ENDOMETRIOSIS AND COMPUTATIONAL SCIENCES

by

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ABSTRACT

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Endometriosis is a woman's disease of multifactorial etiology. Its primary symptoms are pelvic pain and infertility. Most women suffering from the disease also experience gastro-intestinal issues. The magnitude of the pain ranges from "difficult periods" to becoming bedridden and unable to function in any meaningful manner for most of their lives. While a number of treatments are available that attempt to abate the pain, none of them offer guaranteed or lasting solutions. There is no cure for the disease. Its cause is unknown. As many as 89 million woman worldwide suffer from this disease. Research focuses on many disparate elements of the disease. The purpose of this article is to introduce the disease, key aspects and systems, and propose interesting areas for modeling to learn more about the cause of this disease.

1   Endometriosis and Computational Sciences

When problems are not suitable for experimentation, for example involving disease, another approach for study of the disease is for science to simulate both the person and the disease. Because of the inherent complexity of reality, that simulation must involve simplifications.

Endometriosis is a debilitating disease suffered by millions of women in every country. Although there is no cure, there are treatments to manage the two recognized primary symptoms, pain and infertility. Due to the complexity of the systems involved (the reproductive, endocrine, and immune system), knowledge of the cause of the disease is incomplete. The location of the disease, typically the peritoneal cavity (see Figure 1), along with the systemic complexity, make it a very difficult disease to study. These traits make it a good candidate for modeling.

Computational modeling (computational science) is a form of applied mathematical modeling useful for providing insights in problems like this. The goal of this paper is to discuss the disease, pose questions about it, and look at a simple model as a starting point for exploration.

2   The Disease

Endometriosis is a disease characterized by the implantation of ectopic (wrong place) endometrial cells outside of a woman's uterus, typically in her peritoneal cavity. Broadly, there are three classifications of ectopic endometrial implantation: peritoneal (the lining of the lower part of the pelvic cavity), ovarian (the reproductive organs), and recto-vaginal (the rectum, upper and lower bowel, and vagina) (see Figure 2) [9]. The implanted tissue ranges from a clear color to dark red and even black (see Figure 3). Its primary symptom is pain caused by the massive release of inflammation cytokines (immune system message passing chemicals) that
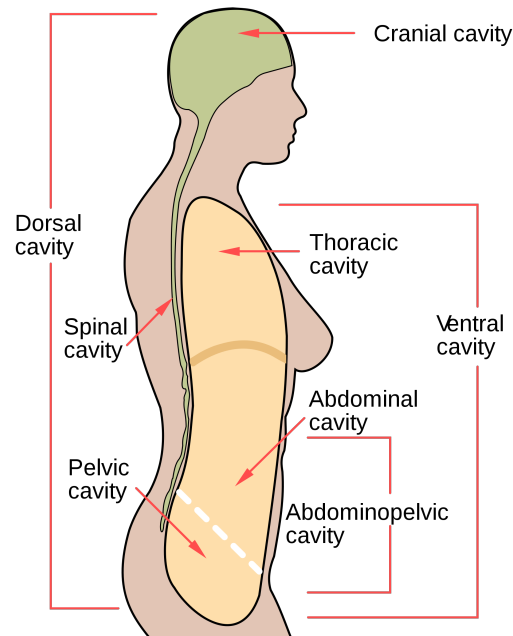
Figure 1: The lower portion of the female pelvis holds the pelvic cavity. Src:
`http://en.wikipedia.org/wiki/File:Scheme_body_cavities-en.svg`.

occur as part of the disease process. Symptoms of the pain range from difficult
menses to being incapacitated and bed-ridden. Infertility, the other primary symptom of the disease, is less understood in its cause. In addition to the primary symptoms, there are a number of less publicized symptoms.

Suspected to be an auto-immune disease itself, women with endometriosis
were found to have high rates of auto-immune and endocrine diseases such as fibromyalgia, chronic fatigue syndrome, and other atopic diseases [20]. Women with
endometriosis are also more likely to get ovarian cancer than those without [11].
Although not commonly studied, women with endometriosis are reported to experience food allergies and gastrointestinal issues which they had not experienced before the onset of the disease [4]. All of the symptoms can be present in anyone who
suffers from the disease.

