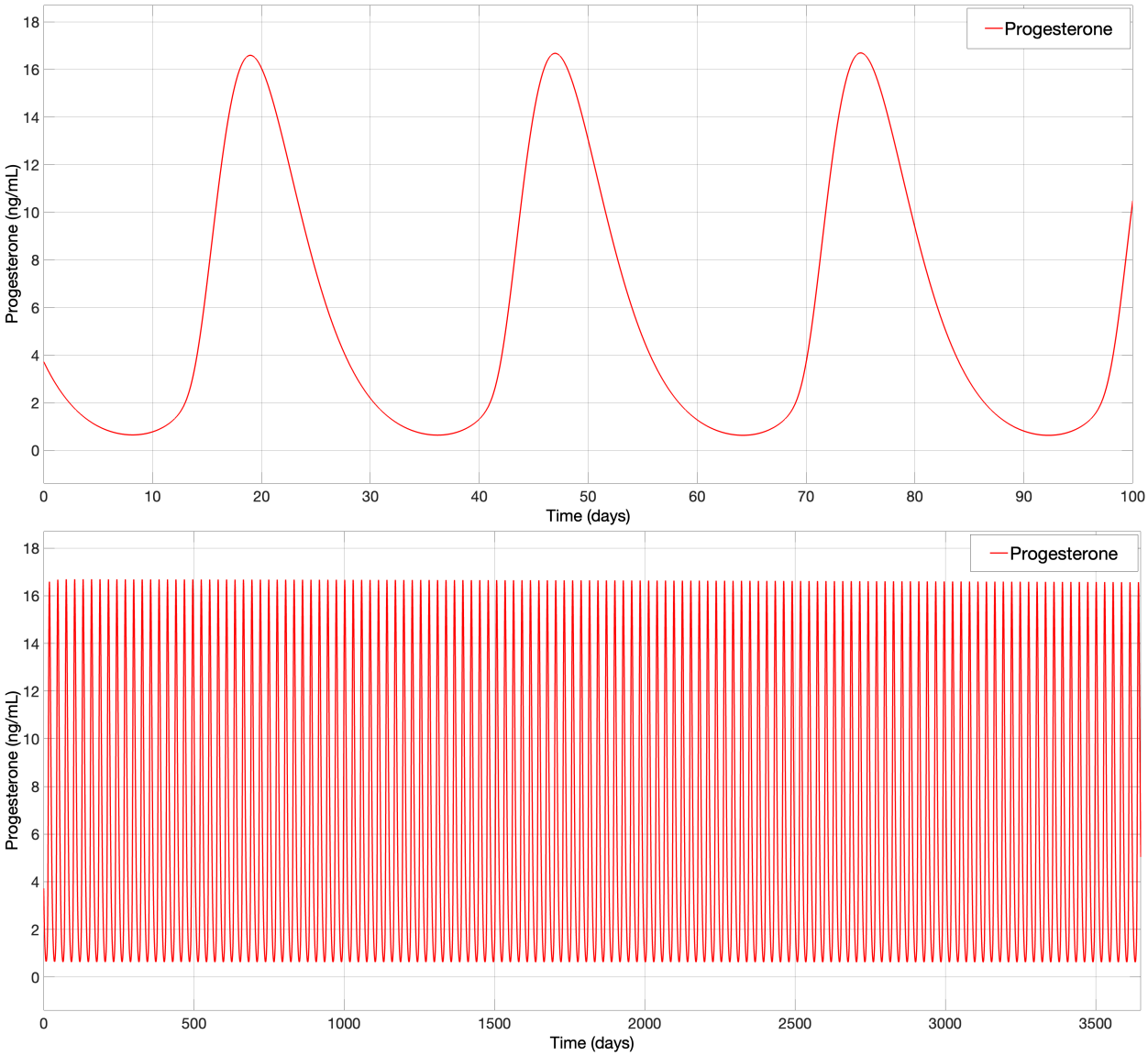

Figure 5: Progesterone levels over 100 days and 3650 days, respectively

The long-term behavior of estrogen and progesterone can be seen in Figure (6).

