Dynamics of the competition between cancer cells and infected cells, and the immune system - a mathematical modelling study

Master Thesis in Mathematics and Medical Biology

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Abstract

Mathematical models can be used in medicine to provide a picture of a biological system, such as cancer growth or response of the immune system.
In this master thesis we developed and investigated a mathematical model of coupled differential equations, describing the dynamics and interaction of cancer cells, infected cells and T-cells. We performed a mathematical analysis containing a numerical approach, finding steady states and their stability. We considered two cases, one where we assumed the elimination of cancer cells and infected cells to be certain, and one where we assumed the elimination to be uncertain.
In the case of certain elimination, we found one stable steady state of the coexistence of cancer cells and infected cells. At this stable steady state there was a low cancer burden and a low infection burden, meaning that when elimination is certain the system will be attracted to this state.
In the case of uncertain elimination, we found two stable steady states of the coexistence of cancer cells and infected cells. At one stable steady state there was both a low cancer burden and a low infection burden. At the other steady state there was both a high cancer burden and a high infection burden. This suggests that either the cancer cells and infected cells will be in a hibernation state, or there will be a full outbreak of cancer and infection.

Resume

Matematiske modeller kan bruges indenfor medicin, til at give et billede af et biologisk system. Sådan et system kan være tumor vækst eller respons af immune systemet.
I dette speciale har vi udviklet og undersøgt en matematisk model bestående af koblede differentialligninger, der beskriver dynamikken og interaktionen af cancerceller, inficerede celler og T-celler. Vi har lavet en matematisk analyse indeholdende en numerisk tilgang, fundet stationære tilstande og deres stabilitet. Vi undersøgte to tilfælde, et hvor vi antog, at elimineringen af cancer celler og inficerede celler var sikker, og et hvor vi antog, at elimineringen var usikker.
I tilfældet af sikker eliminering fandt vi én stationær tilstand når cancerceller og inficerede celler eksisterede på samme tid. Ved denne stationære tilstand var der både en lav cancer byrde og en lav infektions byrde, hvilket kan betyde at når elimineringen er sikker, vil systemet tiltrækkes denne tilstand.
I tilfældet hvor elimineringen er usikker, fandt vi to stabile stationære tilstande, når cancerceller og inficerede celler eksisterede på samme tid. I den ene tilstand var der både en lav cancer byrde og en lav infektions byrde, og i den anden tilstand var der både en høj cancer byrde og en høj infektions byrde. Dette tyder på, at når elimineringen er usikker, vil systemet enten forholde sig i en slags hviletilstand eller i et fuldt udbrud af cancer og infektion.

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1 Introduction

Cancer is one of the leading causes of death worldwide, and affects all people of all age groups [1]. One of the hallmarks of cancer is chronic inflammation [2], and many cancer patients die with unresolved infections [3]. Inflammation is a result of the immune system recognizing and acting on foreign pathogens presenting unknown antigens on their surface. Such pathogens can be a virus or sick cells from within the body such as cancer cells [4].

The immune system consists of two parts, the innate immune response and the adaptive immune response. The innate response is the first to react and fight. If this part is unable to win and kill the pathogen, it results in a chronic inflammation, and the adaptive response is activated [4].

Cancer cells present antigens on their surface [5], which activates the immune system which tries to fight the cancer cells and thereby preventing tumor growth [4]. Similarly, a virus entering the body also present antigens on their surface which activates the immune system trying to fight the infection [4]. In 2020 severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is currently causing a global pandemic, and can cause severe health problems for people with an already existence illness [6]. This raises the the question of what kind of dynamic there is in a system where both cancer cells, infected cells and immune cells are present, and whether such a virus may occupy the immune system, causing the cancer cells to escape the immune system and initiate tumor growth.

Mathematical models, such as differential equations, have through the last century become an important tool in medicine. A mathematical model can be used to describe a biological system and the dynamic of such. Cancer cells and tumor growth is an example of a biological system. Further, mathematical models can be used to describe the interaction and dynamics of several populations in a biological system [7]. Such a biological system is the interaction between cancer cells, infected cells, and the cells of the immune system, which is investigated in this master thesis. The interaction and dynamics between tumor growth and the immune system are studied in a large scale in studies such as [8, 9, 10], and so are the dynamics between infections and the immune system in [6, 11, 12]. The model presented in this master thesis is based on the differential equations performed by Kuznetsov et al. 2001 [8], investigating the dynamic and interaction between cancer cells and effector cells of the immune system. In this master thesis these equations are expanded adding an infection to the model, resulting in two coupled differential equations, one for the cancer cells and one for the infected cells, in which the immune system response is incorporated. Investigating this model we are interested in the dynamics and interaction between cancer cells and infected cells, and the immune system.

1.1 Research Question

As described above, the interest of this thesis is to investigate the dynamics of a biological environment consisting of cancer cells, virus infected cells and T-cells of the immune system. I will use a mathematical model of coupled differential equations to describe the biological system, and through a mathematical analysis investigate the dynamics of the system, finding the steady states of the system and their stability.

2 Methodology

This master thesis is a project performing a mathematical analysis of a system of ordinary differential equations (ODEs). These ODEs describe the dynamics between cancer cells and infected cells and in addition their interaction with the immune system. The overall question in this investigation was, how is the dynamic of the immune system, when both cancer cells and infected cells are present. The ODEs of the model in this master thesis is based on the model presented by Kuznetsov et al. [8], and expanded such that the system includes an infection.

In order to answer the research question this master thesis is built up of three main sections. The first section contains the theory giving the knowledge relevant for the research question.

The theory section is based on books and articles giving the theoretical background. The database PubMed was used to find articles of relevance. For this research relevant words were used such as: mathematical analysis, modeling, immune system, cancer, infection, dynamics.

The second section contains the analysis of the mathematical model. This form of investigation of a model was chosen based on the interest of the dynamics and interaction of both cancer cells and the immune system, but also what happens when a virus is added to this type of model, and also interacts with the immune system. The mathematical analysis includes both qualitative research and a quantitative approach. The analysis of the model found expression for the steady states of the model. In order to find the steady states explicitly and determine their stability a numerical approach was performed.

For the numerical part of the analysis the program Maple was used for calculations, and for plotting the functions and steady states. This can be seen in appendix (9.3) and (9.4). The online program Geogebra was also used for plotting the functions, and creating the figures presented in the analysis.

The last section in this master thesis is the discussion. In this section the the results found in the analysis are discussed. Further the model developed is discussed.

3 Theory

In this section the theory of relevance in this thesis will be presented. In the first part of this section the biology of relevance is introduced. This contains a brief introduction to the immune system, and in addition the immune system and its interaction with cancer and infection.
In the second part of this section the mathematical theory used in this thesis will be presented. Lastly an example of a mathematical model is reviewed.

3.1 The Biology

Cells are the building blocks of the body, and exist in many different forms according to their function. The interaction between different cells plays a critical role in the normal development of organs and their function. The term 'cell competition', which is a certain kind of interaction, describes the existence of two groups of different cell types in the same tissue. The competition between two or more cell types includes the control of organ size development and control of cells against pathogen events [13]. In the fight against pathogens the body's own defence system plays a critical part. This defence system is called the immune system [4].

3.1.1 The immune system

The immune system is the body's own defence system and consist of proteins, cells (leukocytes) and organs. The immune system defends the host against infectious organisms, called pathogens. Pathogens can be viruses or bacteria that invade the host, or they can be sick cells within the host, such as disease causing cancer cells [4]. The cells of the immune system are found in the bloodstream and lymph, and in tissue and organs in the body [14].
The blood in the body consists of red blood cells (erythrocytes), white blood cells (leukocytes), and the cellsfragments (platelets) all in a liquid called plasma. All these cells come from the same population of cells called *multipotent hematopoietic stem cells* which differentiate into different precursors of the blood cells. One type of precursors is the bone marrow lymphocyte precursor, which gives rise to lymphocytes. Lymphocytes have the ability to travel through the bloodstream and enter tissue or organs. This is called cell migration [4]. The majority of lymphocytes are found in the primary lymphoid organs including the bone marrow and thymus. In these organs the lymphocytes develop and mature into naive lymphocytes. The naive lymphocytes are activated in the secondary organs which include the lymph nodes, spleen and tonsils [14].
Leukocytes can be divided into two groups, myeloid cells and lymphoid cells. The Myeloid cells include neutrophils, basophils, eosinophils, dendritic cells (DCs), mast cells, and monocytes which can evolve to macrophages. The lymphoid cells include B lymphocytes (B-cells), T lymphocytes (T-cells), natural killer (NK) cells, and plasma cells [14].

The immune system is divided into two parts, the innate immune response and the adaptive immune response [4], which work together, since cells of the innate immune response activate cells of the adaptive response [14]. Cells included in the two parts of the immune system are given in table (1).

The innate immune response

The innate immune system is the first to respond to foreign pathogens. The cells of the innate immune system include monocytes, macrophages, NK cells, DCs, and neutrophil leukocytes [14]. These cells are not specific, but recognize general molecules, often called antigens, on invaders or sick cells.

Monocytes circulate the bloodstream and are recruited to tissue as a consequence of infection or injury. At the site of infection the monocytes differentiate into macrophages [15], which initiate an inflammatory response by phagocytosis of the foreign particle [3]. At the site of inflammation also neutrophils and DCs act as phagocytes [14]. NK cells have the ability to target and kill cancer cells, and neutrophils can migrate through tissue to kill and destroy bacteria [15]. All of these cells are recruited by increased expression of chemokine growth factors and cytokines [3]. There are many different types of cytokines divided into families as interleukines (IL), colony-stimulating factors, interferons (IFN), tumour necrosis factors (TNF), chemokines and growth factors [4].

The aim of the cells of the innate immune response is to neutralize the inflammation. If they don't succeed in neutralization, a chronic inflammation will persist [3].

The adaptive immune response

The adaptive part of the immune system is more slow, and comes into action up to 7 days later than the innate response. The cells of the adaptive immune response consist mainly of lymphocytes [14] including B-cells and T-cells. The adaptive immune response is activated by DCs from the innate immune response which are antigen-presenting, travelling to lymphoid organs activating naive lymphocytes [15].

The lymphocytes express certain receptors on their surface which can recognize antigens and bind to these. This binding leads to activation of the lymphocytes, and as a result they undergo cell differentiation. The B-cells differentiate into plasma cells which secrete antibodies (Ab) into the bloodstream which can bind to antigens, and into memory cells recognising the antigen if it returns [14].

The T-cells differentiate into cells including Cytotoxic T lymphocytes or killer cells (CD8+ T-cells), which have the ability to directly kill cells not belonging to the host, and CD4+ T-cells which are further classified into regulatory T-cells (Tregs) and T helper cells (Th-cells). Some T-cells also differentiate into T memory cells [15]. Th-cells help macrophages and NK cells by secretion of different cytokines. Tregs suppress certain B-cells and CD8+ T-cells to avoid attack

of the hosts own proteins, and hence avoiding autoimmune diseases [14].

After elimination of the pathogens, the activated immune cells from both the innate immune response and the adaptive immune response, die by apoptosis - except from memory cells [14].

The innate immune system	
Monocytes	
Macrophages: phagocytosis	
Natural killer (NK) cells	
Neutrophil leukocytes	
Dendritic cells (DCs)	
The adaptive immune system	
B lymphocytes (B-cells)	Stemcells: Produce antibodies (Ab) Memory cells.
T lymphocytes (T-cells)	Cytotoxic T-cells (CD8+ T-cells) CD4+ T-cells: T helper cells (Th-cells) and Regulatory T-cells (Tregs) T memory cells

Table 1: Leukocytes included in the two parts of the immune system.

3.1.2 An immunoediting environment

The immune system's ability to look for and discover foreign pathogens is called immunosurveillance. When the immune system monitors cancer cells, it is called cancer immunoediting and an immunoediting environment [16].

Cancer immunoediting consists of three phases: elimination, equilibrium and escape. In the elimination phase the innate and the adaptive part of the immune system is involved in recognizing and fighting the cancer cells killing most of these. But it is possible that some cancer cells are left unnoticed, possibly for a long time. In the equilibrium phase these unnoticed cancer cells exist in the body over a long time, keeping a small population of cancer cell at a equilibrium and in a dormant stage. This equilibrium is a result of balance between cell growth and cell death. The dormant stage may be a result of the tumor's inability to induce angiogenesis, or it may be the immune system keeping the tumor at a dormant stage. In the last phase cancer cells escape the immune system by genetic and epigenetic changes, letting the tumor grow unseen [16].

3.1.3 Cancer and the immune system

Cancer is a major health problem in many parts of the world, and affects all age groups. Cancer is not a single disease, but can originate in any organ in the body. This also makes curing cancer depending on the type of disease and the extent of it [1]. Cancer is a long process involving uncontrolled cell growth and proliferation, evasion from apoptosis and the immune system, and the ability to metastasize [3].

Cancer cells express antigens unique to the tumor [5]. In an immunoediting environment the immune system constantly controls the body looking for cancerous cells expressing antigens. Macrophages are activated after engulfing antigens from cancer cells, initiating an inflammatory response. Inflammation is one of the hallmarks of cancer, and cancer patients with elevated inflammatory mediators have a poorer prognosis. A majority of cancer deaths are related to unresolved infections. Hence chronic inflammation results in higher risk of tumor initiation [3].

After phagocytosis macrophages process and express antigens on their surface to Th-cells which bind to the antigen and gets activated. The macrophages secrete IL-1 and TNF-α, and the activated Th-cells release IL-2 and IFN-γ which activates the CD8+ T-cell, such that other possible existing cancer cells will be eliminated. The elimination occurs by the CD8+ T-cells inducing apoptosis [14].

When NK cells enter the site of inflammation they are stimulated by cytokines produced by activated macrophages, or by IL-2 and IFN-γ secreted by activated Th-cells. This stimulates the NK cells to secrete toxic chemicals. Further these cytokines stimulates the NK cells to produce IFN-γ which activates macrophages and other NK cells. This makes a loop of activation of NK cells and macrophages [4].

NK cells are part of both the innate and adaptive immune response. Since NK cells are not antigen-specific they can attack virus-infected cells and cancer cells without recognizing a specific antigen [14]. Tregs regulate Th-cells which control the adaptive immunity by activating other affecter cells such as macrophages, B-cells and CD8+ T-cells, and hence attacking cancer cells [15]. CD4+ T-cells activates CD8+ T-cells [9] which have antitumor activity killing cancer cells by direct cytotoxicity [3]. In order for tumor growth to happen, the cancer cells must escape the immune system [15].

Cancer cells have the ability to downregulate receptors on their surface hence not presenting antigens, making them invisible to the immune system. Another way cancer cells can escape the immune system is through chronic inflammation, where T-cells eventually lose their effectiveness, called T-cell exhaustion [5]. Both NK cells and CD8+ T-cells become inactive after a certain amount of encounters with tumor cells [9]

The immune response in tumor development is both stimulatory and inhibitory [17]. Inflammation is a part of the immune response which is connected to tumor initiation, progression and metastasis. It is the intracellular interactions and cytokine signalling of the immune system that determines the role in tumor initiation [3]. For instance macrophages can be classified into two types: M1 which is immuno-enhancing, and M2 which is immunosuppressing [5]; they both have the ability to kill cancer cells through phagocytosis, but they can also stimulate tumor development through the expression of cytokines and chemokines [17]. Tregs can promote tumor growth by reducing the immune response by CD4+ T-cells and CD8+ T-cells, by inhibiting the activation of these effector immune cells preventing autoimmune diseases [3].
Other mechanisms that stimulation tumor initiation includes DNA damage by free radicals, promotion of angiogenesis, suppression of antitumor immune activity and promotion of chronic inflammation in the tumor environment [17].

3.1.4 Infections and the immune system

When the body is fighting an infection, the symptoms of the disease is caused by the immune system response. The most commen sign of infection is fever. Another response is the production and release of neutrophils and monocytes. All of these responses are evoked by cytokines released from activated macrophages and other cells [14].
There are many factors that influence the body's ability to resist an infection. A person's state of mind or stress can reduce the resistance to both infections and cancer. It has been indicated that physical exercise influences the body's resistance to infection and cancer both positive and negative, for instance by regulating the number of circulating NK cells. The lack of sleep reduces the activity of NK cells in the blood [14].
Viruses attack the body by entering a cell and killing it, and then move on to other cells. But some viruses may hide inside other cells dormant for a long time before killing it. Further some viruses have the ability to transform their host cell into cancer cells [14]. The human papilloma virus (HPV) is such a type of virus, which among others can induce cervical cancer [1].