It is estimated that 10% of women of reproductive age (roughly 12-50) worldwide, or about 89 million women, suffer from endometriosis [5, 8]. It is reported
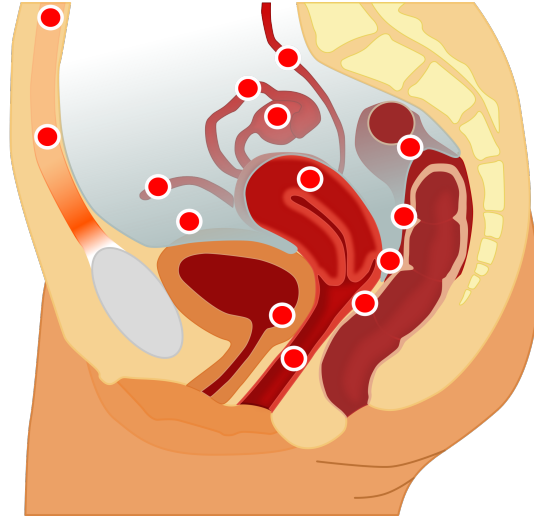
Figure 2: There are a number of locations in which ectopic endometrial cells can implant themselves. Src: `http://en.wikipedia.org/wiki/File:Endometriosis_loc_en.svg`.

more in developed countries due to better medical care which is available for these women.

The only means of diagnosis is laparoscopic surgery, a process of minimal invasion which involves micro-instruments and cameras that are inserted through three cuts in the abdomen [7]. Due to the difficulty of diagnosing the disease, the number of actual cases is expected to be higher than reported. The average time between onset of the first symptoms and the eventual diagnosis is 7 years [11]. By the time that most women are aware they have the disease, they are in a compromised position to pursue available treatments so progress on early and non-invasive detection is paramount. Approaches include comparison of the difference in the presence of nerve fibers in the ectopic endometrial cells of women with the disease, versus those who do not have endometriosis and do not have nerve fibers present [1]. Another approach being studied works by using a blood-test. Initial results have demonstrated that it works nearly as well as diagnosis via laparoscopy [10].

Treatments for pain typically involve over-the-counter or prescription painkillers, although lifestyle changes of diet, exercise, and the practice of relaxation techniques
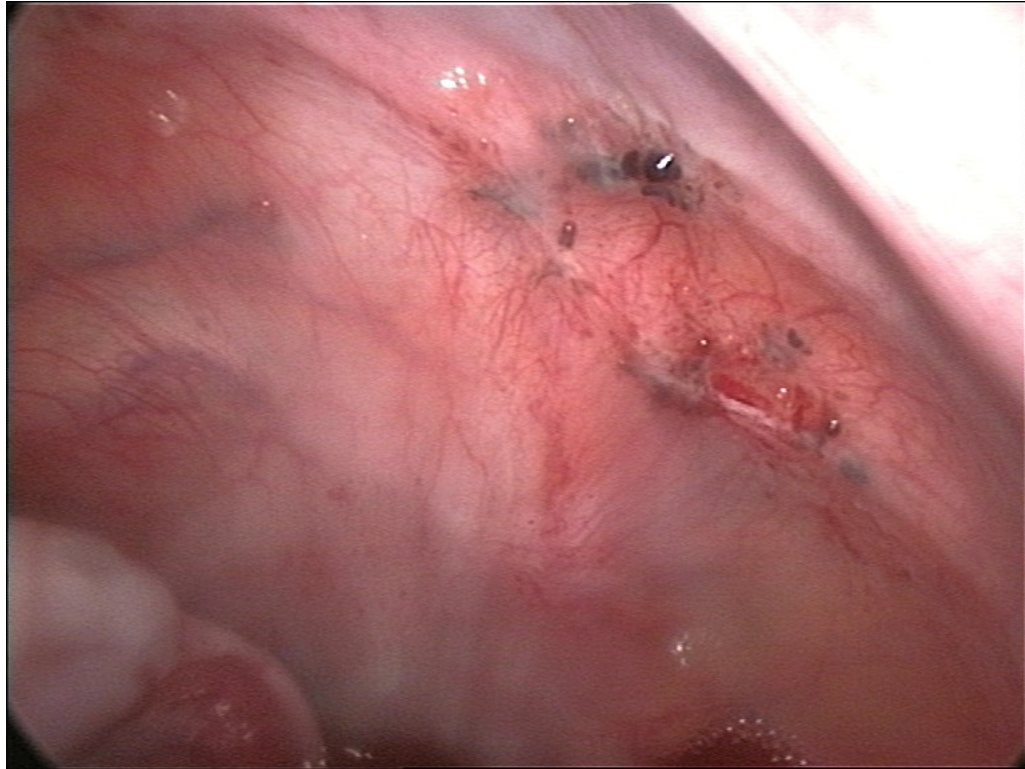
Figure 3: Ectopic endometrial cells implanted on the peritoneum, the membrane that lines the abdominal cavity. The endometrial cells are a deep, dark red. Src: `http://en.wikipedia.org/wiki/File:Peritoneal_endometriosis.jpg`.

such as massage and meditation are recommended [2, 4]. Research on foods that affect the disease also offer additional treatment options. For example, a recent study found that increased caffeine consumption resulted in increased production of estrogen which would then aggravate estrogen-sensitive diseases such as endometriosis [18].