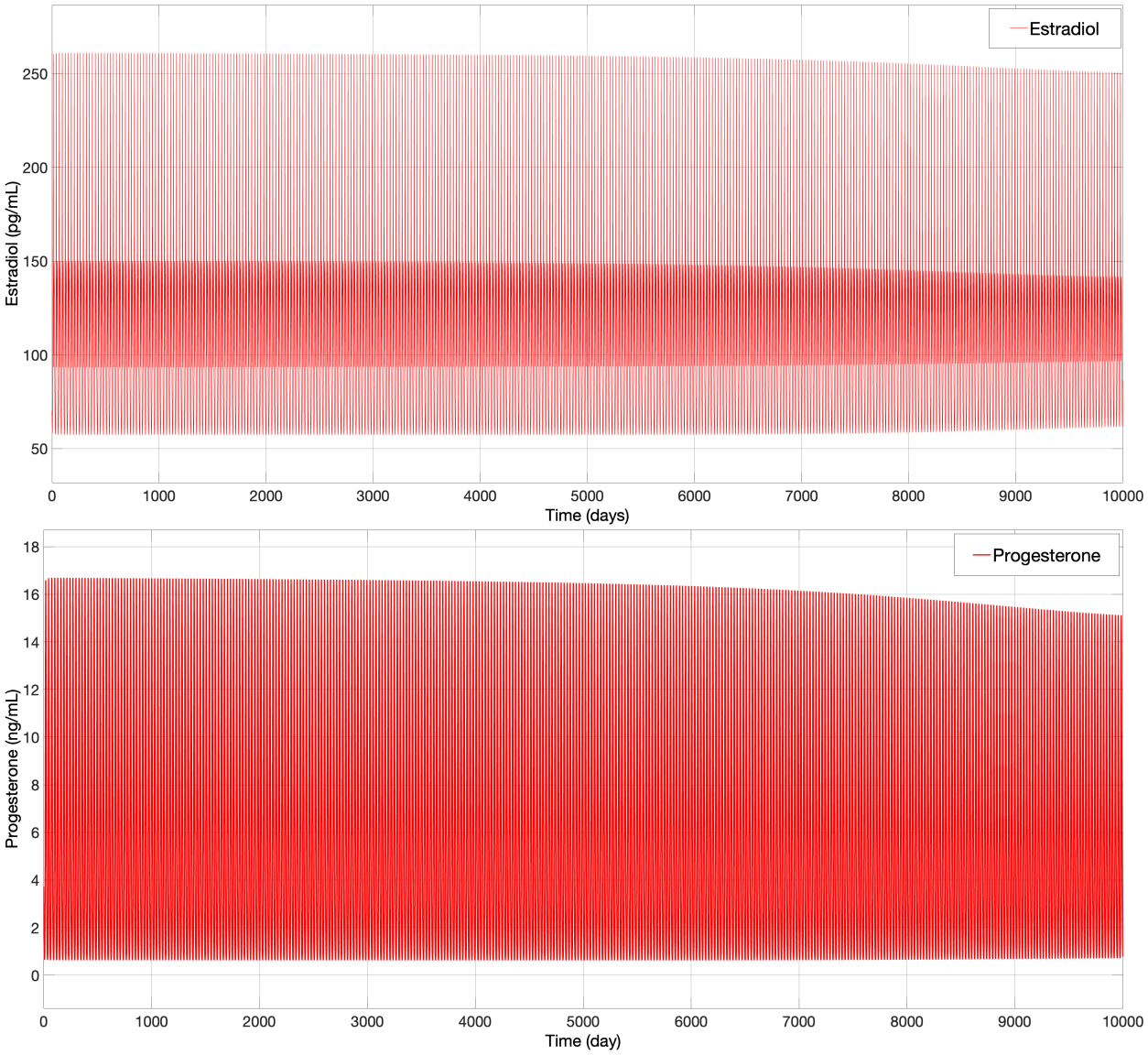

Figure 6: Estrogen and progesterone levels, respectively, over 10000 days.