Since 2019 severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has spread across the globe, and resulted in a worldwide pandemic. The Coronavirus disease-2019 (COVID19) symptoms varies from patient to patient, but include fever, cough and shortness of breath. Many people don't show any symptoms, while others with already severe illness can get pneumonia, acute respiratory distress and may die after getting infected with this virus [6]. The amount of symptoms may be related to the viral load [18].
It has been shown that the level of T-cell, especially CD8+ T-cells, is significant decreased in severe COVID19 patients compared to mild cases. Further the amount of Ab has showed to be

significantly higher in severe cases. In all, COVID19 impact different biological mechanism, such as elevated pro-inflammatory levels and activation of immune cells [18]. Since cancer patients is at high risk of infections, COVID19 may be more severe for these patients [19].

3.2 The Mathematics

Over the last few decades mathematical models have become an important tool in medicine, and understanding different diseases and their development such as cancer cells and tumor growth [7]. An ordinary differential equation (ODE) is an equation with only time as the independent variable. A mathematical model can be a system of ODEs, which can be used to describe the dynamic of a biological system. Such a model can be used to represent the growth of a cellular population, and the interaction of a biological system, such as cell-cell interaction [15, 20, 21].

3.2.1 Mathematical models

If we consider the cells of the human body, we consider a biological system of a population. In this system some cells will proliferate, some will be constant, and some cells will die [22].
Let P define a population. Then there will be added an amount f to the population, and a fraction q of the population will die ($0 < q < 1$). Further we let dP be a small change in the population over a single day. Then we get a simple model

$$dP = fP - qP = (f - q)P$$

Further letting $P(t)$ be the size of the population at time t, where t is one day, we get

$$dP = P(t + 1) - P(t)$$

to be the difference in the population between two consecutive days. Whit this equation we can rewrite

$$P(t + 1) = P(t) + dP = P(t) + (f - q)P(t) = (1 + f - q)P(t)$$

and letting $\lambda = 1 + f - q$ be the final growth rate, we get the final model of population growth to be

$$P(t + 1) = \lambda P(t) \tag{1}$$

The problem with this type of model is that it insinuates that the growth of a population is exponential and without a bound [22].
In order to get a more realistic model, instead consider the change in population per individual, or *per-capita growth rate*, dP/P. For small values of the population P, the per-capita growth rate should be large, and for small population the per-capita growth rate should be small [22]. A logistic model is given by one differential equation

$$\frac{dP}{P} = rP\left(1 - \frac{P}{K}\right)$$

The factor r is the proliferation rate or growth rate of the population, and K is the carrying capacity, representing the limiting of resources and so the maximal size of P. All parameters in this model are assumed to be positive [13].

When considering the interaction of two populations x and y, potentially cancer cells and cells of the immune system, the dynamics of the competition can be evaluated using a Lotka-Volterra model. This model is given by the system of two differential equations

$$\frac{dx}{dt} = r_x x\left(1 - \frac{x + a_x y}{K_x}\right)$$
$$\frac{dy}{dt} = r_y y\left(1 - \frac{y + a_y x}{K_y}\right)$$

Also in this system all the parameters are assumed to be positive. Again here $r_i, i = x, y$ is the growth rate for the two populations respectively, and $K_i, i = x, y$ represent the carrying capacity of the two populations.
In this system the two populations are competing for the same limiting resources, which is represented by the competition coefficient a. This coefficient represents the effect of one population against the other. If $a_x > 1$ then cell population y is better at getting a resource of K_x than cell population x. If $a_x = a_y = 0$ there is no direct competition. [13].

When working with ODE and models of such a mathematical analysis of the model can give important information. Such an analysis includes determination of steady states and their stability [23].

3.2.2 Steady states and stability

We define a first-order autonomous differential system with two variables x and y as the two equations given by

$$\begin{aligned} \frac{dx}{dt} &= f(x, y) \\ \frac{dy}{dt} &= g(x, y). \end{aligned} \tag{2}$$

From this system we have the following definition.

Definition 3.1 (Steady state)**.** *A steady state solution of the differential system (2) are the solutions* $(\bar{x}, \bar{y})$ *satisfying*

$$f(\bar{x}, \bar{y}) = 0 \quad \textit{and} \quad g(\bar{x}, \bar{y}) = 0 \ [23].$$

So in order to find the steady states of a system of two differential equations we must set each equation equal to zero, and further solve for expressions for x and y. This will give the solutions

satisfying the condition.

When considering ODE representing a biological system, for example the interaction between cancer cells and cells of the immune system, such a steady state of a system is of interest since it represents a certain event happening in the biological system. The zero solution $(\bar{x}, \bar{y}) = (0, 0)$ is often a solution and represents total extinction of the two populations. On the other hand a positive steady state, where both populations are positive, represents survival of both populations. Negative steady states means negative populations size, and has no biological meaning [23].

When the steady states are identified their stability can be determined. Such a determination can tell whether a steady state is stable or unstable, and therefore if the system will be attracted to the state or repel from it.

For determination of stability of the steady states the Jacobian matrix of system (2) is calculated. The 2×2 Jacobian matrix is defined as

$$J = \begin{pmatrix} f_x(x,y) & f_y(x,y) \\ g_x(x,y) & g_y(x,y) \end{pmatrix}$$

where f_x is the derivative according to x, f_y according to y and so on. The stability is determined using the eigenvalues, λ, of the Jacobian matrix [23].

Definition 3.2 (Eigenvector and eigenvalues)**.** *If A is a $n \times n$ matrix, $\boldsymbol{v}$ is a nonzero vector in $\mathbb{R}^n$, and λ is a scalar such that $A\boldsymbol{v} = \lambda\boldsymbol{v}$, then $\boldsymbol{v}$ is called an eigenvector of A with eigenvalues λ [22].*

We note that we can not have the eigenvectors to be the zero vector [22].

The eigenvalues of the Jacobian matrix are found by solving

$$\det(J - \lambda I) = \det \begin{pmatrix} a_{11} - \lambda & a_{12} \\ a_{21} & a_{22} - \lambda \end{pmatrix} = 0$$

which gives the characteristic polynomial of J

$$\begin{aligned} (a_{11} - \lambda)(a_{22} - \lambda) - a_{12}a_{21} &= a_{11}a_{22} - a_{11}\lambda - a_{22}\lambda + \lambda^2 - a_{12}a_{21} \\ &= \lambda^2 - \lambda(a_{11} + a_{22}) + a_{11}a_{22} - a_{12}a_{21} \\ &= \lambda^2 - Tr(J)\lambda + \det(J) \end{aligned}$$

The eigenvalues are the zeros of the characteristic polynomial [23].

Definition 3.3. *Let A be a 2×2 matrix, and let $S = (\bar{x}, \bar{y})$ be a steady state.*

If the eigenvalues of matrix A are nonpositive or have nonpositive real part then S is stable.

If the eigenvalues are positive or have positive real part then S is unstable.

If the eigenvalues are negative or have negative real part then S is asymptotically stable [23].

In addition the eigenvalues have negative real part if and only if $Tr(J) < 0$ and $\det(J) > 0$.
A steady state can be classified as either a node or a saddle point by the values of the associated eigenvalues.

- **Node**: The eigenvalues have the same sign, and the eigenvalues may be equal or distinct.
- **Saddle**: The eigenvalues have opposite sign.

Asymptotic stability can be determined by calculating the determinant and trace of the Jacobian matrix [23].

Theorem 1. *Assume the first-order partial derivatives of f and g are continuous in some open set containing the steady state $(\bar{x}, \bar{y})$ of system (2). Then the steady state is locally asymptotically stable if*

$$Tr(J) < 0 \text{ and } \det(J) > 0$$

where J is the Jacobian matrix evaluated at the steady state. In addition, the steady state is unstable if either

$$Tr(J) > 0 \text{ or } \det(J) < 0 \text{ [23].}$$

The stability of a steady state is of interest, since it can tell something about what will happen to the population. A population may reach extinction if the zero solution is a stable steady state, but may be able to survive and grow if the steady state is unstable. A stable steady state where one of the values equals the carrying capacity and the other one equals zero, tells that only the one population will survive [23].

3.2.3 Example: Predator-prey model

We consider a predator-prey model given by the two differential equations

$$\frac{dx}{dt} = x\left(r - r\frac{x}{K} - ay\right)$$
$$\frac{dy}{dt} = y(-b + cx)$$

We assume all the parameters r, K, a, b, c to be positive. The first equation represents the prey, and the second equation represents the predator. Without the predator the prey will grow logistically, and without the prey the predator will be extinct. The term ay in the first equation represents the per capacity loss of prey to predator, and the term cx in the second equation represents the per capacity gain to the predator [23].
We find the steady states by solving the system

$$x\left(r - r\frac{x}{K} - ay\right) = 0$$
$$y(-b + cx) = 0.$$

The solutions gives three steady states which we note by S_1, S_2 and S_3

$$S_1 = (\bar{x_1}, \bar{y_1}) = (0, 0)$$
$$S_2 = (\bar{x_2}, \bar{y_2}) = (K, 0)$$
$$S_3 = (\bar{x_3}, \bar{y_3}) = \left(\frac{b}{c}, \frac{r(cK-b)}{Kac}\right)$$

In S_3 we must have $Kac \neq 0$, and further we see $r(cK-b)/Kac = 0 \Rightarrow K = b/c$, so we must have $K > b/c$.

From these steady states we see that there are three possible outcomes in this system. In the first steady state both populations will die. In the second steady state the prey will survive while the predators will die. In the last steady state the populations coexist.

In order to further investigate these steady states their stability must be determined.

We define the Jacobian matrix by finding the derivatives

$$J = \begin{pmatrix} r - \frac{2rx}{K} - ay & -xa \\ yc & cx - b \end{pmatrix}$$

We evaluate each of the steady states by inserting them in the Jacobian matrix.

$$J(S_1) = \begin{pmatrix} r & 0 \\ 0 & -b \end{pmatrix} \ , \ J(S_2) = \begin{pmatrix} -r & -Ka \\ 0 & cK - b \end{pmatrix} \ , \ J(S_3) = \begin{pmatrix} -\frac{rb}{cK} & -\frac{ba}{c} \\ \frac{r(cK-b)}{Ka} & 0 \end{pmatrix}$$

Firstly we consider $J(S_1)$. Here the eigenvalues are r and $-b$, where one is positive and the other is negative. Since the eigenvalues have opposite sign S_1 is a saddle point. Further we have $\det(J(S_1)) = -rb < 0$, so from definition (3.3) the saddle point is unstable. This means that the steady state where both populations reach extinction is not a stable condition, leaving an option for both populations to grow back.

Considering $J(S_2)$ we have an upper triangle. The eigenvalues are $-r$ which is negative and $cK - b$. We see when $K < b/c$ the eigenvalue is negative and S_2 is a node. But if $K > b/c$ the eigenvalue $cK - b$ is positive, and so S_2 is a saddle point. Considering the determinant we get $\det(J(S_2)) = -r(cK - b)$. When $K > b/c$ the determinant is negative and we get from Theorem (1) that the steady state is unstable. But when $K < b/c$ the determinant will be positive and we then get from Theorem (1) that S_2 is locally asymptotically stable, meaning that only the prey survives. Overall the stability of this steady state depends on the values of the parameters in the model.

For the last steady state S_3 one eigenvalue equals zero, so we calculate the determinant of $J(S_3))$

$$\det(J(S_3)) = \frac{br(cK-b)}{cK}.$$

We see that if $K < b/c$ the determinant will be negative and from Theorem (1) the steady state is unstable. But if $K > b/c$ the determinant will be positive and from Theorem (1) the steady state S_3 is locally asymptotically stable, meaning that both the prey and predator survives [23]. As before the stability of this steady state depends on the values of the parameters on the model.

4 The Model

The competition between two type of cells and their interaction with the immune system gives rise to the model developed and analysed in this master thesis.

We let x and y be the density of two type of cells competing; x represent cancer cells and y represent infected cells. We let a_i be the intrinsic growth rate and K_i the carrying capacity for x and y respectively. The parameter b_i is the competition term between x and y for the same resources.

We assume that the two type of cells in the absence of the other will growth logistically to K_i. We always assume $x(0) > 0$ and $y(0) > 0$, and that the parameters a, K and b are positive. Then the growth of the two different cell types x and y is given by the system of two differential equations

$$\begin{aligned} \frac{dx}{dt} &= a_x x\left(1 - \frac{x + b_x y}{K_x}\right) - r_x p_x T_x x \\ \frac{dy}{dt} &= a_y y\left(1 - \frac{y + b_y x}{K_y}\right) - r_y p_y T_y y \end{aligned} \tag{3}$$

The last term is the immune response eliminating x and y respectively. Here T_i describes the number of specific immune cells for x and y respectively, and $p_i r_i$ is the elimination rate r_i of x and y with probability p_i by the immune cell [23, 22]. The immune system reduces the population of x and y through the last term.

Considering the immune system the differential equations describing the rate of change of immune cells (naive T-cells, T_n) is given by the differential equation

$$\frac{dT_n}{dt} = \alpha - \beta_x x T_n - \beta_y y T_n - \varepsilon T_n \tag{4}$$

where T_n denotes the amount of naive T-cells, α represents the constant source of naive T-cells, and ε is the natural death of naive T-cells. The parameter β_x is the rate of binding between cancer cells and naive T-cells, and β_y is the rate of binding between infected cells and naive T-cells.

The interaction between cancer cells and naive T-cells results in activation of the T-cells specific for the cancer cells. The amount of cancer specific immune cells can be describe by the differential equation

$$\frac{dT_x}{dt} = \beta_x x T_n - r_x(1 - p_x) T_x x - d_x T_x \tag{5}$$

where d_x is the natural death rate. The parameter β_x is the rate of binding between cancer cells and immune cells, and $r_x(1 - p_x)$ is the rate r_x of inactivation of immune cells by cancer with probability $(1 - p_x)$.

Equivalent the interaction between infected cells and naive T-cells leads to activation of T-cells

specific for the infected cells, and hence we have the equation corresponding to the amount of infected specific immune cells given by the differential equation

$$\frac{dT_y}{dt} = \beta_y y T_n - r_y(1-p_y)T_y y - d_y T_y \tag{6}$$

where d_y is the natural death rate. The parameter β_y is the rate of binding between infected cells and immune cells, and the term $r_y(1-p_y)$ describes the rate r_y of inactivation of immune cells by infected cells with probability $(1-p_y)$.

The rate of change of the immune cells and cancer- or infected specific immune cells occurs at such a slow time, compared to cancer cells and infected cells, that we can apply a quasi-steady-state approximation to the three differential equations (4), (5) and (6), and hence obtain a solution for T_x and T_y. First consider equation (4)

$$\begin{aligned} 0 &= \alpha - \beta_x x T_n - \beta_y y T_n - \varepsilon T_n \\ T_n(\beta_x x + \beta_y y + \varepsilon) &= \alpha \\ T_n &= \frac{\alpha}{(\beta_x x + \beta_y y + \varepsilon)} \end{aligned}$$

Then inserting this expression in (5) we get

$$\begin{aligned} 0 &= \beta_x x \frac{\alpha}{(\beta_x x + \beta_y y + \varepsilon)} - r_x(1-p_x)T_x x - d_x T_x \\ T_x(r_x(1-p_x)x + d_x) &= \frac{\beta_x x \alpha}{(\beta_x x + \beta_y y + \varepsilon)} \\ T_x &= \frac{\beta_x x \alpha}{(\beta_x x + \beta_y y + \varepsilon)(r_x(1-p_x)x + d_x)} \end{aligned}$$

and equivalent for T_y

$$T_y = \frac{\beta_y y \alpha}{(\beta_x x + \beta_y y + \varepsilon)(r_y(1-p_y)y + d_y)}$$

Inserting the expressions for T_x and T_y in (3) gives the final system given by two differential equations

$$\begin{aligned} \frac{dx}{dt} &= a_x x\left(1 - \frac{x + b_x y}{K_x}\right) - \frac{r_x p_x \alpha \beta_x x^2}{(\beta_x x + \beta_y y + \varepsilon)(r_x(1-p_x)x + d_x)} \\ \frac{dy}{dt} &= a_y y\left(1 - \frac{y + b_y x}{K_y}\right) - \frac{r_y p_y \alpha \beta_y y^2}{(\beta_x x + \beta_y y + \varepsilon)(r_y(1-p_y)y + d_y)}. \end{aligned} \tag{7}$$

4.1 Assumptions

The variable x represents the population of cancer cells, and the variable y represents the populations of infected cells. We always assume $x(0) > 0$ and $y(0) > 0$. Negative values of one or the other would mean negative population size, and then the model would have no biological meaning. The parameter a describes the growth rate or proliferation rate of the two populations of cells, why we always assume this to be positive in order for new cells to develop. If this parameter is

zero, no populations will evolve [22].