Another minimally invasive approach is the use of hormone altering drugs that attempt to cut off the primarily stimulating hormone of this disease, estrogen. While many women report positive results, there are also a number of unpleasant side-effects. More invasive options are available in the form of surgery that typically involve the destruction of the ectopic endometrial cells via various techniques; although the disease returns to virtually all who undergo the procedure. Some doctors recommend a hysterectomy (removal of the female reproductive organs), al-

though in some cases, the disease can continue despite the absence of the reproductive organs [8]. One aspect under research for possible treatment is the angiogenesis (creation of new blood vessels) that allows the cells to implant themselves in tissue [21]. This behavior is very similar to how cancer cells behave, so there is an opportunity for common research interests in preventing both kinds of cell propagation. The commonality among all of the treatments is that none of them cure the disease.

The fact that there is no cure for the disease is not actively discussed by medical practitioners with those who suffer from it [17]. The topic is a difficult one because some treatments work well for some women, but the same treatment performed on another women may yield no good results and even make the disease worse. The recognition of the needs for custom-tailored treatments might be helpful in learning how to better tailor the treatment of the disease for individual women. Another issue in treating the disease is the ability for patients to communicate their issues.

In adults, the average diagnosis time is 7 years. Most patients describe their doctors as "simply not believing" the amount of pain that they are suffering from. The issue is more difficult when you consider that young woman today are having their first menstrual cycle (menarche) as early 8 years old, which adds another layer of complexity to an already complex disease because these young girls do not have the vocabulary to begin to describe their symptoms [3].

3   Systemic Complexity

Although the inter-system nature of the disease and interdisciplinary nature of the fields researching endometriosis puts the entire scope of the topic well outside of this essay, there are a number of excellent surveys and sources that would

be useful to anyone new to the topic [5, 6, 9, 12, 19, 22]. The complexity around the disease comes from the fact that it involves the interaction of the reproductive, immune, and endocrine systems [13].

Endometriosis starts with cells from the endometrium, the lining of the uterus, entering the peritoneal cavity. The generally accepted theory is that endometriosis starts with cells from the endometrium (the lining of the unterus), entering the peritoneal cavity. Some theories suggest that progesterone resistance results in the uterine contractions that would normally move sperm to fertilize the egg, instead to cause this retrograde action. 90% of all women have retrograde menstruation [8]. Upon entering the pelvic cavity, these cells trigger an immune system response.

The immune system is responsible for protecting our bodies from antigens (harmful invaders) [22]. It operates with three layers of defense. First, the skin acts as a blockade. Second, the innate immune system handles commonly encountered antigens. Finally, the adaptive immune system handles the most dangerous antigens. In the case of women with endometriosis, ectopic endometrial cells are erroneously not destroyed by the immune system. Neither the apoptotic signals (cell suicide), nor the macrophages in the peritoneal cavity do their job in destroying those cells [14]. Once implanted in the pelvic cavity, the ectopic endometrial cells begin the process of self-support involving key hormones and other chemicals.

Hormones are critical for managing every important event in the human body [13]. With half-lives (the amount of time that it takes to decrease to half of its original volume) ranging from minutes to hours, amounts of hormones measured in nM (nanomolars, a measure of the concentration of one substance within another substance) are constantly flowing through the body to initiate helpful cell processes [6]. In women, hormones are responsible for initiating the menses and ovulation. In women with endometriosis, the ectopic endometrial cells are different. They are less responsive to hormones and chemicals that would prevent the disease, and they are

able to self-produce hormones which help them to survive [8]. The immune and endocrine interactions alone are many and complex in the existing knowledgebase of the disease. Research into endocrine disruptors offers another critical aspect to the disease process [12].

Endocrine disruptors are chemicals that either alter the endocrine function in a person or mimic other hormones, both with negative effects. The connection between dioxin, one of the worst poisons known to man, was made in 1993, and studies continue today [15, 16]. Endocrine disruptors are a much debated issue. One of the controversial arguments is that endocrine disruptors do not only occur in massive doses, but also in minute doses that make testing for their safe consumption very time consuming and expensive [24]. Issues like this are one of many that make research on the disease difficult.

4   Modeling

All scientists are expected to perform their research according to a responsible conduct of research [23]. That standard defines expectations and rights for subjects of research of every living kind. Research of this disease on human subjects would be considered unethical; so instead, experimentation is performed on rats or primates such as rhesus monkeys or baboons [14, 15]. As of this writing, there are no computational models of this disease. This seems like a place where computational sciences may make a contribution.

There are a number of research opportunities in endometriosis including and not limited to:

- What causes the disease?

- How to cure the disease?

- How to find the best treatment for each patient?

- Why don't 90% of women have endometriosis when 90% of all women have retrograde menstruation?

For the purpose of exploration in this essay, a much simpler question was posed: "What chemicals are most important in the aromatization feedback loop that provides estrogen to ectopic endometrial cells?".