The introduction of exogenous E_2 suppression was simulated by letting $e_5 = -12.5$ over days 1000 to 1030 and then $e_5 = -10$ over days 2000 to 2030 and 3000 to 3030; see Figures (7), (8), and (9).

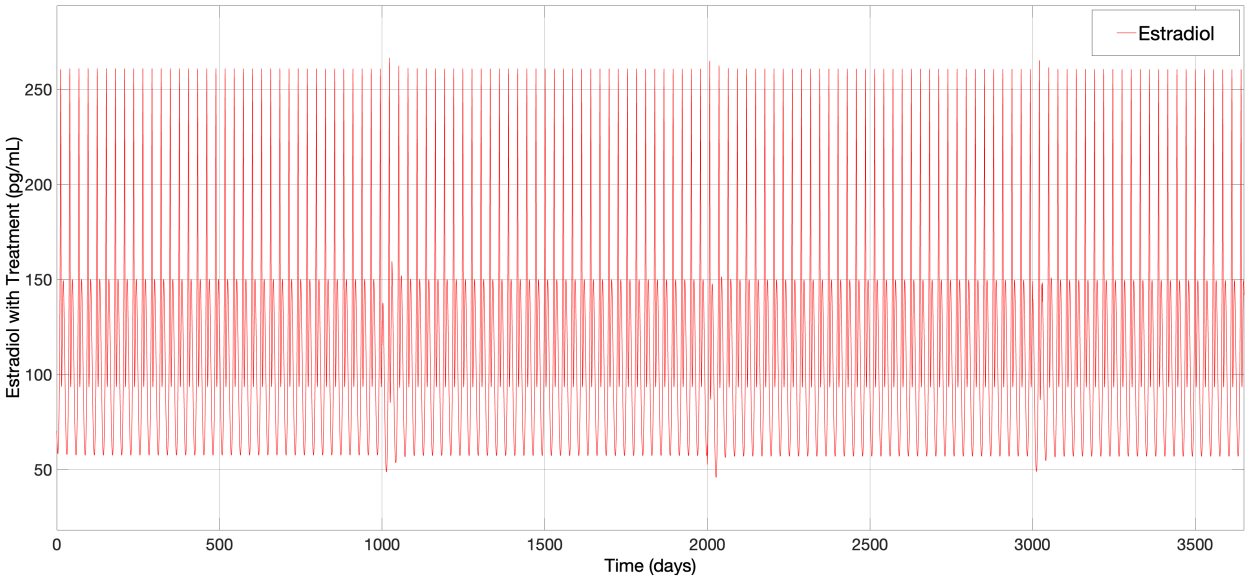

Figure 7: Estradiol levels over 3650 days with E2 suppression.