The carrying capacity K describes the maximum number of cells to be supported, hence this must always be positive [22].

The parameter b is the competition term, and describes that cancer cells and infected cells are competing for the same available resources. The parameter must either be positive, or zero if there is no competition [13].

The parameter T describes the number of immune cells, which is activated in the presence of cancer cells and/or infected cells. These activated immune cells are specific and includes NK cells and CD8+ T-cells. This parameter is either positive, or zero if no immune cells are present.

The terms pr and $r(1-p)$ describes an efficiency and a probability. The parameter r is always positive, and for the parameter p we have $0 \leq p \leq 1$ [8].

The results in the following analysis must be non-negative. Since x and y represents populations of cancer cells and infected cells, complex and negative results has no biological meaning, and is of no interest.

The parameters of the model are summarized in table (4) appendix (9.1).

5 Analysis

In this section the model presented in section (4) will be analysed. In section (5.1) a stability analysis of the model is giving, finding expressions for the steady states and their stability as possible. In section (5.2) a numerical approach of the results found in section (5.1) is giving, finding explicit values for the steady states and determination of their stability.
The results of the analysis will be presented and evaluated accordingly to their relevant biological interpretation.

5.1 Stability analysis

In order to make the model a bit more simple, we are going to assume that x and y don't take resources from each other, hence $b_x = b_y = 0$, which means no direct competition. Then the system simplifies to

$$\begin{aligned} \frac{dx}{dt} &= a_x x\left(1 - \frac{x}{K_x}\right) - \frac{r_x p_x \alpha \beta x^2}{(\beta_x x + \beta_y y + \varepsilon)(r_x(1-p_x)x + d_x)} \\ \frac{dy}{dt} &= a_y y\left(1 - \frac{y}{K_y}\right) - \frac{r_y p_y \alpha \beta_y y^2}{(\beta_x x + \beta_y y + \varepsilon)(r_y(1-p_y)y + d_y)} \end{aligned} \tag{8}$$

In order to find the steady states and their stability of system (8), we use the theory presented in section (3.2). At a steady state we have

$$\frac{dx}{dt} = \frac{dy}{dt} = 0$$

First we investigate the case where no cancer cells are present and no infected cells are present, $x = 0$ and $y = 0$. In this case the steady state is at the origin, and we denote it $S_0 = (0, 0)$.
For determination of the stability of this steady state, S_0, we calculate the Jacobian matrix of system (8)

$$J = \begin{pmatrix} f_x(x,y) & \dfrac{r_x p_x \alpha \beta_x x^2 \beta_y}{(\beta_x x + \beta_y y + \varepsilon)^2 (r_x(1-p_x)x + d_x)} \\ \dfrac{r_y p_y \alpha \beta_y y^2 \beta_x}{(\beta_x x + \beta_y y + \varepsilon)^2 (r_y(1-p_y)y + d_y)} & g_y(x,y) \end{pmatrix}$$

where

$$\begin{aligned} f_x(x,y) &= a_x\left(1 - \frac{x}{K_x}\right) - \frac{a_x x}{K_x} - \frac{2 r_x p_x \alpha \beta_x x}{(\beta_x x + \beta_y y + \varepsilon)(r_x(1-p_x)x + d_x)} \\ &\quad + \frac{r_x p_x \alpha x^2 \beta_x^2}{(\beta_x x + \beta_y y + \varepsilon)^2 (r_x(1-p_x)x + d_x)} + \frac{r_x p_x \alpha \beta_x x^2 r_x(1-p_x)}{(\beta_x x + \beta_y y + \varepsilon)(r_x(1-p_x)x + d_x)^2} \\ g_y(x,y) &= a_y\left(1 - \frac{y}{K_y}\right) - \frac{a_y y}{K_y} - \frac{2 r_y p_y \alpha \beta_y y}{(\beta_x x + \beta_y y + \varepsilon)(r_y(1-p_y)y + d_y)} \\ &\quad + \frac{r_y p_y \alpha y^2 \beta_y^2}{(\beta_x x + \beta_y y + \varepsilon)^2 (r_y(1-p_y)y + d_y)} + \frac{r_y p_y \alpha \beta_y y^2 r_y(1-p_y)}{(\beta_x x + \beta_y y + \varepsilon)(r_y(1-p_y)y + d_y)^2} \end{aligned}$$

Calculating the Jacobian matrix at S_0 we find

$$J(S_0) = \begin{pmatrix} a_x & 0 \\ 0 & a_y \end{pmatrix}.$$

The eigenvalues of this matrix are $\lambda_1 = a_x$ and $\lambda_2 = a_y$. In section (4.1) we assumed that a_x and a_y are positive, and hence λ_1 and λ_2 are positive, which implies that the origin is an unstable steady state. In addition since the eigenvalues have same sign the origin is a node.
This means that the total extinction of the cancer cells and infected cells is not a stable condition, meaning that both populations have the option to grow back, if there is some disturbance to the system.

For making further analysis a bit easier we simplify the model such that $u = {}^{x}/_{K_x}$, $v = {}^{y}/_{K_y}$ and $\tau = {}^{t}/_{a_x}$. Hence u is the ratio between the current cancer burden and the capacity, and v is the ratio between the current infection burden and the capacity. We get the model

$$\begin{aligned} \frac{du}{d\tau} &= u(1-u) - \frac{\varphi_x u^2}{(u+\mu v+\delta)(\omega_x u+1)} \\ \frac{dv}{d\tau} &= \rho v(1-v) - \frac{\varphi_y v^2}{(u+\mu v+\delta)(\omega_y v+1)} \end{aligned} \tag{9}$$

where

$$\begin{aligned} \varphi_x = \frac{r_x p_x \alpha}{d_x a_x},\ \mu = \frac{\beta_y K_y}{\beta_x K_x},\ \delta = \frac{\varepsilon}{\beta_x K_x},\ \omega_x = \frac{r_x(1-p_x)K_x}{d_x}, \\ \rho = \frac{a_y}{a_x},\ \varphi_y = \frac{r_y p_y \alpha \beta_y K_y}{\beta_x K_x d_y a_x},\ \omega_y = \frac{r_y(1-p_y)K_y}{d_y} \end{aligned}$$

5.1.1 Certain elimination

In the first approach we start by considering the case $p_x = 1$ and $p_y = 1$ such that $\omega_x = 0$ and $\omega_y = 0$. This means that the elimination of cancer cells and infected cells by immune cells will happen, the elimination is certain.
With these alterations we have the system

$$\begin{aligned} \frac{du}{d\tau} &= u(1-u) - \frac{\varphi_x u^2}{(u+\mu v+\delta)} \\ \frac{dv}{d\tau} &= \rho v(1-v) - \frac{\varphi_y v^2}{(u+\mu v+\delta)} \end{aligned} \tag{10}$$

We first we consider the infection-free case such that $v = 0$, but where cancer cells is present $u > 0$. Then we find the steady state by solving $^{du}/_{d\tau} = 0$. We find an expression with u

$$\begin{aligned} u(1-u) - \frac{\varphi_x u^2}{(u+\delta)} &= 0 \\ (1-u) &= \frac{\varphi_x u}{(u+\delta)} \\ (1-u)(u+\delta) &= \varphi_x u \\ u + \delta - u^2 - u\delta &= \varphi_x u \\ u^2 + u(\varphi_x - 1 + \delta) - \delta &= 0 \end{aligned} \tag{11}$$

The expression in (11) is a second degree equation. We define it as

$$P_u(u) = u^2 + ub_u + c_u \tag{12}$$

where

$$\begin{aligned} b_u &= \varphi_x - 1 + \delta \\ c_u &= -\delta \end{aligned}$$

We have $b_u > 0$ if and only if $\varphi_x + \delta > 1$. Applying Descartes rule of sign, equation (12) has one sign change and hence one positive real root, and considering $P(-u)$ equation (12) has one negative real root.

We find the root discriminant

$$\begin{aligned} d_u &= (\varphi_x - 1 + \delta)^2 - 4(-\delta) \\ &= (\varphi_x - 1 + \delta)^2 + 4\delta \end{aligned}$$

We see that $d_u > 0$ if and only if $\delta > 0$, and since δ is assumed to be positive, the root discriminant of equation (12) is always positive. We find the solutions to $P_u(u)$, finding the expressions for u

$$\begin{aligned} u_- &= \frac{-(\varphi_x - 1 + \delta) - \sqrt{(\varphi_x + \delta)^2 + 1 - 2(\varphi_x - \delta)}}{2} \\ u_+ &= \frac{-(\varphi_x - 1 + \delta) + \sqrt{(\varphi_x + \delta)^2 + 1 - 2(\varphi_x - \delta)}}{2} \end{aligned}$$

These expressions gives two steady state $S_{u_+} = (u_+, 0)$ and $S_{u_-} = (u_-, 0)$, where $S_{u_+} = (u_+, 0)$ is a positive solution and $S_{u_-} = (u_-, 0)$ is a negative solution. For biological purpose we will only consider the positive solution.

Next we consider the case where no cancer is present $u = 0$, but an infection is present $v > 0$. We considering $^{dv}/_{d\tau} = 0$ and find an expression corresponding to a second degree equation with variable v

$$P_v(v) = v^2 a_v + v b_v + c_v \tag{13}$$

where

$$a_v = \rho\mu$$
$$b_v = \varphi_y - \rho(\mu + \delta)$$
$$c_v = -\rho\delta$$

Here a_v is always positive and c_v is always negative. Further $b_v > 0$ if and only if $\varphi_y/\rho(\mu+\delta) > 1$, and so applying Descartes rule of sign, there is one sign change in equation (13), and therefore (13) has one real positive root and one real negative root. Here we find the root discriminant of equation (13)

$$d_v = (\varphi_y - \rho(\mu + \delta))^2 + 4\rho^2\mu\delta$$

Since ρ, μ and δ are assumed to be positive, we have $a_v > 0$ and $c_v < 0$ and therefore $d_v > 0$. We find the solutions to $P_v(v)$

$$v_- = \frac{-(\varphi_y - \rho(\mu + \delta)) - \sqrt{(\varphi_y - \rho(\mu + \delta))^2 + 4\rho^2\mu\delta}}{2\rho\mu}$$
$$v_+ = \frac{-(\varphi_y - \rho(\mu + \delta)) + \sqrt{(\varphi_y - \rho(\mu + \delta))^2 + 4\rho^2\mu\delta}}{2\rho\mu}$$

which gives two steady state, one positive $S_{v_+} = (0, v_+)$ and one negative $S_{v_-} = (0, v_-)$. Also here we are only interested in the positive steady state.

Next we assume that both cancer cells and infected cells are present such that $u > 0$ and $v > 0$. We solve $du/d\tau = 0$ and $dv/d\tau = 0$ and find two expressions, one for v and and one for u

$$0 = u(1-u) - \frac{\varphi_x u^2}{(u + \mu v + \delta)}$$
$$(1-u) = \frac{\varphi_x u}{(u + \mu v + \delta)}$$
$$(u + \mu v + \delta) = \frac{\varphi_x u}{(1-u)}$$
$$v = \frac{\varphi_x u}{\mu(1-u)} - \frac{(u+\delta)}{\mu}$$

and

$$0 = \rho v(1-v) - \frac{\varphi_y v^2}{(u + \mu v + \delta)}$$
$$(u + \mu v + \delta) = \frac{\varphi_y v}{\rho(1-v)}$$
$$u = \frac{\varphi_y v}{\rho(1-v)} - (\mu v + \delta)$$

We define these expressions as

$$f_u(u) = \frac{\varphi_x u}{\mu(1-u)} - \frac{(u+\delta)}{\mu}$$
$$f_v(v) = \frac{\varphi_y v}{\rho(1-v)} - (\mu v + \delta) \tag{14}$$

We note $u = f_v(v) = f_v(f_v(v)$ and $v = f_u(u) = f_u(f_v(v)$.

In order to find the number of possible solutions to these equations we solve $f_u(u) = v$ and $f_v(v) = u$

$$u = \frac{\varphi_y\left(\frac{\varphi_x u}{\mu(1-u)} - \frac{(u+\delta)}{\mu}\right)}{\rho\left(1 - \left(\frac{\varphi_x u}{\mu(1-u)} - \frac{(u+\delta)}{\mu}\right)\right)} - \left(\mu\left(\frac{\varphi_x u}{\mu(1-u)} - \frac{(u+\delta)}{\mu}\right) + \delta\right)$$

$$u + \left(\frac{\varphi_x u}{(1-u)} - u - \delta\right) + \delta = \frac{\frac{\varphi_y\varphi_x u}{\mu(1-u)} - \frac{\varphi_y(u+\delta)}{\mu}}{\left(\rho - \left(\frac{\rho\varphi_x u}{\mu(1-u)} - \frac{\rho(u+\delta)}{\mu}\right)\right)}$$

$$\frac{\varphi_x u}{(1-u)} = \frac{\frac{\varphi_y\varphi_x u - \varphi_y(u+\delta)(1-u)}{\mu(1-u)}}{\left(\frac{\rho\mu(1-u) - \rho\varphi_x u + \rho(u+\delta)(1-u)}{\mu(1-u)}\right)}$$

$$\frac{\varphi_x u}{(1-u)} = \frac{\varphi_y\varphi_x u - \varphi_y u + \varphi_y u^2 - \varphi_y\delta + \varphi_y u\delta}{(\rho\mu - u\rho\mu - \rho\varphi_x u + \rho u - u^2\rho + \rho\delta - u\rho\delta)}$$

$$\varphi_x u(\rho\mu - u\rho\mu - \rho\varphi_x u + \rho u - u^2\rho + \rho\delta - u\rho\delta) = (1-u)(\varphi_y\varphi_x u - \varphi_y u + \varphi_y u^2 - \varphi_y\delta + \varphi_y u\delta)$$

Cross multiply, expanding both sides and collecting the powers we get a third degree equation for u

$$\begin{aligned}
& u\varphi_x\rho\mu - u^2\varphi_x\rho\mu - u^2\varphi_x^2\rho + u^2\varphi_x\rho - u^3\varphi_x\rho + u\varphi_x\rho\delta - u^2\varphi_x\rho\delta \\
= {} & \varphi_y\varphi_x u - \varphi_y u + \varphi_y u^2 - \varphi_y\delta + \varphi_y u\delta - u^2\varphi_y\varphi_x + u^2\varphi_y - u^3\varphi_y + u\varphi_y\delta - u^2\varphi_y\delta \\
0 = {} & u\varphi_x\rho\mu - u^2\varphi_x\rho\mu - u^2\varphi_x^2\rho + u^2\varphi_x\rho - u^3\varphi_x\rho + u\varphi_x\rho\delta - u^2\varphi_x\rho\delta - \varphi_y\varphi_x u \\
& + \varphi_y u - \varphi_y u^2 + \varphi_y\delta - \varphi_y u\delta + u^2\varphi_y\varphi_x - u^2\varphi_y + u^3\varphi_y - u\varphi_y\delta + u^2\varphi_y\delta \\
0 = {} & u^3(\varphi_y - \varphi_x\rho) + u^2(\varphi_y\varphi_x - \varphi_x\rho\mu - \varphi_x^2\rho + \varphi_x\rho - \varphi_x\rho\delta - 2\varphi_y + \varphi_y\delta) \\
& + u(\varphi_x\rho\mu - \varphi_y\varphi_x + \varphi_y - 2\varphi_y\delta + \varphi_x\rho\delta) + \varphi_y\delta
\end{aligned}$$

Similarly we can find a third equation for v

$$\begin{aligned}
0 = {} & v^3(\varphi_y\rho\mu - \varphi_x\rho^2\mu) + v^2(2\varphi_x\rho^2\mu - \varphi_x\rho^2\delta + \varphi_y\rho\delta - \varphi_y\rho\mu - \varphi_x\varphi_y\rho + \varphi_y\rho + \varphi_y^2) \\
& - v(\varphi_x\rho\mu - 2\varphi_x\rho^2\delta + \varphi_y\rho\delta - \varphi_x\varphi_y\rho + \varphi_y\rho) - \varphi_x\rho^2\delta
\end{aligned}$$

Hence we have found two third degree polynomials

$$\begin{aligned}
Q_u = {} & u^3(\varphi_y - \varphi_x\rho) + u^2(\varphi_y\varphi_x - \varphi_x\rho\mu - \varphi_x^2\rho + \varphi_x\rho - \varphi_x\rho\delta - 2\varphi_y + \varphi_y\delta) \\
& + u(\varphi_x\rho\mu - \varphi_y\varphi_x + \varphi_y - 2\varphi_y\delta + \varphi_x\rho\delta) + \varphi_y\delta \\
Q_v = {} & v^3(\varphi_y\rho\mu - \varphi_x\rho^2\mu) + v^2(2\varphi_x\rho^2\mu - \varphi_x\rho^2\delta + \varphi_y\rho\delta - \varphi_y\rho\mu - \varphi_x\varphi_y\rho + \varphi_y\rho + \varphi_y^2) \\
& - v(\varphi_x\rho\mu - 2\varphi_x\rho^2\delta + \varphi_y\rho\delta - \varphi_x\varphi_y\rho + \varphi_y\rho) - \varphi_x\rho^2\delta
\end{aligned} \tag{15}$$

Since both of these polynomials are of degree three they have at most three roots over $\mathbb{C}$. Further they have at most nine common roots, and therefore intersects at most nine times [24]. Then

solving $f_u(u) = f_v(v) = 0$ can give up to nine steady states, $S_{uv_i} = (u_i, v_i),\ i = 1 \dots 9$.