4.1   Introduction to the Model

Endometriosis needs estrogen to grow and consequently to survive. One of the unique features of endometriosis is the ability of the cells to produce their own estrogen, thereby freeing themselves from being dependent upon the production of estrogen regulated by the reproductive system. This process is governed by a few key chemicals, steroidogenic factor 1 (SF-1), chicken ovalbumin uptake promotion factor (COUP-TF), and androstenedione. Working together with other chemicals, they initiate a feedback loop that promotes the production of estradiol. Unlike eutopic endometrial cells where COUP-TF normally blocks the aromatization process by which cholesterol is converted to estradiol, ectopic endometrial cells face SF-1 and COUP-TF fighting for the same binding site. The question posed here is "At what levels of inhibitor and enabler and supporting chemicals does the disease manage to survive for 7 years?"

4.2   Assumptions about the Model

1. Presence of the disease is defined as the presence of ectopic endometrium. Symptoms of the disease are not considered because the disease is defined only by the presence of ectopic endometrium; the amount of pain or infertility are not considered.

2. Inter-cellular interactions are not considered because to do so would have been too computationally expensive..

3. Age, race, education, emotional support, genetic history, diet, dioxin exposure, medical tradition, occupation, home location, work location, activity alterations, work alterations, location of birth, sexual orientation, sexual activity, history of sexual abuse, previous medical procedures, previous disease history, religion, and drug use (prescription or recreational) are not considered because the data was not available.

4. Endocrine production, consumption, communication, and half-life are not considered because it would have been too complex and computationally expensive to model.

5. Cell creation, death, interaction, chemical production, and chemical consumption are not considered because it would have been too complex and computationally expensive to model.

6. In the human body, there are several thousand kinds of cells and roughly 10^{14} cells in total; this is not considered because the volume was not important to study the relationship, and a smaller number of cells are used.

7. The endocrine and nervous system work intimately together; these interactions are not considered because how they work together is currently not understood.

8. This study does not take the nM concentration into consideration, instead the ratios between the chemicals are studied and simply referred to as "units of item".

9. Estradiol can increase the number of its receptors; this ability along with the number of receptors is not considered to simplify the model.

10. When endometrial cells escape the uterus, they can end up anywhere in the body. This is not considered, and it is assumed that every cell ends up in the peritoneal cavity because most women have implants in their pelvis.

11. When endometrial cells escape the ovaries through retrograde menstruation, a variable number of cells escape, but this is not considered because it simplifies the model. Instead, a fixed number of cells is assumed.

12. The location of the endometrial cells with respect to each other, and to other chemicals such as hormones, steroids, and proteins are not significant. Although important, they are not considered to simplify the model.

13. Ectopic endometrial cells both grow and implant themselves in tissue; both behaviors are not considered to simplify the model.

4.2.1   Traits of the Model's Environment

1. The pelvic peritoneum is like a fishbowl. Endometrial cells are deposited there by retrograde menstruation. Estrogen is deposited there by to be defined mechanisms; as are other chemicals. Most of these numbers are fixed for the simulation and are entered as parameters to the simulation to help see how changes affect the results.

2. The whole story of the simulation revolves around ectopic endometrium. They have escaped the uterus, and now their goal is to survive in the fishbowl. The only way for them to live is to eat estrogen. The simulation revolves around their goal to eat and live.

3. The chemicals required for the ectopic endometrium to survive will be injected into the fishbowl at fixed cycles. Their source is not considered, only

the amounts matter, to simplify the model. Those chemicals do have half-lives, but they are assumed to be one day.

4. An interesting part of this model is recognizing that ectopic endometrium are able to produce their own growth stimulator (estrogen). All chemicals necessary to do this are assumed present and readily available: SF1, COUPTF, PGE2, 17BHSD1, 17BHSD2, androstenedione, and cAMP.

5. There are some key points and assumptions about the life of the cells, the chemicals, and the notion of cycles and timing that have to do with humans suffering from the disease:

   (a) In real life, every month a women starts her menstrual cycle if an implanted egg is not present. The cycles results in many hormones being released into the body by various sites. Ultimately, the goal is for the eutopic endometrium to be sloughed off and carried out of the body. This cycle is assumed to be 30 days, while in fact, it varies among women and probably impacts how the disease works. The woman also never becomes pregnant in our modeling.

   (b) In real life, women miss cycles; but a successful cycle, 12 times a year is assumed here.

   (c) The test of whether a woman has endometriosis is the presence of a single ectopic endometrial cell, seven years after some arbitrary year in which the women "reports pain."

   (d) A fixed number of estrogen food units are released every cycle.

   (e) A fixed number of days will determine whether an ectopic endometrium can live from one cycle to another.

   (f) At the end of every cycle, the estrogen unit food store is cleared. Either

the half-life meant that it died out, or it was flushed out, or it just disappeared. This means that there is no long running accumulation of estrogen that can be eaten over the year. This is close to reality, but ignores the details.