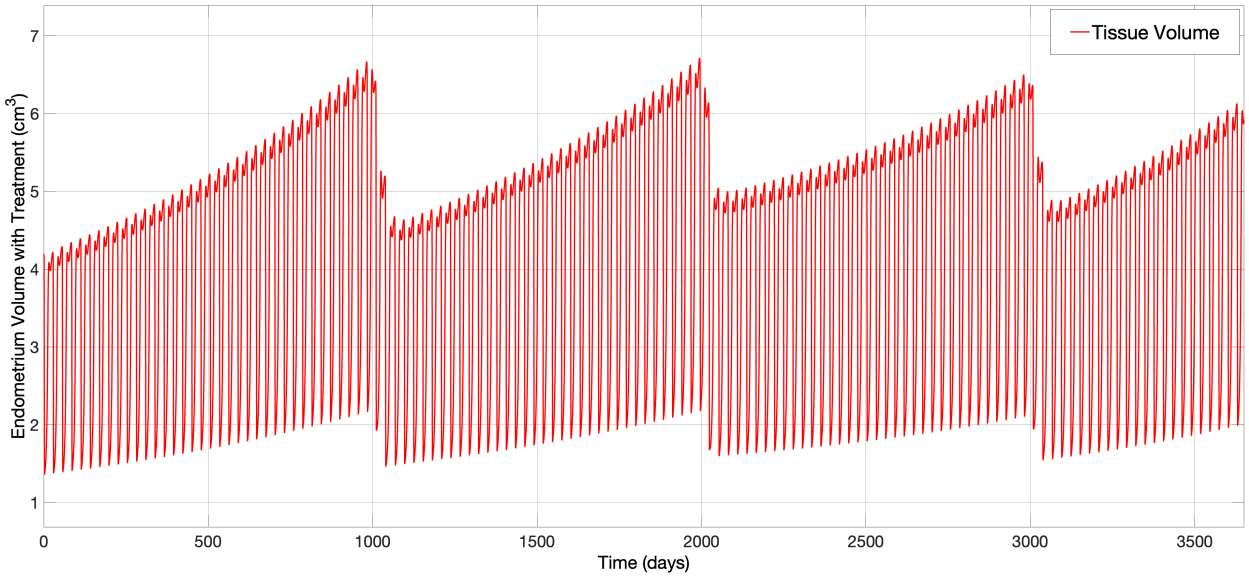

Figure 8: Endometrium volume over 3650 days with E2 suppression.

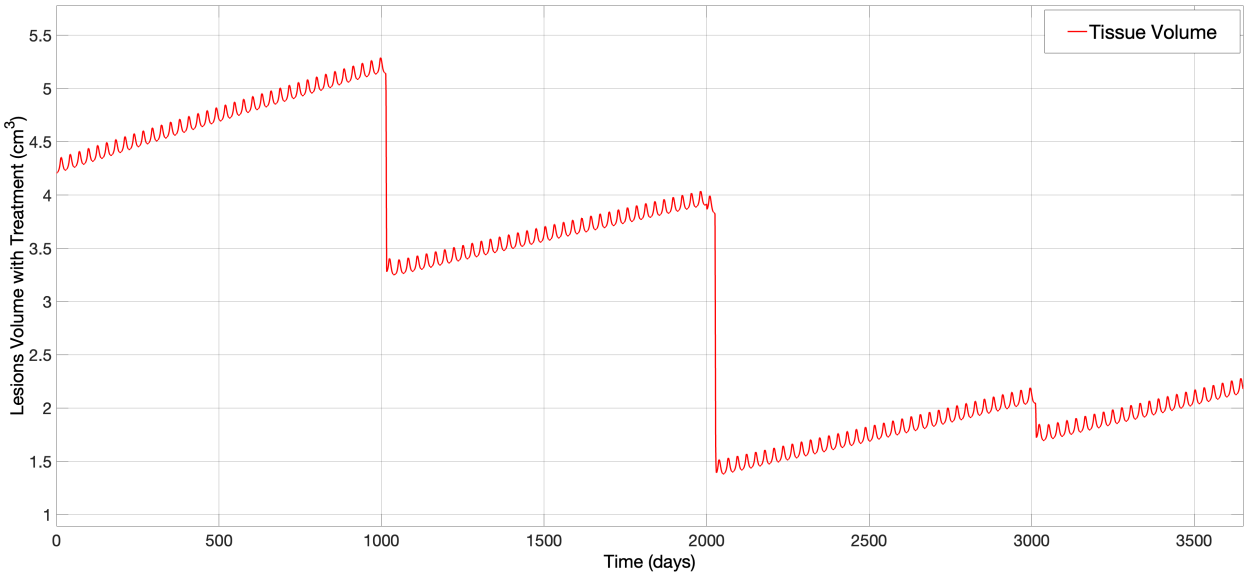

Figure 9: Endometriosis lesion volume over 3650 days with E2 suppression.