For determination of the stability of the steady states found above, we calculate the Jacobian matrix of system (10)

$$J = \begin{pmatrix} 1 - 2u - \dfrac{2\varphi_x u}{u + \mu v + \delta} + \dfrac{\varphi_x u^2}{(u + \mu v + \delta)^2} & \dfrac{\varphi_x u^2 \mu}{(u + \mu v + \delta)^2} \\ \dfrac{\varphi_y v^2}{(u + \mu v + \delta)^2} & \rho(1 - v) - \rho v - \dfrac{2\varphi_y v}{(u + \mu v + \delta)} + \dfrac{\varphi_y v^2 \mu}{(u + \mu v + \delta)^2} \end{pmatrix} \tag{16}$$

Evaluating the steady state S_{u_+} we find

$$J(S_{u_+}) = \begin{pmatrix} d(S_{u_+}) & \dfrac{\varphi_x(-(\varphi_x - 1 + \delta) + \sqrt{d_u})^2 \mu}{(1 + \delta - \varphi_x + \sqrt{d_u})^2} \\ 0 & \rho \end{pmatrix} \tag{17}$$

where

$$d(S_{u_+}) = \varphi_x + \delta - \sqrt{d_u} - \frac{2\varphi_x(-(\varphi_x - 1 + \delta) + \sqrt{d_u})}{(1 + \delta - \varphi_x + \sqrt{d_u})} + \frac{\varphi_x(-(\varphi_x - 1 + \delta) + \sqrt{d_u})^2}{(1 + \delta - \varphi_x + \sqrt{d_u})^2}$$

The eigenvalues of this matrix are $d(S_{u_+})$ and ρ. The parameter ρ is always positive. The value of $d(S_{u_+})$ depends of the values of the parameters, but we have

$d(S_{u_+}) > 0$ if and only if $\varphi_x + \delta + \dfrac{\varphi_x(-(\varphi_x - 1 + \delta) + \sqrt{d_u})^2}{(1 + \delta - \varphi_x + \sqrt{d_u})^2} > \sqrt{d_u} + \dfrac{2\varphi_x(-(\varphi_x - 1 + \delta) + \sqrt{d_u})}{(1 + \delta - \varphi_x + \sqrt{d_u})}$

and

$d(S_{u_+}) < 0$ if and only if $\varphi_x + \delta + \dfrac{\varphi_x(-(\varphi_x - 1 + \delta) + \sqrt{d_u})^2}{(1 + \delta - \varphi_x + \sqrt{d_u})^2} < \sqrt{d_u} + \dfrac{2\varphi_x(-(\varphi_x - 1 + \delta) + \sqrt{d_u})}{(1 + \delta - \varphi_x + \sqrt{d_u})}$

Evaluating the steady state S_{v_+} we find

$$J(S_{v_+}) = \begin{pmatrix} 1 & 0 \\ \dfrac{\varphi_y(-(\varphi_y - (\rho(\mu + \delta))) + \sqrt{d_v})^2}{(\rho(\mu + 3\delta) - \varphi_y + \sqrt{d_v})^2 \mu^2} & d(S_{v_+}) \end{pmatrix} \tag{18}$$

where

$$d(S_{v_+}) = \frac{\varphi_y - \delta\rho - \sqrt{d_v}}{\mu} - \frac{2\varphi_y(-(\varphi_y - \rho(\mu + \delta)) + \sqrt{d_v})}{(\rho(\mu + 3\delta) - \varphi_y + \sqrt{d_v})\mu} + \frac{\varphi_y(-(\varphi_y - \rho(\mu + \delta)) + \sqrt{d_v})^2}{(\rho(\mu + 3\delta) - \varphi_y + \sqrt{d_v})^2 \mu^2}$$

The eigenvalues of this matrix are 1 which is always positive, and $d(S_{v_+})$. The values of $d(S_{v_+})$ depends on the values of the parameters, but as before we have

$d(S_{v_+}) > 0$ if and only if $\dfrac{\varphi_y - \delta\rho - \sqrt{d_v}}{\mu} + \dfrac{\varphi_y(-(\varphi_y - \rho(\mu + \delta)) + \sqrt{d_v})^2}{(\rho(\mu + 3\delta) - \varphi_y + \sqrt{d_v})^2 \mu} > \dfrac{2\varphi_y(-(\varphi_y - \rho(\mu + \delta)) + \sqrt{d_v})}{(\rho(\mu + 3\delta) - \varphi_y + \sqrt{d_v})\mu}$

and

$d(S_{v_+}) < 0$ if and only if $\dfrac{\varphi_y - \delta\rho - \sqrt{d_v}}{\mu} + \dfrac{\varphi_y(-(\varphi_y - \rho(\mu + \delta)) + \sqrt{d_v})^2}{(\rho(\mu + 3\delta) - \varphi_y + \sqrt{d_v})^2 \mu} < \dfrac{2\varphi_y(-(\varphi_y - \rho(\mu + \delta)) + \sqrt{d_v})}{(\rho(\mu + 3\delta) - \varphi_y + \sqrt{d_v})\mu}$

5.1.2 Uncertain elimination

In the next approach we assume $p_x < 1$ and $p_y < 1$, such that the elimination of cancer cells and infected cells by immune cells is no a certain event. We find expressions for the steady states of system (9).

First we consider the infection-free case where only cancer is present, such that $v = 0$ and $u > 0$ and consider $^{du}/_{d\tau} = 0$

$$\begin{aligned} u(1-u) - \frac{\varphi_x u^2}{(u+\delta)(\omega_x u+1)} &= 0 \\ (1-u) &= \frac{\varphi_x u}{(u+\delta)(\omega_x u+1)} \\ (1-u)(u^2\omega_x + u\omega_x\delta + u + \delta) &= u\varphi_x \\ -u^2\omega_x - u\omega_x\delta - u - \delta + u^3\omega_x + u^2\omega_x\delta + u^2 + u\delta + u\varphi_x &= 0 \\ u^3\omega_x + u^2(\omega_x\delta + 1 - \omega_x) - u(\omega_x\delta + 1 - \delta - \varphi_x) - \delta &= 0 \end{aligned} \tag{19}$$

The expression in (19) is a third degree equation, hence the total number of roots in this equation is at most 3 over $\mathbb{C}$. We define it as

$$h(u) = u^3 a_1 + u^2 b_1 + u c_1 + d_1 \tag{20}$$

where

$$\begin{aligned} a_1 &= \omega_x \\ b_1 &= \omega_x\delta + 1 - \omega_x \\ c_1 &= -(\omega_x\delta + 1 - \delta - \varphi_x) \\ d_1 &= -\delta \end{aligned}$$

We note that $a_1 > 0$ and $d_1 < 0$, and $b_1 > 0$ if and only if $\omega_x^{-1} + \delta > 1$, and $c_1 > 0$ if and only if $\omega_x + \delta^{-1}(1 - \varphi_x) > 1$. We get the following conditions

$$\text{If } b_1 \geq 0 \text{ and } c_1 \geq 0 \text{ one sign change} \tag{21}$$

$$\text{If } b_1 \geq 0 \text{ and } c_1 \leq 0 \text{ one sign change} \tag{22}$$

$$\text{If } b_1 < 0 \text{ and } c_1 > 0 \text{ three sign change} \tag{23}$$

$$\text{If } b_1 \leq 0 \text{ and } c_1 \leq 0 \text{ one sign change} \tag{24}$$

Then applying Descartes rule of sign, if condition (21), (22) or (24) holds, equation (20) has one or zero positive real roots. And if condition (23) holds, equation (20) has three or one positive real roots [25].

Similarly considering

$$h(-u) = (-u)^3 a_1 + (-u)^2 b_1 + (-u)c_1 + d_1 = -u^3 a_1 + u^2 b_1 - u c_1 + d_1$$

From this equation we get the following conditions

$$\text{If } b_1 > 0 \text{ and } c_1 \geq 0 \text{ two sign change} \tag{25}$$

$$\text{If } b_1 > 0 \text{ and } c_1 \leq 0 \text{ two sign change} \tag{26}$$

$$\text{If } b_1 \leq 0 \text{ and } c_1 \geq 0 \text{ zero sign change} \tag{27}$$

$$\text{If } b_1 \leq 0 \text{ and } c_1 < 0 \text{ two sign change} \tag{28}$$

Applying Descartes rule of sign, if condition (27) holds, equation (20) has zero negative real roots. If condition (25), (26) and (28) holds, equation (20) has two or zero negative real roots [25]. Since we are only interested in the positive roots, we find that equation (20) has at most three real roots. Hence we find at most three steady states $S_{u_1} = (u_1^*, 0)$, $S_{u_2} = (u_1^*, 0)$ and $S_{u_3} = (u_2^*, 0)$, where u_1^*, u_2^* and u_3^* are positive real roots of equation (20).

Next we consider the cancer-free case where only an infection is present, $u = 0$ and $v > 0$. We consider $^{dv}/_{d\tau} = 0$ and find an expression with v

$$\begin{aligned}
\rho v(1-v) - \frac{\varphi_y v^2}{(\mu v + \delta)(\omega_y v + 1)} &= 0 \\
\rho(1-v) &= \frac{\varphi_y v}{(\mu v + \delta)(\omega_y v + 1)} \\
(\rho - \rho v)(v^2 \mu\omega_y + v\mu + v\delta\omega_y + \delta) &= \varphi_y v \\
-v^2\rho\mu\omega_y - v\rho\mu - v\rho\delta\omega_y - \rho\delta + v^3\rho\mu\omega_y + v^2\rho\mu + v^2\rho\delta\omega_y + v\rho\delta + \varphi_y v &= 0 \\
v^3\omega_y\rho\mu + v^2(\omega_y\delta\rho + \rho\mu - \omega_y\rho\mu) - v(\omega_y\delta\rho + \rho\mu - \delta\rho - \varphi_y) - \rho\delta &= 0
\end{aligned} \tag{29}$$

The expression in equation (29) is a third degree equations. We define it as

$$h(v) = v^3 a_2 + v^2 b_2 + v c_2 + d_2 \tag{30}$$

where

$$\begin{aligned}
a_2 &= \rho\mu\omega_y \\
b_2 &= \rho\mu + \rho\delta\omega_y - \rho\mu\omega_y \\
c_2 &= -(\rho\mu + \rho\delta\omega_y - \rho\delta - \varphi_y) \\
d_2 &= -\rho\delta
\end{aligned}$$

and we note that $b_1 > 0$ if and only if $\omega_x^{-1} + \delta > 1$, and $c_1 > 0$ if and only if $\omega_x + \delta^{-1}(1 - \varphi_x) > 1$. Applying Descartes rule of sign, equivalent as equation (20), equation (30) has at most three positive real roots [25]. Therefore we find at most three steady states $S_{v_1} = (0, v_1^*)$, $S_{v_2} = (0, v_2^*)$ and $S_{v_3} = (0, v_3^*)$, where v_1^*, v_2^* and v_3^* are positive real roots of equation of (30).

Now we assume that both cancer cells and infected cells are present, such that $u > 0$ and $v > 0$. We solve $^{du}/_{d\tau} = 0$ finding an expression for v

$$\begin{aligned} u(1-u) - \frac{\varphi_x u^2}{(u+\mu v+\delta)(\omega_x u+1)} &= 0 \\ (1-u) &= \frac{\varphi_x u}{(u+\mu v+\delta)(\omega_x u+1)} \\ (u+\mu v+\delta) &= \frac{\varphi_x u}{(1-u)(\omega_x u+1)} \\ \mu v &= \frac{\varphi_x u}{(1-u)(\omega_x u+1)} - (u+\delta) \\ v &= \frac{\varphi_x u}{\mu(1-u)(\omega_x u+1)} - \frac{(u+\delta)}{\mu} \end{aligned}$$

and solve $^{dv}/_{d\tau} = 0$ finding an expression for u

$$\begin{aligned} \rho v(1-v) - \frac{\varphi_y v^2}{(u+\mu v+\delta)(\omega_y v+1)} &= 0 \\ \rho(1-v) &= \frac{\varphi_y v}{(u+\mu v+\delta)(\omega_y v+1)} \\ (u+\mu v+\delta) &= \frac{\varphi_y v}{\rho(1-v)(\omega_y v+1)} \\ u &= \frac{\varphi_y v}{\rho(1-v)(\omega_y v+1)} - (\mu v+\delta) \end{aligned}$$

We define the expression for u and v as $g_1(u)$ and $g_2(v)$ such that

$$\begin{aligned} g_u(u) &= \frac{\varphi_x u}{\mu(1-u)(\omega_x u+1)} - \frac{(u+\delta)}{\mu} \\ g_v(v) &= \frac{\varphi_y v}{\rho(1-v)(\omega_y v+1)} - (\mu v+\delta) \end{aligned} \tag{31}$$

We note that $u = g_v(g_u(u))$ and $v = g_u(u) = g_u(g_v(v))$. Solving these will give the last steady states. This will be done on the next section.

5.2 Numerical approach

In this part of the analysis we are going to investigate the results found in section (5.1.1) and (5.1.2) using numerical values for the parameters. The parameters of the model are summarized in table (4) appendix (9.1). In table (5) and (6) in appendix (9.2) values of the parameters are given from different articles. The articles which investigate infected cells, describe cells infected with COVID19. In order to perform a numerical approach of the mathematical model in (10), we choose the values for the parameters to be

$$a_x = 1.5,\ K_x = \frac{1}{2.17\times10^{-8}},\ \beta_x = \frac{1}{1.3\times10^{-7}},\ d_x = 0.12,\ r_x = 0.14,\ p_x = 0.9997,\ r_x(1-p_x) = \frac{1}{1\times10^{-7}}$$

and the parameters for the infected cells to be

$$a_y = 8.57,\ K_y = 10^9,\ \beta_y = 1.26\times10^5,\ d_y = 0.65,\ r_y p_y = \frac{1}{4.88\times10^{-8}},\ r_y(1-p_y) = \frac{1}{3\times10^{-7}}$$

further we chose $\alpha = 1.3 \times 10^4$ and $\varepsilon = \dfrac{1}{2.4 \times 10^{-2}}$.

Then we get the parameter values given in table (2). With these chosen values we can find the steady states explicitly.

Parameter	**Value**
φ_x	10108.078
ω_x	3.842×10^{15}
φ_y	9.712×10^{10}
ω_y	5.128×10^{15}
μ	0.355
ρ	5.713
δ	1.175×10^{-13}

Table 2: The table shows values for the simplified model.

5.2.1 Certain elimination

At first we are going to consider the case of certain elimination, $p_x = 1$ and $p_y = 1$, and the results found in section (5.1.1). The calculations for the explicit values are done in maple, and the calculations can be found in appendix (9.3).

We first consider the infection-free case where only cancer cells are present, $u > 0$ and $v = 0$. We looked at $^{du}/_{d\tau} = 0$ and found a second degree equation for u given in equation (11). Solutions to this equation corresponds to the solutions to $P_{u_1}(u) = P_{u_2}(u)$ where $P_{u_1}(u)$ and $P_{u_2}(u)$ are defined as

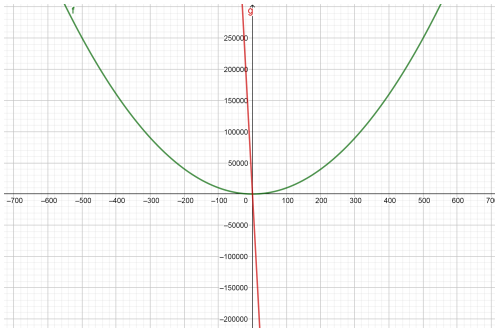
$$P_{u_1}(u) = u^2 + u(\delta - 1) - \delta$$
$$P_{u_2}(u) = -u\varphi_x$$

We find the steady state by solving $P_{u_1}(u) = P_{u_2}(u)$, see appendix (9.3). We find one positive steady state, which correspond to the steady state S_{u_+}. We find the values for this steady state to be

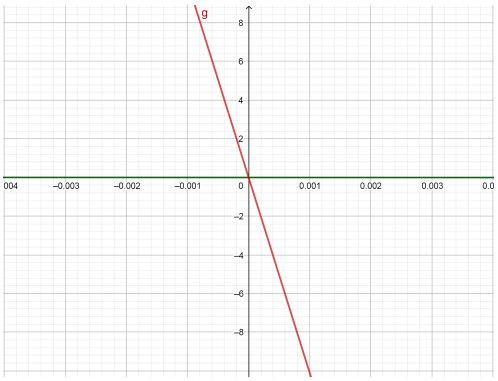
$$S_{u+} = (1.163 \times 10^{-17}, 0)$$

In this steady state their is a very low cancer burden. Figure (1) shows the two functions $P_{u_1}(u)$ and $P_{u_2}(u)$ and their intersection corresponding to the positive steady state.