(g) SF1 and COUPTF concentrations are fixed per cycle, even though in real life they vary.

4.2.2   Lifecycle of the Simulation

See Figures 4 and 5 for a visual representation.

1. The analysis performed is per cycle.

   (a) Ectopic endometrium and supporting chemicals are released at the beginning of every cycle.

   (b) There is a starting amount of ectopic endometrium at the beginning of the cycle. At the end, there can be more or less because ectopic endometrium can starve to death.

2. Ectopic endometrial cells starve to death if they run out of food before the end of the cycle.

3. Ectopic endometrial cells may or may not find food to eat.

4. Ectopic endometrial cells may or may not be able to produce enough food to survive; it depends on SF1 and COUPTF concentrations.

5. Ectopic endometrial cells can produce varying amounts of food to eat; this is how effective or productive they are in estrogen production.

6. Typically it takes 7 years for women to reach the point where they have a laporoscopy performed. During that procedure, existence of the disease is confirmed by the presence of ectopic endometrial cells. This simulation will run

for 7 years, and if any ectopic endometrial cells are still alive, then it will re-
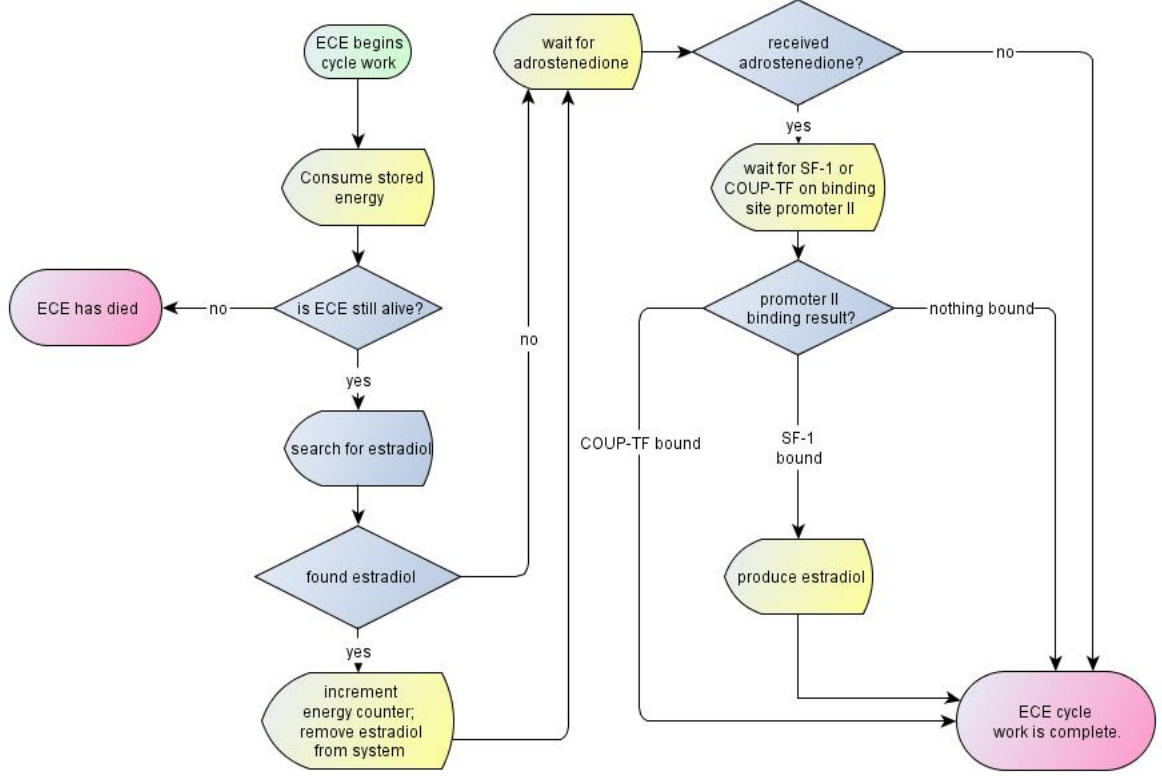port that the women has the disease.

Figure 4: The model is a stepwise discrete event simulation with a time-step of one
day.

4.3   The Implementation

The simulation takes a discrete approach. Both its functions and its simula-
tion environment are parameterized with configurable variables.

4.3.1   Simulation Parameters

1. τ: The number of years that the simulation should be run, assuming that
   there are 12 months in a year and 30 days in a month.

2. c_a^m: At the end of every month, this is the number of ectopic endometrial cells that are released into the pelvic cavity via retrograde menstruation.

3. ϵ_a^d: Every day skin and adipose tissue (body fat) deposit estradiol into the body. This is the number of units of estradiol assumed to be released into the pelvic cavity daily.