Discussion

Using Margolskee et al.'s model of a normal menstrual cycle and Arbeláez-Gómez et al.'s model of endometrial volume growth, a model of the relationship between endometriosis lesions and estradiol was successfully made. Figures (2) and (3) show that as estradiol produced by endometriosis lesions was continuously fed into the model of endometrium volume, persistent lesion growth occurred. Biologically, such behavior was expected: The larger an endometriosis lesion is, the more estradiol it produces, and the more estradiol present in the body, the larger the endometrium grows. Figures (4) and (5) indicate a gradual decrease in estrogen and progesterone, respectively, where the decreased estrogen levels were not expected; additional sources of estrogen production in the form of endometriosis lesions would suggest increased estrogen levels, so further investigation of this behavior is required. However, Figure (6) shows that progesterone decreases faster than estradiol, verifying a greater ratio of E2 to P4 in the case of a person with endometriosis.

Figure (7) shows that introducing an exogenous E2 suppressor decreases estrogen levels over the days it is in effect; the estrogen levels then increase to greater than before as the body returns the levels to homeostasis. Figures (8) and (9) demonstrate the effects of E2 suppression on endometrium and lesion volume were as anticipated: When an exogenous estrogen suppressor was introduced, a drop in lesion and endometrium volume was observed. Because the proposed model correctly portrayed this medically proven treatment for endometriosis, the other observations made about this model serve as sound motivation for endocrinologists to look further into the cyclic relationship between estradiol and lesion growth.

Conclusion

The model proposed in this write-up mathematically mimicked endometriosis lesion volume growth over time and the relationship between lesion volume and estradiol. The equations of lesion volume and growth of the proposed model were inspired by those of Arbeláez-Gómez et al.'s model of endometrium volume and growth. Progesterone and estradiol levels generated by Margolskee et al.'s model were fed into the proposed model, allowing for an accurate depiction of endometriosis lesion volume growth. A percentage of lesion volume was added to the original E2 equation used in Margolskee et al.'s model, creating a cyclic relationship between lesion volume and estradiol. Figures (2) and (3) showed an increase in lesion and endometrium volume over time, as was expected, but figures (4) and (6) showed no increase in estradiol levels, which was not anticipated. Figure (6) also demonstrates the increased ratio of E2 to P4 and Figures (8) and (9) show successful treatment through periodic exogenous estradiol suppression.

Although endometriosis affects nearly one in every ten people with uteri, the disease remains severely under-researched. One way the scarcity of endometriosis research presented itself during the creation of the model was in parameter accuracy. New parameters for the proposed model were searched for in literature. Ultimately, biologically accurate parameters for equations used to model the lesions were deemed improbable to find, so the original parameters used in Arbeláez-Gómez et al.'s model were scaled down by a factor of ten for the proposed model. Another way the scarcity of endometriosis research affected the creation of the proposed model was in the lack of datasets available. The idea of creating a secondary predictive, binary logistic regression model was initially proposed. Eventually, the predictive model idea was scrapped because no public endometriosis datasets could be found.

The motivation behind creating this model was to encourage endocrinologists and other medical professionals to further explore the apparent relationship between estradiol and long-term endometriosis lesion growth. If more research is done on endometriosis, a revised model incorporating these features will be made. The new model will also include a more detailed depiction of how endometrial tissue travels from the endometrium to different parts of the body while accounting for the different stages of lesions and other forms of treatment.