Next we consider the cancer-free case, where $u = 0$ and $v > 0$. In equation (13) we found a second degree equation for v. The solutions to this equation correspond to the solutions to



(a) The intersection $(1.163 \times 10^{-17}, 0)$.



(b) Zoomed in at the intersection $(1.163 \times 10^{-17}, 0)$.

Figure 1: The figure shows the function $P_{u_1}(u)$ as the green graph, and $P_{u_2}(u)$ as the red graph and their positive intersection. To the right is zoomed in near the origin.

$P_{v_1}(v) = P_{v_2}(v)$, where these two functions are defined by

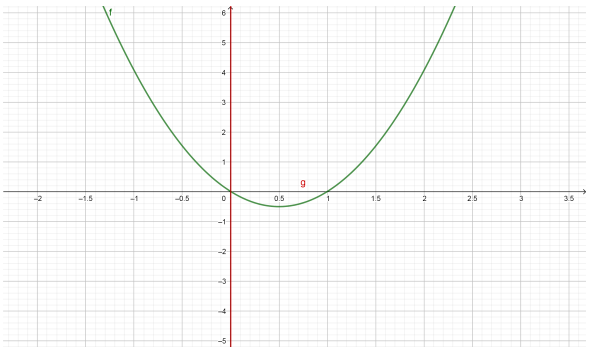
$$P_{v_1}(v) = v^2\rho\mu + v(\rho(\delta - \mu)) - \rho\delta$$

$$P_{v_2}(v) = -v\varphi_y$$

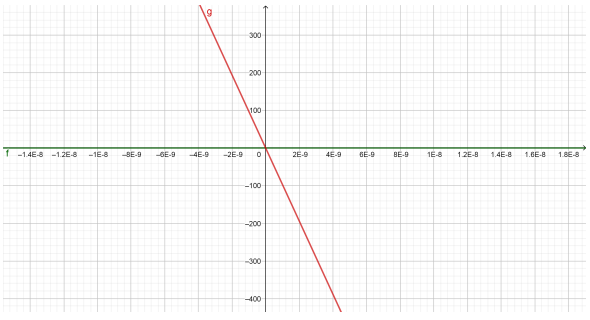
We find the solutions by solving $P_{v_1}(v) = P_{v_2}(v)$, see appendix (9.3). We find one positive solution to these equations corresponding to the solution S_{v+}. With the chosen parameter values we get the steady state

$$S_{v+} = \left(0, 6.915 \times 10^{-24}\right)$$

At this steady state there is a very low infection burden. Figure (2) shows the two functions $P_{v_1}(v)$ and $P_{v_2}(v)$ and their intersection corresponding to the steady states S_{v+}. At the figure to the left, the graph for the function $P_{v_2}(v)$ is very close to the y-axis, and at the figure to the right, the graph for the function $P_{v_1}(v)$ is very close to the x-axis.



(a) $P_{v_1}(v)$ and $P_{v_2}(v)$.

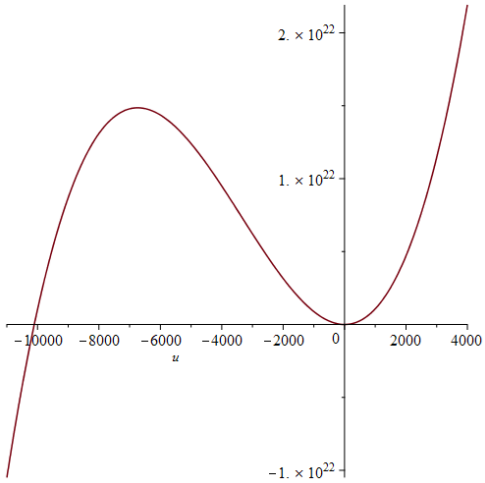


(b) Intersection $(0, 6.91 * 10^{-24})$.

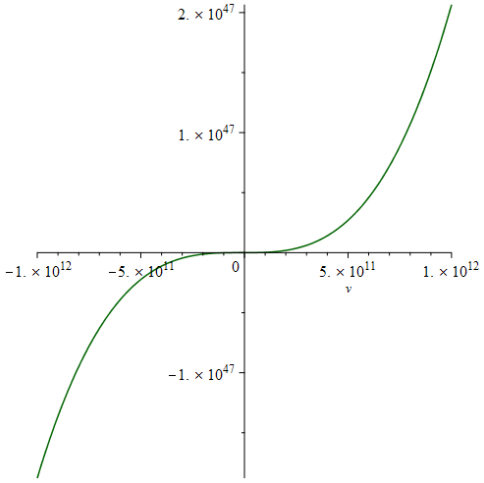
Figure 2: The figure shows the function $P_{v_1}(v)$ as the blue graph, and $P_{v_2}(v)$ as the red graph and their intersection. To the right is zoomed in near the origin. The graphs intersect in $(0, -4.782 \times 10^{10}$ and $(0, 6.915 * 10^{-24})$.

Next we consider the case where both cancer cells and infected cells are present such that $u > 0$ and $v > 0$. This case is given by the equations in (15). These are two third degree equations, and

their functions are shown in figure (3). We evaluated these functions to intersect at most nine times.



(a) The graph given by Q_u.



(b) The graph given by Q_v.

Figure 3: The figure shows the function Q_u to the left, and the function Q_v to the right.

By inserting the chosen parameter values, and solving the system $Q_u = Q_v = 0$ we find one positive intersection, hence one positive steady states $S_{uv} = (1.163 \times 10^{-17}, 6.916 \times 10^{-24})$. The steady state is shown as a yellow point in figure (4). At this steady state there is both a very low cancer burden and a very low infection burden.

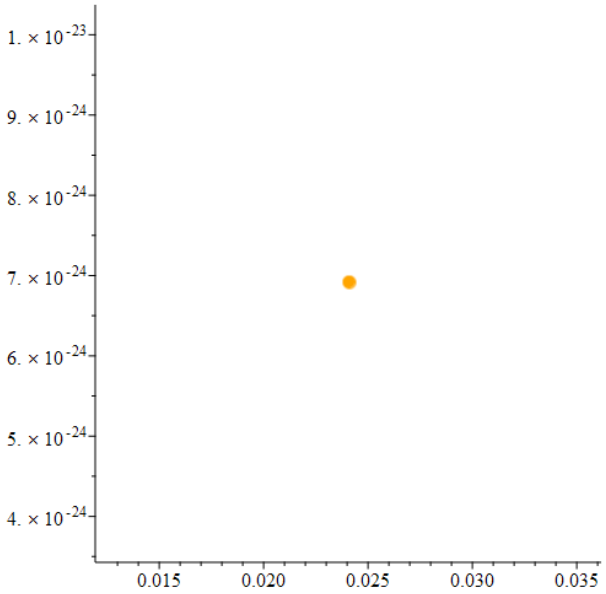


Figure 4: The positive steady states $S_{uv} = (1.163 \times 10^{-17}, 6.916 \times 10^{-24})$ shown as a yellow dot.

In all we have found the steady states S_{u+}, S_{v+} and S_{uv}. For evaluation of the steady states we determine the stability of the steady states. Therefore we calculate the Jacobian matrix of system (10) using the chosen parameter values. The calculation for the matrix is done in maple,

see appendix (9.3). The Jacobian matrix is calculated as

$$J = \begin{pmatrix} m_u & \frac{3592.876u^2}{(u+0.355v+1.175\times10^{-13})^2} \\ \frac{9.712\times10^{10}v^2}{(u+0.355v+1.175\times10^{-13})^2} & m_v \end{pmatrix}$$

where

$$m_u = 1-2u-\frac{20216.1556u}{u+0.355v+1.175\times10^{-13}}+\frac{10108.078u^2}{(u+0.355v+1.175\times10^{-13})^2}$$
$$m_v = 5.713-11.427v-\frac{1.942\times10^{11}v}{u+0.355v+1.175\times10^{-13}}+\frac{3.452\times10^{10}v^2}{(u+0.355v+1.175\times10^{-13})^2}$$

We now evaluate each of the steady states by inserting their values in the Jacobian matrix. This calculation is done in maple, see appendix (9.3).

We first evaluate the steady state $S_{u+} = (1.163\times10^{-17}, 0)$. The Jacobian matrix for this steady state is

$$J(S_{u_+}) = \begin{pmatrix} -0.999 & 0.0000352 \\ 0 & 5.713 \end{pmatrix}$$

The eigenvalues of $J(S_{u_+})$ are $\lambda_1 = -0.999$ and $\lambda_2 = 5.713$. Since these have opposite sign, the steady state is a saddle point. And since one eigenvalue is positive the steady state is unstable. In this steady state we have a low cancer burden. This can be interpreted as the cancer is at a dormant stage, and a small disturbance in the system, such as a mutation of the cells, could lead to cancer growth and tumor initiation.

Next we evaluate the stability of the steady state $S_{v+} = \left(0, 6.915\times10^{-24}\right)$. We find the Jacobian matrix of this steady state

$$J(S_{v_+}) = \begin{pmatrix} 1 & 0 \\ 3.361\times10^{-10} & -5.713 \end{pmatrix}$$

The eigenvalues of $J(S_{v_+})$ are $\lambda_1 = 1$ and $\lambda_2 = -5.713$. These eigenvalues have opposite sign, one is positive making the steady state unstable, and so the steady state is an unstable saddle. At this steady state there is a low infection burden. Since it is unstable a small disturbance of the system could make an infection evolve and move the system away from the steady state.

The last steady state we evaluate is $S_{uv} = (1.163\times10^{-17}, 6.916\times10^{-24})$ which is a steady state where both cancer cells and infected cells are present, both at a very low amount. We find the value of the Jacobian matrix of the steady state

$$J(S_{uv}) = \begin{pmatrix} -0.999 & 0.0000352 \\ 3.361\times10^{-10} & -5.713 \end{pmatrix}$$

We further calculate the determinant and trace of the Jacobian matrix

$$\det(J(S_{uv})) = 5.713$$
$$Tr(J(S_{uv})) = -6.713$$

Since the determinant is a positive value, and the trace is a negative values, the steady state S_{uv} is an asymptotically stable steady state. This means that when a low burden of cancer cells and infected cells are present, the two type of cells are coexistence and stable, and the system will be attracted to this steady state.

5.2.2 Uncertain elimination

Next we are going to consider the case of uncertain elimination, $p_x < 1$ and $p_y < 1$, and the results found in section (5.1.2). The calculations are done in maple, and is found in appendix (9.4).
We first consider the infection-free case where $v = 0$ and $u > 0$. We found the expression given in equation (19), which is a third degree equation for u. The solutions to the equation (19), corresponds to the solutions to $H_{v1}(v) = H_{v2}(v)$ where $H_{v1}(v)$ and $H_{v2}(v)$ are defined by

$$H_{u_1}(v) = u^3\omega_x + u^2(\omega_x\delta + 1 - \omega_x) - u(\omega_w\delta + 1 - \delta) - \delta$$
$$H_{u_2}(v) = -u\varphi_x$$

With the chosen parameter values, we solve $H_{v1}(v) = H_{v2}(v)$, see appendix (9.4), and find three positive solutions, corresponding to the steady states

$$S_{u_1^*} = (1.217 \times 10^{-17}, 0)$$
$$S_{u_2^*} = (2.514 \times 10^{-12}, 0)$$
$$S_{u_3^*} = (0.999, 0)$$

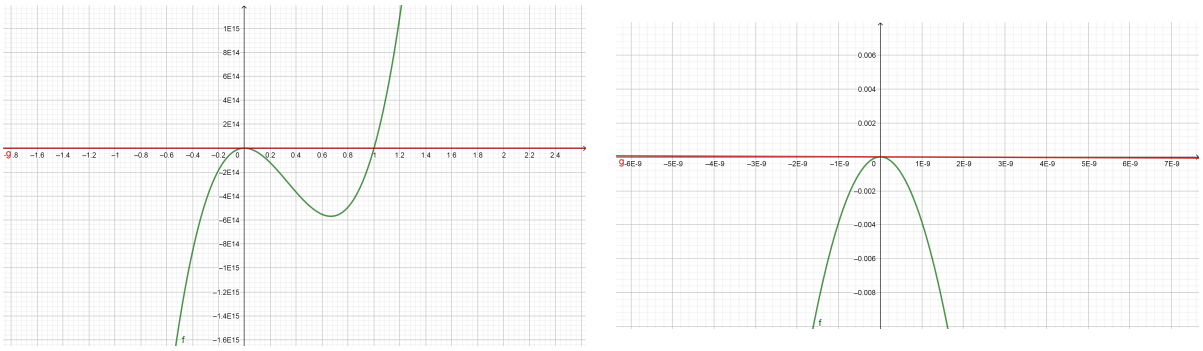
Figure (5) show the two graphs for $H_{u_1}(v)$ and $H_{u_2}(v)$ and their intersections.

At the two steady state $S_{u_1^*}$ and $S_{u_2^*}$ there is a very low cancer burden, and at the steady state $S_{u_3^*}$ there is a very high cancer burden.

Next we consider the cancer-free case, where $u = 0$ and $v > 0$. In this case we found the expressions in equation (29). The expression is a third degree equation for v, and solutions to the equation equal solutions to $H_{v_1}(v) = H_{v_2}(v)$, which are given by

$$H_{v_1}(v) = v^3\omega_y\rho\mu + u^2(\omega_y\delta\rho + \rho\mu - \omega_y\rho\mu) - v(\omega_y\delta\rho + \rho\mu - \delta\rho) - \delta\rho$$
$$H_{v_2}(v) = -u\varphi_y$$

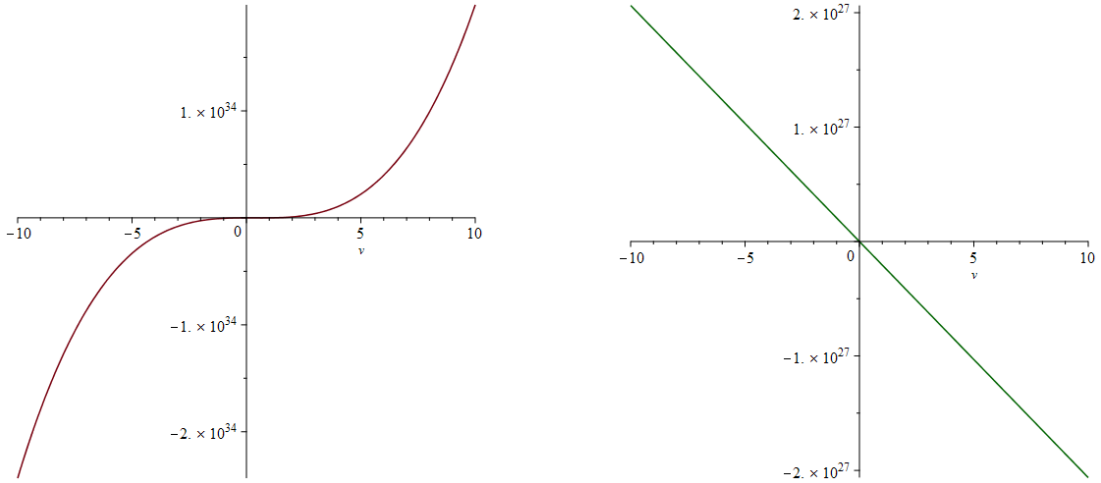
The two graphs are showed in figure (6).



(a) The two graphs $H_{u_1}(v)$ and $H_{u_2}(v)$.

(b) The positive intersection $S_{u_1^*}$, $S_{u_2^*}$ and $S_{u_3^*}$.

Figure 5: The figure to the left shows $H_{u_1}(u)$ as the green graph, and $H_{u_2}(u)$ as the red graph and their intersections. To the right there is zoomed in at the intersection $S_{u_1^*}$ and $S_{u_2^*}$.



(a) The graph by $H_{v_1}(v)$.

(b) The graph by $H_{v_2}(v)$.