4. ϵ_a^m: At the end of every month, there is an estradiol surge that comes as part of the reproductive cycle. This is the amount of estradiol assumed to be released into the pelvic cavity at this time.

5. α_a^d: Every day, the adrenal glands deposit androstenedione into the body. This is the number of units of androstenedione assumed to be released into the pelvic cavity daily.

6. α_a^m: At the end of every month, there is an androstenedione surge that comes as part of the reproductive cycle. This is the amount of androstenedione assumed to be released into the pelvic cavity at this time. It usually close to the amount released daily.

7. $\bar{\epsilon}$: Although there is estradiol circulating in the pelvic milieu, there is no guarantee that an ectopic endometrial cell will actually find it. This number is between 0 and 1; the lower the value, the more likely estradiol will be found, the larger, the more likely it will not be found. 0 will guarantee that it is found; 1 will get close to guaranteeing that it is not found.

8. $\bar{\alpha}$: Although there is androstenedione circulating in the pelvic milieu, there is no guarantee that an ectopic endometrial cell will actually find it. This number is between 0 and 1; the lower the value, the more likely estradiol will be found, the larger, the more likely it will not be found. 0 will guarantee that it is found; 1 will get close to guaranteeing that it is not found.

9. $\bar{\sigma}$: In a real human, there is something producing SF-1 and COUP-TF; research shows that women with endometriosis have more SF-1 than COUP-TF, and that is why estradiol is more easily produced. This number is between 0 and 1. The lower the value, the more likely SF-1 will be found, the larger; the more likely it will not be found. 0 will guarantee that it is found; 1 will get close to guaranteeing that it is not found.

10. r_{sc}: The ratio of SF1 to COUPTF units.

4.3.2 Simulation Variables

1. $\boxed{\alpha}$: The amount of androstenedione present in the pelvis.

2. $\boxed{\epsilon}$: The amount of estradiol present in the pelvis.

3. $\boxed{s}$: The amount of SF-1 present in the pelvis.

4. $\boxed{\Omega_L}$: The living ectopic endometrial cells in the pelvis.

5. $\boxed{\Omega_D}$: The dead ectopic endometrial cells in the pelvis.

6. ω: An ectopic endometrial cell which contains a stored variable ω_l, representing its "life points". It starts with 5 life points. When its life points reach 0, it dies.

4.3.3 Functions

1. $r() \rightarrow$ *[random number between 0 and 1]*: a random number

2. $A_s(\alpha) \rightarrow$ *boolean*: whether androstenedione is found given the amount in the pelvic cavity, α, $r()$, and $\bar{\alpha}$.

3. $E_s(\epsilon) \rightarrow$ *boolean*: whether estradiol is found given the amount in the pelvic cavity, ϵ, $r()$, and $\bar{\epsilon}$.

4. $\Sigma_b() \rightarrow$ *boolean*: whether SF1 binds to the P450arom receptor, thus enabling estradiol to be produced, given $r()$ and $\bar{\sigma}$.

5. $alive(\omega) \rightarrow$ *boolean*: true if the cell has more than 0 life points.

4.3.4   Simulation Execution

for all *months* in τ **do**

$\qquad \boxed{\alpha} \leftarrow \boxed{\alpha} + \alpha_a^m$ $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad$ ▷ At month start

$\qquad \boxed{\epsilon} \leftarrow \boxed{\epsilon} + \epsilon_a^m$

$\qquad \boxed{\Omega_L} \leftarrow \boxed{\Omega_L} + c_a^m$

$\qquad$ **for all** *days* in month **do**

$\qquad\qquad \boxed{\alpha} \leftarrow \boxed{\alpha} + \alpha_a^d$ $\qquad\qquad\qquad\qquad\qquad\qquad\qquad$ ▷ Daily

$\qquad\qquad \boxed{\epsilon} \leftarrow \boxed{\epsilon} + \epsilon_a^d$

$\qquad\qquad$ **for all** ω in $\boxed{\Omega_L}$ **do**

$\qquad\qquad\qquad \omega_l \leftarrow \omega_l - 1$ $\qquad\qquad\qquad\qquad\qquad\qquad\qquad$ ▷ Eat

$\qquad\qquad\qquad$ **if** $alive(\omega)$ **then**

$\qquad\qquad\qquad\qquad$ **if** $E_s(\boxed{\epsilon})$ **then** $\qquad\qquad\qquad\qquad\qquad$ ▷ Seek estradiol

$\qquad\qquad\qquad\qquad\qquad \omega_l \leftarrow \omega_l + 1$

$\qquad\qquad\qquad\qquad$ **end if**

$\qquad\qquad\qquad\qquad$ **if** $A_s(\boxed{\alpha})$ **then** $\qquad\qquad\qquad\qquad$ ▷ Seek androstenedione

$\qquad\qquad\qquad\qquad\qquad \boxed{\alpha} \leftarrow \boxed{\alpha} - 1$

$\qquad\qquad\qquad\qquad\qquad$ **if** $\Sigma_b()$ **then** $\qquad\qquad\qquad\qquad\qquad$ ▷ Enabled production?