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Appendix

Additional Figures

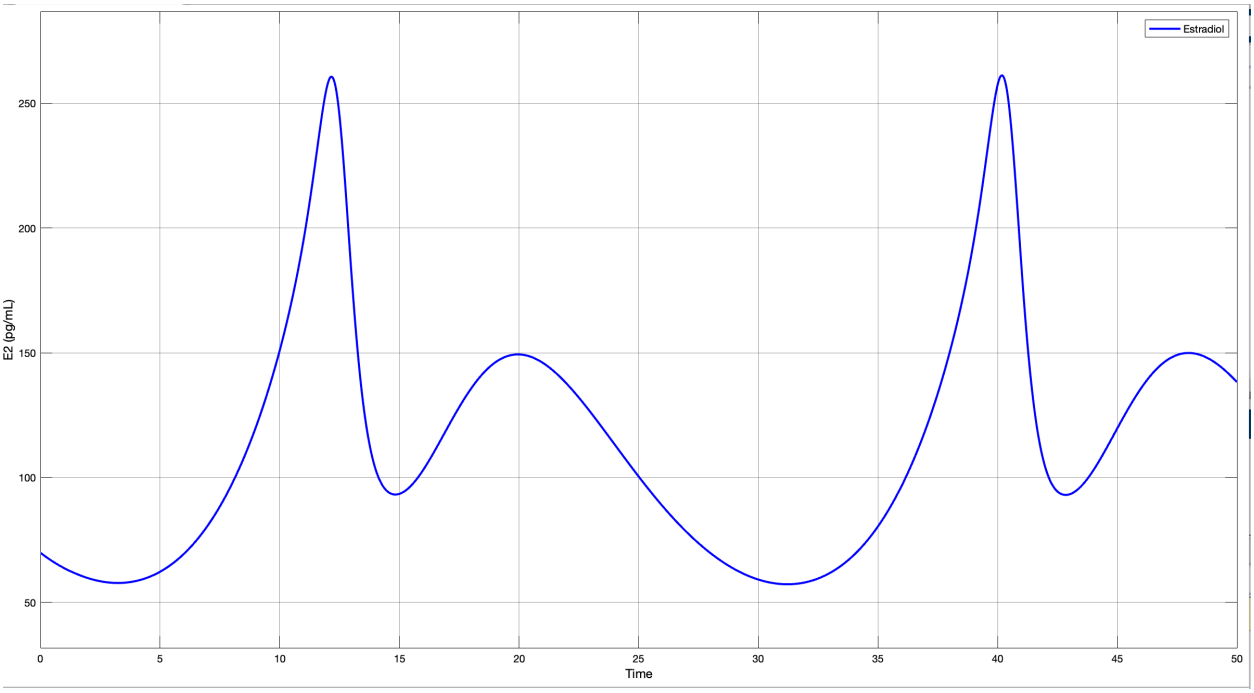

Figure 10: Plot of Estradiol Levels Over 50 Days or 1-2 Menstrual Cycles (Margolskee et al.'s Model)