Figure 6: The figure shows $H_{v_1}(v)$ and $H_{v_2}(v)$.

Solving $H_{v_1}(v) = H_{v_2}(v)$ we find three positive values for v and hence three positive steady states

$$S_{v_1^*} = \left(0, 6.915 \times 10^{-24}\right)$$
$$S_{v_2^*} = \left(0, 9.325 \times 10^{-6}\right)$$
$$S_{v_3^*} = (0, 0.999)$$

At the two steady states $S_{v_1^*}$ and $S_{v_2^*}$ there is a very low infection burden, and at the steady state $S_{v_3^*}$ there is a very high infection burden.

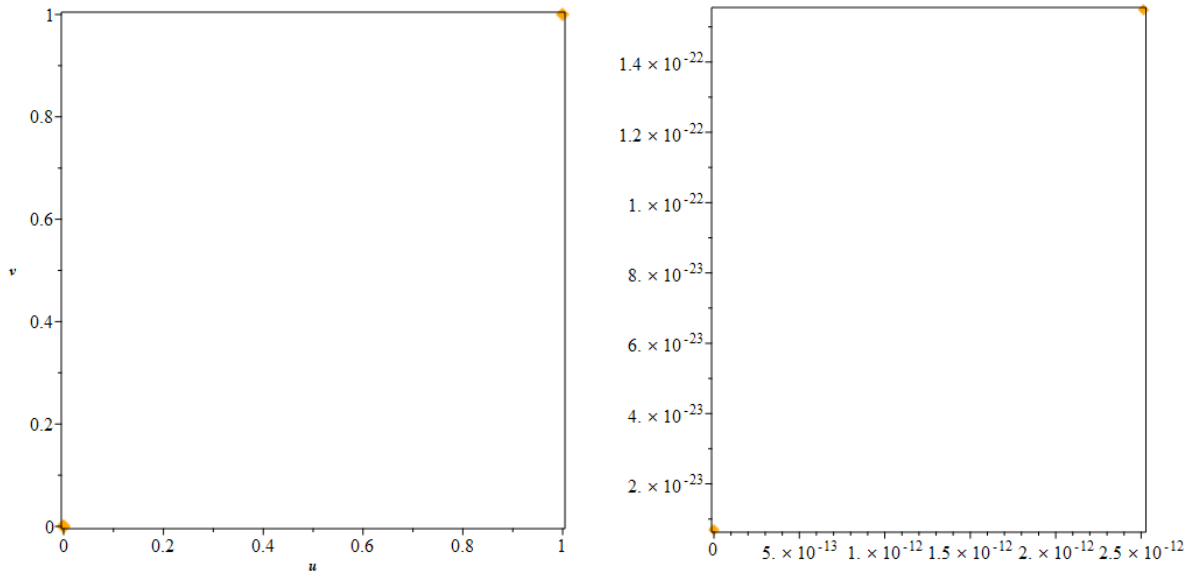
The last case we consider is the case where both cancer cells and infected cells are present, such that $u > 0$ and $v > 0$. In this case we found the two expression given in (31) defined by

$$g_u(u) = \frac{\varphi_x u}{\mu(1-u)(\omega_x u + 1)} - \frac{(u+\delta)}{\mu}$$
$$g_v(v) = \frac{\varphi_y v}{\rho(1-v)(\omega_y v + 1)} - (\mu v + \delta)$$

By using the chosen parameter values, and solving $g_u(u) = v$ and $g_v(v) = u$ we find three positive solutions, and therefore three positive steady states

$$S_{u^*v_1^*} = \left(1.217 \times 10^{-17}, 6.917 \times 10^{-24}\right)$$
$$S_{u^*v_2^*} = \left(2.514 \times 10^{-12}, 1.548 \times 10^{-22}\right)$$
$$S_{u^*v_3^*} = (0.999, 0.999)$$

These three steady states are shown in figure (7) as three yellow points. The figure to the left shows all three steady states, where the two steady states $S_{u^*v_1^*}$ and $S_{u^*v_2^*}$ are very close to each other. The figure to the right shows the two steady states $S_{u^*v_1^*}$ and $S_{u^*v_2^*}$.



(a) The three positive steady states $S_{u^*v_1^*}, S_{u^*v_2^*}, S_{u^*v_3^*}$. (b) The two positive steady states $S_{u^*v_1^*}$ and $S_{u^*v_2^*}$.

Figure 7: The figure shows the three positive steady state $S_{u^*v_1^*}, S_{u^*v_2^*}, S_{u^*v_3^*}$ shown as yellow dots.

For the evaluation and determination of the stability of the steady states found above, we find the Jacobian matrix of system (9), see appendix (9.4) for calculations.
We find

$$J_p = \begin{pmatrix} J_{p_1} & \dfrac{3592.876u^2}{m^2 \cdot n_1} \\ \dfrac{9.712 \times 10^{10} v^2}{m^2 \cdot n_2} & J_{p_2} \end{pmatrix}$$

where

$$J_{p_1} = 1 - 2u - \frac{20216.156u}{m \cdot n_1} + \frac{10108.078u^2}{m^2 \cdot n_1} + \frac{3.882 \times 10^{19})u^2}{m \cdot n_1^2}$$
$$J_{p_2} = 5.713 - 11.427v - \frac{1.942 \times 10^{11} v}{m \cdot n_2} + \frac{3.452 \times 10^{10} v^2}{m^2 \cdot n_2} + \frac{4.980 \times 10^{26} v^2}{m \cdot n_2^2}$$

and

$$m = u + 0.355v + 1.175 \times 10^{-13}$$
$$n_1 = 3.840 \times^{15} u + 1$$
$$n_2 = 5.128 \times 10^{15} v + 1$$

First we determine the stability of the infection-free case, where we found three positive steady states

$$S_{u_1^*} = (1.217 \times 10^{-17}, 0)$$
$$S_{u_2^*} = (2.514 \times 10^{-12}, 0)$$
$$S_{u_3^*} = (0.999, 0)$$

For the first steady state $S_{u_1^*} = (1.217 \times 10^{-17}, 0)$, we find the Jacobian matrix

$$J(S_{u_1^*}) = \begin{pmatrix} -0.957 & 0.0000368 \\ 0 & 5.713 \end{pmatrix}$$

The eigenvalues of this matrix is $\lambda_1 = -0.957$ and $\lambda_2 = 5.713$. We have one positive eigenvalue and one negative eigenvalue, and therefore the steady state S_{u^*} is an unstable saddle point. In this steady state we have a very low cancer burden, which could mean that the cancer is at a dormant stage. Since the steady state is unstable, a disturbance in the system could lead to tumor growth. Such a disturbance could be a mutation of the cancer cells, or the cancer cells escaping the immune system initiating tumor growth.

For the next steady state $S_{u_2^*} = (2.514 \times 10^{-12}, 0)$, we find the Jacobin matrix

$$J(S_{u_2^*}) = \begin{pmatrix} 0.955 & 0.340 \\ 0 & 5.713 \end{pmatrix}$$

We further calculate the determinant $\det(J(S_{u_2^*})) = 5.458$. Since the determinant is a positive value, the steady state is unstable. And the eigenvalues have same sign, so the steady state is an unstable node. Also at this steady state there is a vry low cancer burden, meaning that a tumor could be at a dormant stage as described above.

The last steady state in the infection-free case is $S_{u_3^*} = (0.999, 0)$, which is a state with a very high cancer burden, which could mean a fully evolved cancer. We find the Jacobian matrix of the steady state

$$J(S_{u_3^*}) = \begin{pmatrix} -1 & 9.356 \times 10^{-13} \\ 0 & 5.713 \end{pmatrix}$$

Here we have the eigenvalues are $\lambda_1 = -1$ and $\lambda_2 = 5.713$, they have opposite sign, and therefore the steady states is a saddle, and since one eigenvalue is positive the steady state is unstable.
In all we have found that in the positive steady states where only cancer is present all are unstable steady states. This means that the system will repel from these steady states.

The next three steady states are the cancer-free cases, where only an infection is present. In this case we found three positive steady states

$$S_{v_1^*} = \left(0, 6.915 \times 10^{-24}\right)$$
$$S_{v_2^*} = \left(0, 9.325 \times 10^{-6}\right)$$
$$S_{v_3^*} = (0, 0.999)$$

The first steady state we evaluate is $S_{v_1^*} = \left(0, 6.915 \times 10^{-24}\right)$, and we find the Jacobian matrix

$$J(S_{v_1^*}) = \begin{pmatrix} 1 & 0 \\ 3.361 \times 10^{-10} & -5.713 \end{pmatrix}$$

The eigenvalues of this matrix are $\lambda_1 = 1$ and $\lambda_2 = -5.713$. These eigenvalues have opposite sign why this steady state is a saddle. Further the steady state is unstable since one eigenvalue is positive. At this steady stage we have a very low infection burden, but the steady state is unstable, and therefore an infection can evolve, moving the system away from the steady state.

Next we consider the steady state $S_{v_2^*} = \left(0, 9.325 \times 10^{-6}\right)$ and find the Jacobian matrix

$$J(S_{v_2^*}) = \begin{pmatrix} 1 & 0 \\ 16.074 & 5.713 \end{pmatrix}$$

The eigenvalues for this matrix is $\lambda_1 = 1$ and $\lambda_2 = 5.713$. Both eigenvalues are positive and therefore have same sign, meaning that the steady state is a node. Further we calculate the determinant $\det(J(S_{v_2^*})) = 5.713$ and the trace $Tr(J(S_{v_2^*})) = 6.713$. Both of these values are positive, which means that this steady state is unstable. Also at this steady state, we have a very low infection burden. Since the steady state is unstable a disturbance in the system can make the system repel away from this steady state.

The last steady state is $S_{v_3^*} = (0, 0.999)$, and we find the Jacobian matrix

$$J(S_{v_3^*}) = \begin{pmatrix} 1 & 0 \\ 0.000149 & -5.713 \end{pmatrix}$$

The eigenvalues for this matrix is $\lambda_1 = 1$ and $\lambda_2 = -5.713$. These eigenvalues have opposite sign making the steady state a saddle point, and since one eigenvalue is positive the steady state is

unstable. At this steady state we have a very high infection-burden, meaning an infection is at its highest. But since the steady state is unstable, the system will be repelled away from this steady state.

In all we have found that in the three cancer-free cases, all the steady states S_{u^*}, $S_{v_1^*}$, $S_{v_2^*}$ are unstable steady states, and the system will be repelled from these steady states.

The last three steady states we evaluate are the cases where both cancer cells and infected cells are present. The steady states are

$$S_{u^*v_1^*} = (1.217 \times 10^{-17}, 6.916 \times 10^{-24})$$
$$S_{u^*v_2^*} = (2.514 \times 10^{-12}, 1.548 \times 10^{-22})$$
$$S_{u^*v_3^*} = (0.999, 0.999)$$

We first consider the steady state $S_{u^*v_1^*} = (1.217 \times 10^{-17}, 6.916 \times 10^{-24})$, where both cancer cells and infected cells is at a low burden. We find the Jacobian matrix of this steady state

$$J(S_{u^*v_1^*}) = \begin{pmatrix} -0.955 & 0.0000368 \\ 3.361 \times 10^{-10} & -5.713 \end{pmatrix}$$

We further calculate the determinant $\det(J(S_{u^*v_1^*})) = 5.458$ and the trace $Tr(J(S_{u^*v_1^*}) = -6.669$. We find that the determinant is positive, and the trace is negative, and therefore this steady state is an asymptotically stable steady state. At this steady state the cancer cells and infected cells coexist, and the system will be attracted to this steady state.

The next steady state we evaluate is the steady state $S_{u^*v_2^*} = (2.514 \times 10^{-12}, 1.548 \times 10^{-22})$. In this steady state we have a low cancer burden, and a low infection burden, but slightly more then in the previous steady state. We find the Jacobian matrix of the steady state

$$J(S_{u^*v_2^*}) = \begin{pmatrix} 0.955 & 0.340 \\ 3.361 \times 10^{-10} & -5.713 \end{pmatrix}$$

The eigenvalues have opposite sign, one is positive and one is negative, making this steady state an unstable saddle. Since the steady state is unstable, the system will be repelled from this steady state. Since the steady state $S_{u^*v_1^*}$ is very close to the steady state $S_{u^*v_2^*}$ the system will repel from $S_{u^*v_2^*}$ and be attracted to $S_{u^*v_1^*}$.

The last steady state we evaluate is the steady state $S_{u^*v_3^*} = (0.999, 0.999)$. At this steady state we have both a high cancer burden, and a high infection burden. For this steady state we find the Jacobian matrix

$$J(S_{u^*v_3^*}) = \begin{pmatrix} -1 & 5.092 \times 10^{-13} \\ 0.0000103 & -5.713 \end{pmatrix}$$

Both the eigenvalues are negative and therefore we calculate the determinant and the trace of the steady state. We find $\det(J(S_{u^*v_3^*})) = 5.713$ and $Tr(J(S_{u^*v_3^*})) = -6.713$. We find the determinant to be positive and the trace to be negative, meaning that this steady state is asymptotically stable, and the cancer cells and infected cells are coexistence. Since this steady state is stable, the system will we attracted to this steady state, with high burden of both type of cells.

In the three steady states where both cancer cells and infected cells are present, we have found two stable steady states, $S_{u^*v_1^*}, S_{u^*v_3^*}$, and one unstable steady state, $S_{u^*v_2^*}$. The three steady states are their stability are shown in figure (8).

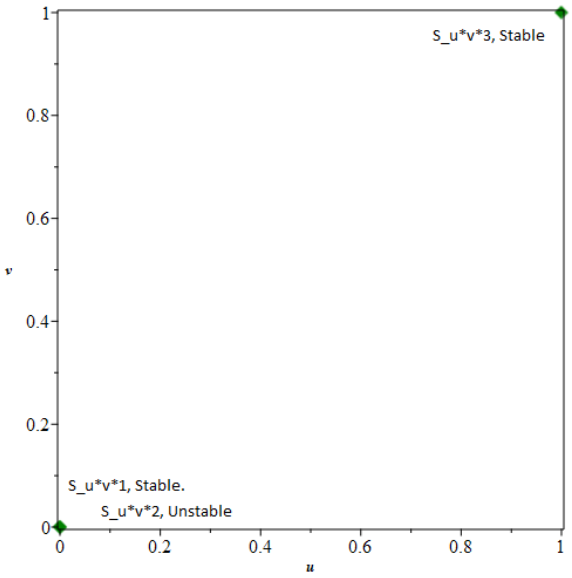


Figure 8: The three positive steady state $S_{u^*v_1^*}, S_{u^*v_2^*}, S_{u^*v_3^*}$ shown as green dots.

6 Discussion

In this master thesis we developed and studied a mathematical model consisting of two coupled differential equations describing the dynamics between cancer cells, infected cells and cells of the immune system. The aim of this master thesis was to study this mathematical model which included to find the steady states of the model and determine their stability. Through these findings we determine the dynamics of the model when only cancer cells are present and interacting with the immune system, when only infected cells are present and interacting with the immune system, or when both cancer cells and infected cells are present and interacting with the immune system.

In the analysis section (5) we investigated two approaches, one qualitative and one quantitative.

6.1 Stability analysis

In the first part of the stability analysis, section (5.1), we studied the model without any numerical values.

First we considered the case of certain elimination, $p_x = 1$ and $p_y = 1$. We were able to find expressions for the two positive steady states S_{u+}, where only cancer cells are present, and S_{v+}, where only infected cells are present, derived from two second degree equations. Further we were able to find that when both cancer cells and infected cells are present the system consists of two third degree equations, and therefore there will be at most nine steady states, $S_{uv_i} = (u_i, v_i), i = 1 \dots 9$. We were unstable to find exact expressions for these steady states.

Further we were able to find exact expressions for the Jacobian matrix of each of the steady states S_{u+} and S_{v+}, but not for the steady states $S_{uv_i} = (u_i, v_i), i = 1 \dots 9$.

In the second part of the stability analysis we assumed that elimination of the cancer cells and infected cells by the immune system was uncertain, $p_x < 1$ and $p_y < 1$. In this case we considered both the infection-free case and the cancer-free case. In both these cases we found a third degree equation for u and for v, and therefore at most three positive steady states in both cases. We were unable to find explicit expressions for the steady states.

In the case where both cancer cells and infected cells are present we found two functions, one containing u and one containing v. We were unable to find an exact number of steady states for these functions.

Further in the uncertain elimination case we were unable to determine the stability of the steady states found in this section. This led to the motivation of a numerical approach to the analysis.

6.2 Numerical approach

Choosing numerical values for the parameters of the model, we were able to find the steady states explicitly. The steady states and their stability is given in table (3).