$\qquad\qquad\qquad\qquad\qquad\qquad \boxed{s} \leftarrow \boxed{s} - 1$

$\qquad\qquad\qquad\qquad\qquad\qquad \boxed{\epsilon} \leftarrow \boxed{\epsilon} + 1$

$\qquad\qquad\qquad\qquad\qquad$ **end if**

$\qquad\qquad\qquad\qquad$ **end if**

$\qquad\qquad\qquad$ **else**

$\qquad\qquad\qquad\qquad \boxed{\Omega_D} \leftarrow \boxed{\Omega_D} + \omega$

> **end if**

> **end for**

end for

$\boxed{\Omega_L} \leftarrow \boxed{\Omega_L} - \boxed{\Omega_D}$ ▷ At month end

$\boxed{\Omega_D} \leftarrow \boxed{\Omega_D} - \boxed{\Omega_D}$

$\boxed{\alpha} \leftarrow 0$

$\boxed{\epsilon} \leftarrow 0$

end for

4.3.5   Simulation Outputs

1. The number of cells that were alive at the end of each month.

2. The number of cells that were dead at the end of each month.

3. The number of units of estradiol removed from the system each month.

4. The number of units of androstenedione removed from the system each month.

5. The number of units of SF-1 removed from the system each month.

6. The number of units of E2 added by ectopic endometrial cells each month.

7. How much estradiol was left remaining at the end of each month.

8. How much androstenedione was left remaining at the end of each month.

Figures 6 and 7 are possible results of such a simulation.

4.3.6   Simulation Possible Results

In figure 6 we see a woman who has endometrial cells introduced to her system every month that are guaranteed both to find food and produce estrogen. The process of producing estrogen depends on androstenedione to act as an enabler.

When androstenedione is set at a fixed amount, the number of ectopic endometrial cells will increase until they also reach a fixed amount, limited by the androstenedione. Figure 7 is a different, it demonstrates continued growth of the disease.

In figure 7 we see a woman who has a large amount of enabling hormones, androstenedione and SF-1, introduced every month. The enabling hormones, along with the successful production of estrogen by the ectopic endometrial cells, enable both the survival and growth of the ectopic endometrial cells. The unique ability of the ectopic endometrial cells to produce their own food source may be an important aspect in the survival of the disease.
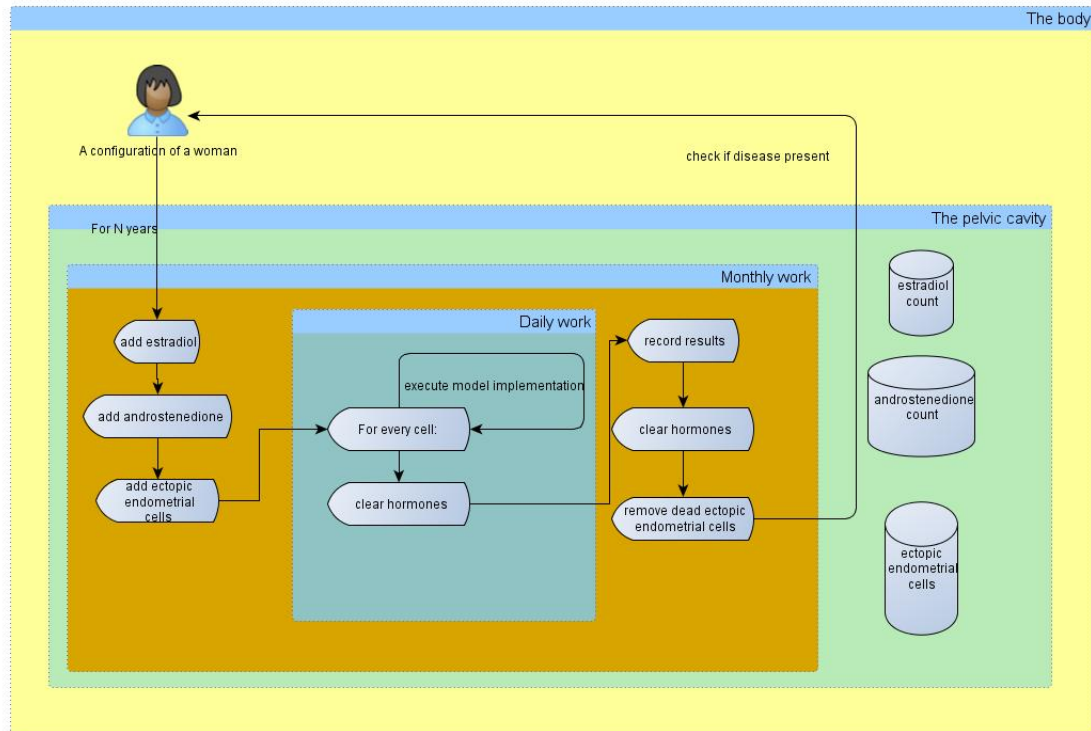