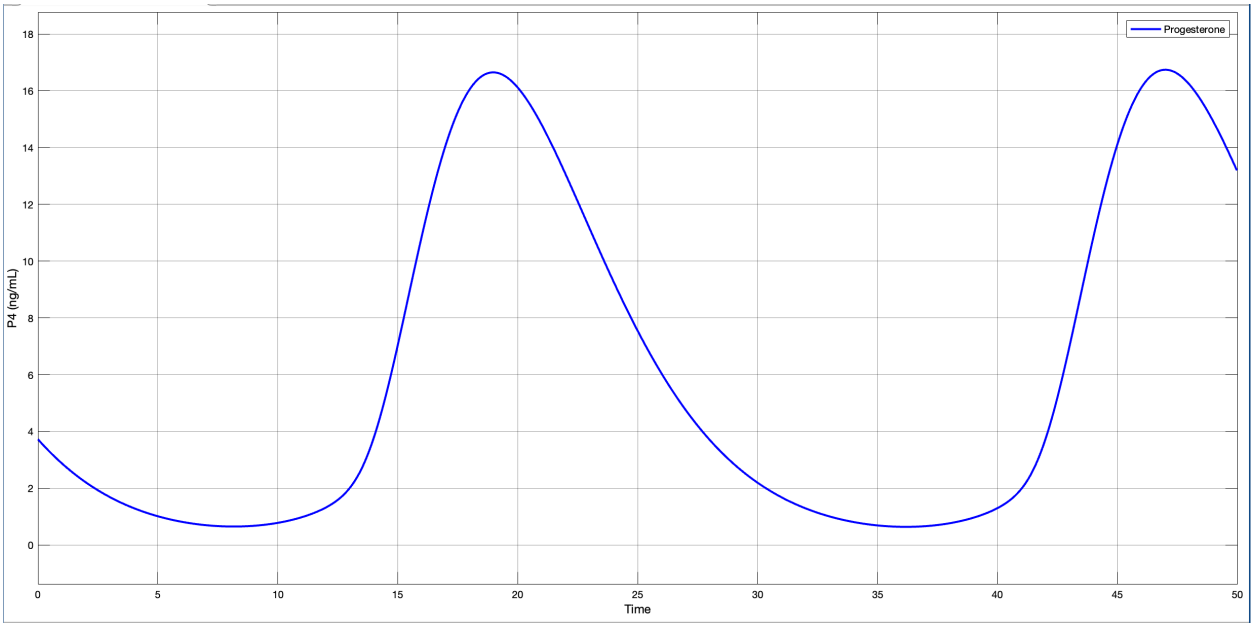

Figure 11: Plot of Progesterone Levels Over 50 Days or 1-2 Menstrual Cycles (Margolskee et al.'s Model)

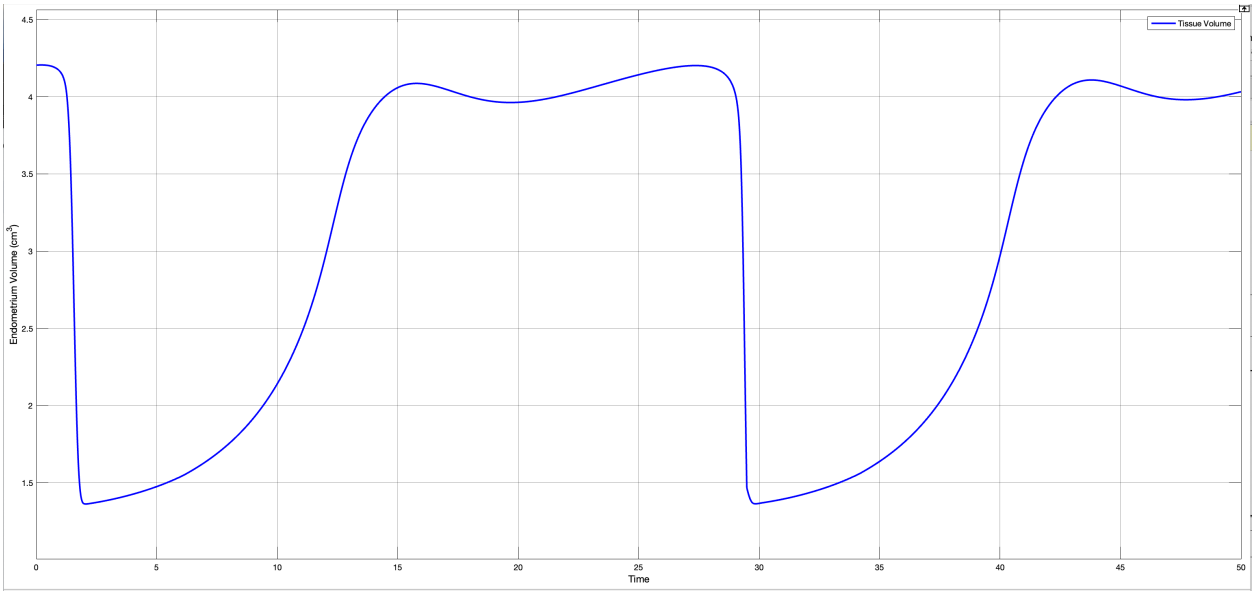

Figure 12: Plot of Endometrium Volume Over 50 Days or 1-2 Menstrual Cycles (Arbeláez-Gómez et al.'s Model)