Steady state	**Stability**
Certain elimination, $p_x = 1$ and $p_y = 1$	
$S_{u+} = (1.163 \times 10^{-17}, 0)$	Unstable
$S_{v+} = (0, 6.915 \times 10^{-24})$	Unstable
$S_{uv} = (1.163 \times 10^{-17}, 6.916 \times 10^{-24})$	Stable
Uncertain elimination, $p_x < 1$ and $p_y < 1$	
$S_{u_1^*} = (1.217 \times 10^{-17}, 0)$	Unstable
$S_{u_2^*} = (2.514 \times 10^{-12}, 0)$	Unstable
$S_{u_3^*} = (0.999, 0)$	Unstable
$S_{v_1^*} = (0, 6.915 \times 10^{-24})$	Unstable
$S_{v_2^*} = (0, 9.325 \times 10^{-6})$	Unstable
$S_{v_3^*} = (0, 0.999)$	Unstable
$S_{u^*v_1^*} = (1.217 \times 10^{-17}, 6.917 \times 10^{-24})$	Stable
$S_{u^*v_2^*} = (2.514 \times 10^{-12}, 1.548 \times 10^{-22})$	Unstable
$S_{u^*v_3^*} = (0.999, 0.999)$	Stable

Table 3: The table shows the steady states and their stability.

First we considered the case of certain elimination, such that the event of immune cells killing cancer cells and infected cells will happen.

In the infection-free case, we found one positive steady state S_{u+}. This steady state has a very low cancer burden which could be interpreted as a tumor at a dormant stage. The steady state showed to be unstable, so the system will repel from this steady state.

In the cancer-free case we found one positive steady state S_{v+}. This steady state has a very small amount of infection cells, and is an unstable steady state. Therefore the system will also repel from this steady state.

In the case where both cancer cells and infected cells were present, we found one steady state S_{uv}. In this steady state there is both a low cancer burden and a low infection burden. This steady states showed to be an asymptotically stable steady state, meaning that the system will be attracted to the steady state. This implies that when elimination of cancer cells and infected cells is certain the system will be at a low burden of both cancer cells and infected cells.

In our second attempt we assumed the the elimination by the immune cells was uncertain, $p_x < 1$

and $p_y < 1$. We first considered the infection-free case and found three positive steady states $S_{u_1^*}$, $S_{u_2^*}$ and $S_{u_3^*}$. In the two first steady states there is a low cancer burden, and in the last steady state there is a very high cancer burden. All of these steady states showed to be unstable, meaning that the system will be repelled from these steady states.

In the cancer-free case we found three positive steady states $S_{v_1^*}$, $S_{v_2^*}$ and $S_{v_3^*}$. In the two first steady states there is a very low infection burden, and in the last steady state there is a very high infection burden. All of these steady states showed to be unstable, and therefore the system will repel from these cases.

In the last case where both cancer cells and infected cells are present we found three positive steady states $S_{u^*v_1^*}$, $S_{u^*v_2^*}$ and $S_{u^*v_3^*}$. At the steady states $S_{u^*v_1^*}$ and $S_{u^*v_2^*}$ there is a very low cancer burden and a very low infection burden. At the steady state $S_{u^*v_3^*}$ there is a very high cancer burden and a high infection burden. We found that the steady states $S_{u^*v_1^*}$ and $S_{u^*v_3^*}$ are stable steady states, and that the $S_{u^*v_2^*}$ is an unstable steady state. This means the the system will be attracted to either the case of low burden of both cancer cells and infected cells, or the case with high burden of cancer cells and infected cells. If the system is near the steady state $S_{u^*v_2^*}$, it is also close to the stable steady state $S_{u^*v_1^*}$ and will be attracted to this stable steady state.

The results found in the analysis shows that when only cancer cells or infected cells are present, the steady states are all unstable and therefore the system will repel from these steady states. We found no stable steady states in these cases, and therefore no case the system will be attracted to. When adding cancer cells or infected cells to the system, we were able to find steady states which are stable, meaning that the system will be attracted to one of these stable steady states, and the cancer cells and infected cells coexist. One stable steady state had both low cancer burden and low infection burden, and another had both high cancer burden and high infection burden. This could indicate that when elimination of cancer cells and infected cells are uncertain, the system will either go into a sort of hibernation state or into a full outbreak of cancer and infection. Which of the stable steady states the system will be attracted to depends on the amount of cancer cells and infected cells present in the system.

6.3 The model

The model analysed in this master thesis was presented in section (4), and was based on a list of assumptions. One assumption was about the immune cells in the model. Modelling the immune system we only considered activated T-cells. The immune system consists of many different types of cells acting in the immune response having a wide range of functions, contributing to the response against cancer and infections. But the model we developed only contained one type of

cells from the immune system. The model could be expanded incorporating other cells from the immune system. Unni et al. [7] present a model of four differential equations containing both tumor cells, NK cells, DCs and CD8+ T-cells.
The novelty of the model studied in this master thesis is that it does not only consider the case of either cancer cells and immune cells, or the case of infected cells and immune cells, but considers all three type of cells in a system of two coupled differential equations, where an additional term of the immune response is incorporated. In this sense the dynamics and interaction of the system can be studied.

The model presented and analysed in this master thesis is based solely on the cells interacting without treatment. An extension of the model including treatment could be of interest in future studies. The dynamics of a system of cancer cells and a treatment using a mathematical model is a widely studied field. Sahoo [26] studied a mathematical model, based on a Lotka-Volterra predator-prey model, of CAR T-cell therapy which is a targeted immunotherapy, in the treatment of solid tumors in an *in vitro* system. In addition they applied their model to *in vivo* human data. Unni and Seshaiyer [7] studied the interaction between tumor growth and the immune system, and the effect of antitumor vaccination and immunotherapy along with chemotherapy. Liu and Yang [27] studied the dynamics of cancer cells and healthy cells, and the dynamics with radiotherapy followed by chemotherapy. Adding such a treatment to the model could be of interest.

The values chosen for the parameters in the model developed in this master thesis were chosen from different articles. The model contains many different parameters, and therefore many values which each chosen differently could give a different outcome. Using *in vivo* human data from cancer patients and patients with an infection, the values for the parameters could be selected more carefully. This would give a more realistic view of the situation for the individual patient. In this sense the model could be used in a specific situation customized to the patient according to the type of cancer and the exact type of infection.

7 Conclusion

In this master thesis we developed a mathematical model consisting of two coupled differential equations. These equations describe the dynamics and interactions of cancer cells and infected cells, and activated T-cells from the immune system. The novelty of this model was the combined interaction between these three type of cells, giving in two differential equations. For the study of the model we performed an analysis which included both a qualitative and a quantitative approach. In both of these approaches we considered both the case of certain elimination of cancer cells and infected cells by the immune cells, and the case of uncertain elimination.

First in the analysis of certain elimination, we considered the infection-free case and found one positive steady state. Then we considered the cancer-free case and found one positive steady state. Lastly in the case where both cancer cells and infected cells are present we found that the system could have at most nine steady states. We were unable to determine the stability of the steady states found in this case.

Second in the analysis of uncertain elimination, we found in the infection-free case that the system could have at most three positive steady states. Also in the cancer-free case we found that the system could have at most three positive steady states. In the case where both cancer cells and infected cells are present we found two expressions one for the cancer cells and one for the infected cells, but we found no expressions for the steady states.

Due to the limits of the first analysis, we were motivated to investigate the model using values for the parameters. Therefore we performed a numerical approach, and found the steady states and there stability explicitly.

In the numerical approach we first considered the case of certain elimination. In the infection free case where only cancer is present, we found one positive steady states. In the cancer-free case where only an infection is present we also found one positive steady state. These two steady states showed to be unstable. In the case where both cancer cells and infected cells are present we found one steady state. At this steady state there is both a low cancer burden and a low infection burden, due to the certain elimination. This steady state showed to be stable, why the system will be attracted to this state.

Next in the numerical approach we considered the case of uncertain elimination. We found three steady states in both the infection-free case and in the cancer-free case. All of these steady states showed to be unstable. In the case where both cancer cells and infected cells are present we found three steady states. One of these steady states were unstable, and two of the steady states were stable and therefore the cancer cells and infected cells coexist.

In one of the stable steady states there is a low cancer burden and a low infection burden. In the other stable steady state there is a high cancer burden and a high infection burden. Then

when the elimination is uncertain the the system will either be at the low burden case in a sort of dormancy, or it will be at the high burden case with a full blown cancer and infection.

8 References

References

[1] Carol Porth. *Essentials of pathophysiology : concepts of altered health states.* Wolters Kluwer, Philadelphia, 2015.

[2] Douglas Hanahan and Robert A. Weinberg. Hallmarks of cancer: The next generation. *Cell*, 144(5):646–674, mar 2011.

[3] Xinglong Qu, Ying Tang, and Shucheng Hua. Immunological approaches towards cancer and inflammation: A cross talk. *Frontiers in Immunology*, 9, mar 2018.

[4] Peter Wood. *Understanding immunology.* Pearson Prentice Hall, Harlow, England New York, 2006.

[5] Kerri-Ann Norton, Chang Gong, Samira Jamalian, and Aleksander Popel. Multiscale agent-based and hybrid modeling of the tumor immune microenvironment. *Processes*, 7(1):37, jan 2019.

[6] Sean Quan Du and Weiming Yuan. Mathematical modeling of interaction between innate and adaptive immune responses in COVID-19 and implications for viral pathogenesis. *Journal of Medical Virology*, 92(9):1615–1628, may 2020.

[7] Pranav Unni and Padmanabhan Seshaiyer. Mathematical modeling, analysis, and simulation of tumor dynamics with drug interventions. *Computational and Mathematical Methods in Medicine*, 2019:1–13, oct 2019.

[8] V.A. Kuznetsov and G.D. Knott. Modeling tumor regrowth and immunotherapy. *Mathematical and Computer Modelling*, 33(12-13):1275–1287, jun 2001.

[9] Ahmed M. Makhlouf, Lamiaa El-Shennawy, and Hesham A. Elkaranshawy. Mathematical modelling for the role of cd4+t cells in tumor-immune interactions. *Computational and Mathematical Methods in Medicine*, 2020:1–16, feb 2020.

[10] Fuat Gurcan, Senol Kartal, Ilhan Ozturk, and Fatma Bozkurt. Stability and bifurcation analysis of a mathematical model for tumor–immune interaction with piecewise constant arguments of delay. *Chaos, Solitons & Fractals*, 68:169–179, nov 2014.

[11] Rahim Ud Din, Kamal Shah, Imtiaz Ahmad, and Thabet Abdeljawad. Study of transmission dynamics of novel COVID-19 by using mathematical model. *Advances in Difference Equations*, 2020(1), jul 2020.

[12] Esteban A. Hernandez-Vargas and Jorge X. Velasco-Hernandez. In-host mathematical modelling of COVID-19 in humans. *Annual Reviews in Control*, sep 2020.

[13] Seiya Nishikawa, Atsuko Takamatsu, Shizue Ohsawa, and Tatsushi Igaki. Mathematical model for cell competition: Predator–prey interactions at the interface between two groups of cells in monolayer tissue. *Journal of Theoretical Biology*, 404:40–50, sep 2016.

[14] Eric Widmaier. *Vander's human physiology : the mechanisms of body function*. McGraw-Hill Education, New York, NY, 2016.

[15] Grace E. Mahlbacher, Kara C. Reihmer, and Hermann B. Frieboes. Mathematical modeling of tumor-immune cell interactions. *Journal of Theoretical Biology*, 469:47–60, may 2019.

[16] Álvaro G. López, Jesús M. Seoane, and Miguel A. F. Sanjuán. Dynamics of the cell-mediated immune response to tumour growth. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 375(2096):20160291, may 2017.

[17] Kathleen P. Wilkie and Philip Hahnfeldt. Modeling the dichotomy of the immune response to cancer: Cytotoxic effects and tumor-promoting inflammation. *Bulletin of Mathematical Biology*, 79(6):1426–1448, jun 2017.

[18] Alexis Erich S. Almocera, Griselda Quiroz, and Esteban A. Hernandez-Vargas. Stability analysis in COVID-19 within-host model with immune response. *Communications in Nonlinear Science and Numerical Simulation*, page 105584, nov 2020.

[19] Alice Indini, Erika Rijavec, Michele Ghidini, Claudia Bareggi, Monica Cattaneo, Barbara Galassi, Donatella Gambini, and Francesco Grossi. Coronavirus infection and immune system: An insight of COVID-19 in cancer patients. *Critical Reviews in Oncology/Hematology*, 153:103059, sep 2020.

[20] Zhiwei Ji, Ke Yan, Wenyang Li, Haigen Hu, and Xiaoliang Zhu. Mathematical and computational modeling in complex biological systems. *BioMed Research International*, 2017:1–16, 2017.

[21] Angela M. Jarrett, Ernesto A.B.F. Lima, David A. Hormuth, Matthew T. McKenna, Xinzeng Feng, David A. Ekrut, Anna Claudia M. Resende, Amy Brock, and Thomas E. Yankeelov. Mathematical models of tumor cell proliferation: A review of the literature. *Expert Review of Anticancer Therapy*, 18(12):1271–1286, oct 2018.

[22] Elizabeth S. Allman, John A. Rhodes, and Elizabeth S. Allamn. *Mathematical Models in Biology*. Cambridge University Press, 2004.

[23] Linda Allen. *Introduction to Mathematical Biology, An*. Pearson Education (US), 2006.

[24] David S. Dummit and Richard M. Foote. *Abstract Algebra third eidition*. Wiley, Hoboken, NJ, 2004.

[25] D. R. Curtiss. Recent extentions of descartes' rule of signs. *The Annals of Mathematics*, 19(4):251, jun 1918.

[26] Prativa Sahoo, Xin Yang, Daniel Abler, Davide Maestrini, Vikram Adhikarla, David Frankhouser, Heyrim Cho, Vanessa Machuca, Dongrui Wang, Michael Barish, Margarita Gutova, Sergio Branciamore, Christine E. Brown, and Russell C. Rockne. Mathematical deconvolution of CAR t-cell proliferation and exhaustion from real-time killing assay data. *Journal of The Royal Society Interface*, 17(162):20190734, jan 2020.

[27] Zijian Liu and Chenxue Yang. A mathematical model of cancer treatment by radiotherapy followed by chemotherapy. *Mathematics and Computers in Simulation*, 124:1–15, jun 2016.

[28] AmirHomayoun Jafari, Armin Allahverdy, AlirezaKhorrami Moghaddam, Sarah Rahbar, Sadjad Shafiekhani, HamidReza Mirzaie, Saeid Amanpour, Yasaman Etemadi, and Jamshid Hadjati. An agent-based model for investigating the effect of myeloid-derived suppressor cells and its depletion on tumor immune surveillance. *Journal of Medical Signals & Sensors*, 9(1):15, 2019.

[29] Wesley F. F. M. Gil, Tiago Carvalho, Paulo F. A. Mancera, and Diego Samuel Rodrigues. A mathematical model on the immune system role in achieving better outcomes of cancer chemotherapy. *TEMA - Tendências em Matemática Aplicada e Computacional*, 20(2):343, jul 2019.

[30] Subhas Khajanchi and Sandip Banerjee. Stability and bifurcation analysis of delay induced tumor immune interaction model. *Applied Mathematics and Computation*, 248:652–671, dec 2014.

[31] Lisette G. de Pillis, Ami E. Radunskaya, and Charles L. Wiseman. A validated mathematical model of cell-mediated immune response to tumor growth. *Cancer Research*, 65(17):7950–7958, sep 2005.

[32] V. A. Kuznetsov A. Matzavinos, M. A. J. Chaplain. Mathematical modelling of the spatio-temporal response of cytotoxic t-lymphocytes to a solid tumour. *Mathematical Medicine and Biology*, 21(1):1–34, mar 2004.

[33] L.G De Pillis and A Radunskaya. The dynamics of an optimally controlled tumor model: A case study. *Mathematical and Computer Modelling*, 37(11):1221–1244, jun 2003.

[34] Indrajit Ghosh. Within host dynamics of sars-cov-2 in humans: Modeling immune responses and antiviral treatments, 2020.

9 Appendix

9.1 A

Parameter, $i = x, y$	**Discription**
a_i	Intrinsic growth rate.
K_i	Carrying capacity.
b_i	Competition factor.
T_i	Number of specific immune cells.
p_i	Probability that the immune system eliminate cancer cells or infected cells.
$1 - p_i$	Probability that the immune system fails in eliminating cancer cells or infected cells.
$r_i p_i$	Elimination rate of cancer cells and infected cells by immune cells with probability p_i.
$r_i(1 - p_i)$	Elimination rate of immune cells by cancer cells and infected cells with probability $1 - p_i$.
α	Constant source of immune cells.
β_x	Rate of binding of cancer cells and immune cell.
β_y	Rate of binding of infected cell and immune cell.
ε	Natural death rate of immune cells.
d_x	Natural death rate of cancer specific immune cells
d_y	Natural death rate of infection specific immune cells

Table 4: Models parameters. All parameters are assumed to be non-negative.