Figure 5: The simulation works by executing the model for every ectopic endometrial cell over the course of 7 years.
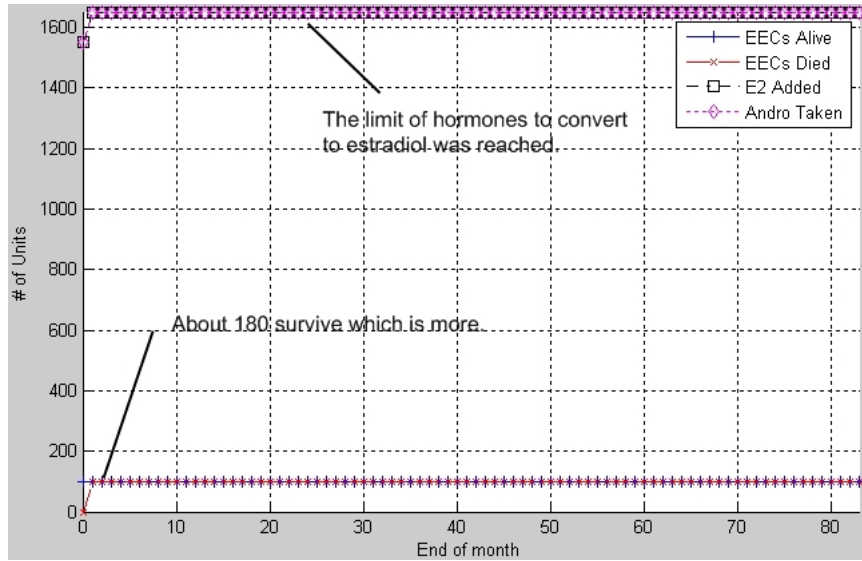
Figure 6: A system guaranteed to find and produce is always limited by androstenedione.

5   Conclusion

Endometriosis is a debilitating, widespread, and uncurable disease due to the complexity of the systems involved. More research is needed to gain a complete understanding of the disease and its cure. Due to the inherent complexity along with the difficulty in experimentation, it seems like a good candidate for computational modeling. This very simplified model explores the effects of some of the variables involved, serving only as an introduction. The next step is to construct a more comprehensive model to look at more significant parts of the disease.
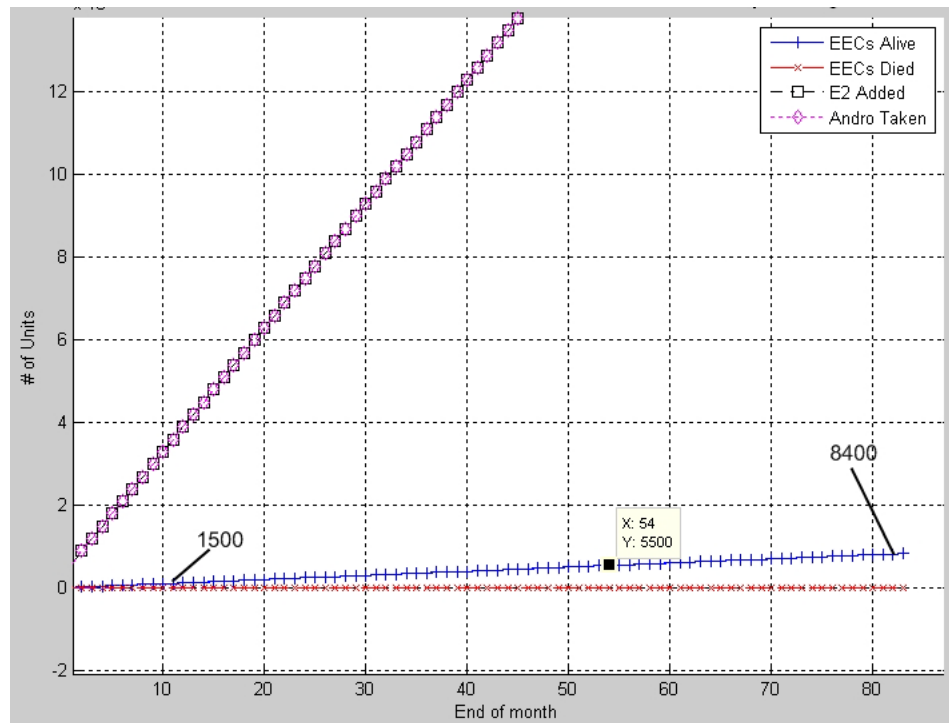
Figure 7: With enough androstenedione and enabler hormone; the cell count grows

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