Additional Equations from Arbeláez-Gómez et al.'s model: Spiral Arteries

$$\frac{dLB_L}{dt} = \frac{\dot{v}1_L - \dot{v}2_L - \dot{v}5_L}{AB_L} \tag{5}$$

$$\frac{dSBst_L}{dt} = rPBE_L - rETR_L \tag{6}$$

$$rPBEmax_L = kPBE_L \tag{7}$$

$$rETRmaxL = kETR_L * E_2 \tag{8}$$

$$rPBE_L = \frac{rPBEmax_L * (1 - SBst_L)}{KmPBE_L + (1 - SBst_L)} * \frac{KiPBE_L}{KiPBE_L + P_4} \tag{9}$$

$$rETR_L = \frac{rETRmax_L * SBst_L}{KmETR_L + SBst_L} * \frac{KiETR_L}{KiETR_L + P_4} \tag{10}$$

$$\dot{v}1_L = v1_L * Aau_L \tag{11}$$

$$\dot{v}2_L = \lambda * v1_L * Aau_L \tag{12}$$

$$r_L = k_L * LB_L \tag{13}$$

$$Poiseuillevol_L = \frac{\delta * P_L * \pi * r_L^4}{8 * \mu B_L * LB_L} \tag{14}$$

$$\dot{v}5_L = SBst_L * Poiseuillevol_L * n_L \tag{15}$$

$$AB_L = \pi * r_L^2 * n_L \tag{16}$$

$$\mu pro_L = \frac{\mu maxPro_L * Ms_L}{Ks_L + Ms_L} \tag{17}$$

$$\mu maxPro_L = kPro_L * E_2 \tag{18}$$

$$\mu sec_L = \frac{\mu maxsec_L * Ms_L}{Ks_L + Ms_L} \tag{19}$$

$$\mu maxSec_L = kSec_L * P_4 \tag{20}$$

$$\dot{m}6_L = kd_L * SBst_L * (\frac{M\chi sec_L}{w\chi sec6_L} + \frac{M\chi p_L}{wp6_L}) \tag{21}$$

$$qP_L = YP\chi sec_L \mu sec_L + mP_L \tag{22}$$

Paramter Values

Table

Parameters of the model.

Symbols	Description	Value
$kPro_L$	Estrogen Effect on the maximum growth velocity of the cells	0.0008417 $\frac{cm^3}{pg*day}$
$kSec_L$	Progesterone effect on the maximum growth velocity of the cells	0.0154731 $\frac{cm^3}{pg*day}$
K_{dL}	Constant for the inverse effect of progesterone upon cell death	2 adim
K_{sL}	Substrate constant	1 mg
m_{pL}	Specific product formation rate	$0.0001\frac{1}{day}$
M_{sL}	Mass of substrate inside the tissue	0.117 mg
Y_{PXsecL}	Yield coefficient of product from secretory cells	0.01 $\frac{mg}{mg}$
$Y_{XsecXproL}$	Yield coefficient of secretory from proliferative cells	0.045 $\frac{mg}{mg}$
$W_{Xsec,6L}$	Mass fraction of proliferative cells in stream 6	0.09 $\frac{mg}{mg}$
$W_{P,6L}$	Mass fraction of product in stream 6	0.01 $\frac{mg}{mg}$
ρ_{XproL}	Density of cells in proliferative phase	105 $\frac{mg}{cm^3}$
ρ_{XsecL}	Density of cells in secretory phase	105 $\frac{mg}{cm^3}$
ρ_{XPL}	Density of cellular product	140 $\frac{mg}{cm^3}$
μB_L	Viscosity of blood	0.00035 Pas
A_{au}	Cross-sectional area of uterine artery	0.0015 cm^2
n_L	Number of spiral arteries	300
ΔP	Blood pressure gradient	0.00005 Pa
k_L	Ratio of radius and length of spiral artery	0.01 adim
λ	Relationship between v1 and v2	0.09998 adim
$v1_L$	Velocity of blood inside the uterine artery	77760 $\frac{cm}{day}$
K_{PBEL}	Maximum rate of PBE reaction	7 $\frac{1}{day}$
K_{ETRL}	Maximum rate of ETR reaction	0.1 $\frac{mL}{day*pg}$
K_{MPBEL}	Affinity constant of the PBE reaction	0.00005 adim
K_{METRL}	Affinity constant of the ETR reaction	0.00001 adim
K_{iPBEL}	Inverse affinity constant of the PBE reaction	$0.8\frac{ng}{mL}$
K_{iETRL}	Inverse affinity constant of the ETR reaction	$1.4\frac{ng}{mL}$