9.2 B

Articles	**Parameters**									
	a_x	K_x	β_x	d_x	$r_x p_x$	r_x	p_x	$r_x(1-p_x)$	α	ε
Jafari et al. [28]	1.05	0.0022	0.03	0.12	0.015					
Gil et al. [29]	0.01 d	10^{12} c	10^{-12} d		5×10^{-11} cd			10^{-13} cd	3×10^{5}d	10^{-3} d
Makhlouf et al. [9]	4.31×10^{-1} d	1.02×10^{-9} c	1.1×10^{-7} cd	4.12×10^{-2}	1.1×10^{-7} cd			3.42×10^{-6} cd	7.5×10^{8} cd	1.2×10^{-7} d
Unni and Seshaiyer [7]	4.31×10^{-1} d	2.17×10^{-8} c	1.0×10^{-6} c	4.12×10^{-2} d	3.5×10^{-6} c			1.0×10^{-7} cd	4.8×10^{2} c	2.4×10^{-2} c
Gurcan et al. [10]	0.18 d	5.0×10^{6} c	0.1045 d	0.0412 d	4.401×10^{-8} cd			3.422×10^{-9} cd		
Khajanchi et al. [30]	0.18 d	1.0×10^{-6} c		0.412 d				2.2×10^{-8} cd	1.3×10^{4} cd	
Pillis et al. [31]	5.14×10^{-1} d	1.02×10^{-9} c	1.1×10^{-7} cd	$4.12 \times 10^{-2}d$	3.50×10^{-6}			1.0×10^{-7} cd	1.30×10^{4} cd	
Kuznetsov et al. [32]	0.18 d	2.0×10^{-9} c cm	1.3×10^{-7} dc cm			7.2 d	0.9997	0.00216 d	1.36×10^{4} dc cm	0.0412 d
Pillis et al. [33]	1.5	1	1		0.5			1	0.33	0.2
Kuznetsov et al. [8]	0.187701546	531.8980644				0.138698686	0.998200283	0.000249618	0.195030254	0.591000768

Table 5: In this table numerical values for the cancer cells from selected articles are shown. If β_x is not given, it is interpreted as the growth rate of immune cells. c: cells^{-1}; d:day^{-1}

Articles	**Parameters**							
	a_y	K_y	β_y	d_y	$r_y p_y$	$r_y(1-p_y)$	α	ε
Almocera et al. [18]	1.62	10^{9}	0.96	0.6	4.88×10^{-8}		2×10^{5}	2×10^{-1}
Ghosh, I. [34]			0.52 d	0.65 d	5.74×10^{-4} cd	3×10^{-7} d	0.1	1 cd
Hernandez-Vargas et al. [12]	8.57		1.26×10^{5}		1.89×10^{6}	10^{6}		

Table 6: In this table numerical values for the infected cells from selected articles are shown. If β_y is not given, it is interpreted as the growth rate of immune cells. c: cells^{-1}; d:day^{-1}

9.3 C1

```
restart
with(LinearAlgebra) :
with(plots) :
```

$$\alpha := 1.3 \cdot 10^{4} :$$

$$\varepsilon := \frac{1}{2.4 \cdot 10^{-2}} :$$

$$ax := 1.5 :$$

$$Kx := \frac{1}{2.17 \cdot 10^{-8}} :$$

$$rx := 0.14 :$$

$$px := 0.9997 :$$

$$dx := 0.12 :$$

$$\beta x := \frac{1}{1.3 \cdot 10^{-7}} :$$

$$Rx := \frac{1}{1 \cdot 10^{-7}} :$$

$$ay := 8.57 :$$

$$Ky := 10^{9} :$$

$$rypy := \frac{1}{4.88 \cdot 10^{-8}} :$$

$$dy := 0.65 :$$

$$\beta y := 1.26 \cdot 10^{5} :$$

$$Ry := \frac{1}{3 \cdot 10^{-7}} :$$

$$\varphi x := \frac{rx \cdot px \cdot \alpha}{dx \cdot ax}$$

$$\varphi x := 10108.07778 \quad \textbf{(1)}$$

$$\varphi y := \frac{rypy \cdot \alpha \cdot \beta y \cdot Ky}{\beta x \cdot Kx \cdot dy \cdot ax}$$

$$\varphi y := 9.711639347\ 10^{10} \quad \textbf{(2)}$$

$$\mu := \frac{\beta y \cdot Ky}{\beta x \cdot Kx}$$

$$\mu := 0.3554460000 \quad \textbf{(3)}$$

$$\rho := \frac{ay}{ax}$$

$$\rho := 5.713333333 \quad \textbf{(4)}$$

$$\delta := \frac{\varepsilon}{\beta x \cdot Kx}$$

$$\delta := 1.175416667\ 10^{-13} \quad \textbf{(5)}$$

We define the second degree equation for u, as two equal equations:

$$Pu1 := u^{2} + u \cdot (\delta - 1) - \delta$$

$$Pu1 := u^2 - u - 1.175416667\ 10^{-13} \tag{6}$$

$Pu2 := -u \cdot \varphi x$

$$Pu2 := -10108.07778\ u \tag{7}$$

Solving these equations and finding u:

$solu := solve([Pu1 = Pu2], u)$

$$solu := \{u = 1.162963908\ 10^{-17}\}, \{u = -10107.07778\} \tag{8}$$

We find one positive solution for u, corresponding to the steady state S_u+

$solu1 := solu[1]$

$$solu1 := \{u = 1.162963908\ 10^{-17}\} \tag{9}$$

We define the second degree equation for v, as two equal equations:

$Pv1 := v^2 \cdot \rho \cdot \mu + v \cdot (\rho \cdot \delta - \rho \cdot \mu) - \rho \cdot \delta$

$$Pv1 := 2.030781480\ v^2 - 2.030781480\ v - 6.715547224\ 10^{-13} \tag{10}$$

$Pv2 := -v \cdot \varphi y$

$$Pv2 := -9.711639347\ 10^{10}\ v \tag{11}$$

Solving these equations and finding v:

$solv := solve([Pv1 = Pv2], v)$

$$solv := \{v = 6.914947090\ 10^{-24}\}, \{v = -4.782217803\ 10^{10}\} \tag{12}$$

We find one positive solution for v, corresponding to the steady state Sv+.

$solv[1]$

$$\{v = 6.914947090\ 10^{-24}\} \tag{13}$$

For determination of the stability of the steady states we find the Jacobian matric of the system with px= 1 and py=1, which is given by

$$du := u \cdot (1 - u) - \frac{\varphi x \cdot u^2}{(u + \mu \cdot v + \delta)}$$

$$du := u\ (1 - u) - \frac{10108.07778\ u^2}{u + 0.3554460000\ v + 1.175416667\ 10^{-13}} \tag{14}$$

$$dv := \rho \cdot v \cdot (1 - v) - \frac{\varphi y \cdot v^2}{(u + \mu \cdot v + \delta)}$$

$$dv := 5.713333333\ v\ (1 - v) - \frac{9.711639347\ 10^{10}\ v^2}{u + 0.3554460000\ v + 1.175416667\ 10^{-13}} \tag{15}$$

The solutions to the system corresonds to the solutions found above:

$sol := solve([du = 0, dv = 0], \{u, v\})$

$$sol := \{u = 0., v = 0.\}, \{u = 0., v = 6.914947090\ 10^{-24}\}, \{u = 0., v = -4.782217803\ 10^{10}\}, \{u = 1.162963908\ 10^{-17}, v = 0.\}, \{u = -10107.07778, v = 0.\}, \{u = 1.162963908\ 10^{-17}, v = 6.915631258\ 10^{-24}\}, \{u = 1.000000595, v = -4.782217803\ 10^{10}\}, \{u = -10107.07778, v = -5.945972317\ 10^{-7}\} \tag{16}$$

$sol[4]$

$$\{u = 1.162963908\ 10^{-17}, v = 0.\} \tag{17}$$

$sol[2]$

$$\{u = 0.,\ v = 6.914947090\ 10^{-24}\} \tag{18}$$

$sol[6]$

$$\{u = 1.162963908\ 10^{-17},\ v = 6.915631258\ 10^{-24}\} \tag{19}$$

We find the Jacobian mtrix

$A := evalf(VectorCalculus[Jacobian]([du, dv], [u, v]), 25)$

$$A := \left[\left[1. - 2.\,u - \frac{20216.15556\,u}{u + 0.3554460000\,v + 1.175416667\ 10^{-13}} + \frac{10108.07778\,u^2}{\left(u + 0.3554460000\,v + 1.175416667\ 10^{-13}\right)^2},\ \frac{3592.875814589880000\,u^2}{\left(u + 0.3554460000\,v + 1.175416667\ 10^{-13}\right)^2}\right],\right.$$
$$\left[\frac{9.711639347\ 10^{10}\,v^2}{\left(u + 0.3554460000\,v + 1.175416667\ 10^{-13}\right)^2},\ 5.713333333 - 11.426666666\,v - \frac{1.9423278694\ 10^{11}\,v}{u + 0.3554460000\,v + 1.175416667\ 10^{-13}} + \frac{3.4519633593337620000\ 10^{10}\,v^2}{\left(u + 0.3554460000\,v + 1.175416667\ 10^{-13}\right)^2}\right]\Bigg] \tag{20}$$

We evaluate the steady states.

The Jacobian matrix of the steady state S_u+:

$Au := simplify(subs(sol[4], A))$

$$Au := \begin{bmatrix} -0.9999010702 & 0.00003516454940 \\ 0. & 5.713333333 \end{bmatrix} \tag{21}$$

$Determinant(Au)$

$$-5.712768114 \tag{22}$$

$Trace(Au)$

$$4.713432263 \tag{23}$$

The Jacobian matrix of the steady state S_v+:

$Av := simplify(subs(sol[2], A))$

$$Av := \begin{bmatrix} 1. & 0. \\ 3.361139826\ 10^{-10} & -5.713333327 \end{bmatrix} \tag{24}$$

$Determinant(Av)$

$$-5.713333327 \tag{25}$$

$Trace(Av)$

$$-4.713333327 \tag{26}$$

Considering the functions found when u>0 and v>0.

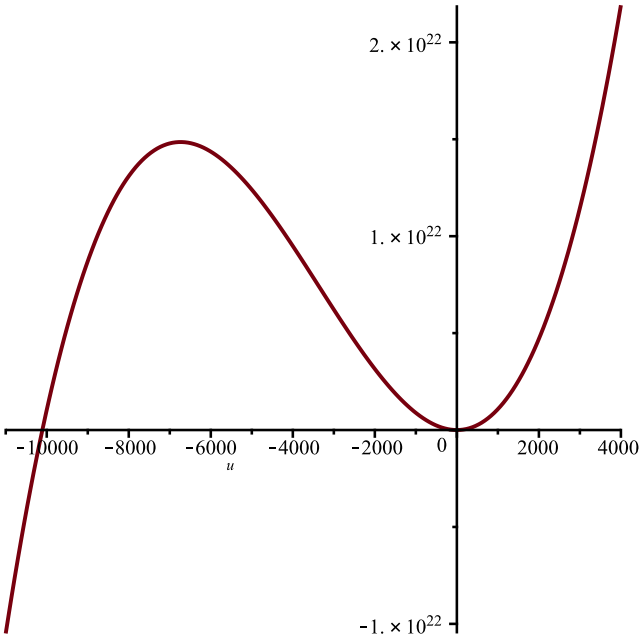
$$fum := u^3\cdot(\varphi y - \varphi x\cdot\rho) + u^2\cdot(\varphi y\cdot\varphi x - \varphi x\cdot\rho\cdot\mu - \varphi x^2\cdot\rho + \varphi x\cdot\rho - \varphi x\cdot\rho\cdot\delta - 2\cdot\varphi y + \varphi y\cdot\delta) + u\cdot(\varphi x\cdot\rho\cdot\mu - \varphi y\cdot\varphi x + \varphi y - 2\cdot\varphi y\cdot\delta + \varphi x\cdot\rho\cdot\delta) + \varphi y\cdot\delta$$

$$fum := 9.711633572\,10^{10}\,u^3 + 9.814652424\,10^{14}\,u^2 - 9.815629425\,10^{14}\,u + 0.01141522275 \quad \textbf{(27)}$$

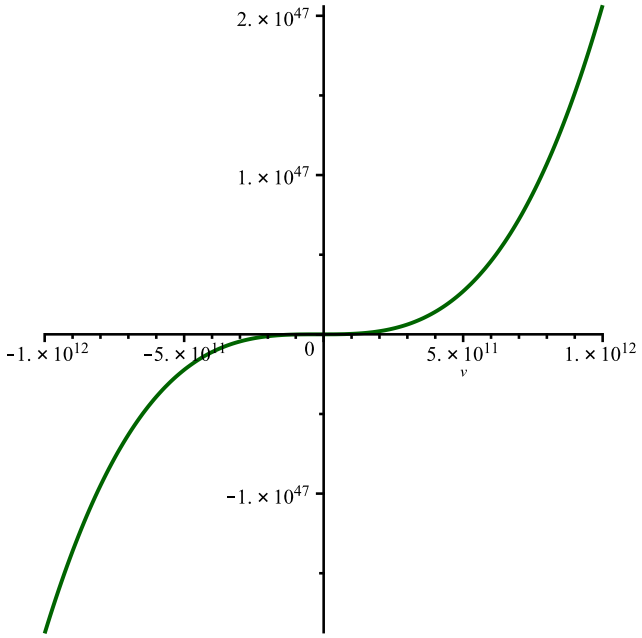
$$fvm := v^3\cdot\left(\varphi y\cdot\rho\cdot\mu - \varphi x\cdot\rho^2\cdot\mu\right) + v^2\cdot\left(2\cdot\varphi x\cdot\rho^2\cdot\mu - \varphi x\cdot\rho^2\cdot\delta + \varphi y\cdot\rho\cdot\delta - \varphi y\cdot\rho\cdot\mu - \varphi x\cdot\varphi y\cdot\rho + \varphi y\cdot\rho + \varphi y^2\right) - v\cdot\left(\varphi x\cdot\rho\cdot\mu - 2\cdot\varphi x\cdot\rho^2\cdot\delta + \varphi y\cdot\rho\cdot\delta - \varphi x\cdot\varphi y\cdot\rho + \varphi y\cdot\rho\right) - \varphi x\cdot\rho^2\cdot\delta$$

$$fvm := 1.972220560\,10^{11}\,v^3 + 9.431588273\,10^{21}\,v^2 + 5.607996278\,10^{15}\,v - 3.878283435\,10^{-8} \quad \textbf{(28)}$$

$P1 := plot(fum, u = -11000..4000)$



$P2 := plot(fvm, v = -1000000000000..1000000000000, color = "DarkGreen")$



We find the solutions to the system:

$soluv := solve([fum = 0, fvm = 0], \{u, v\})$

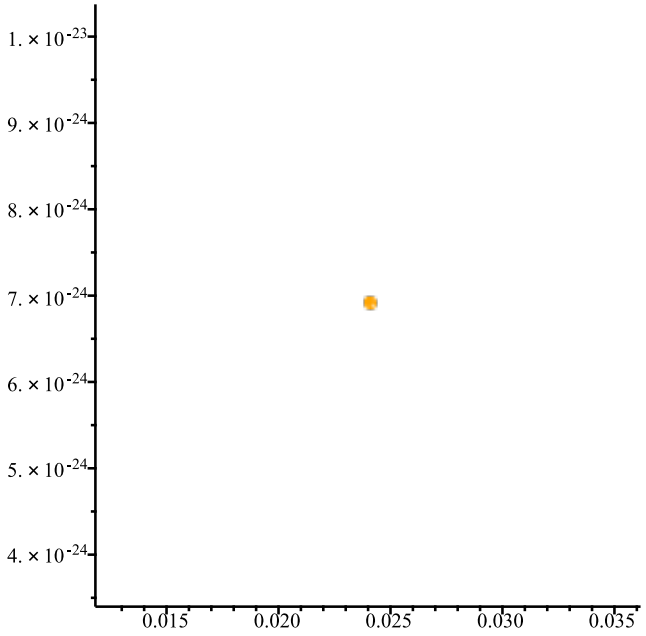
$$soluv := \{u = 1.162963907\ 10^{-17}, v = 6.915631257\ 10^{-24}\}, \{u = 1.162963907\ 10^{-17}, v = -5.945972317\ 10^{-7}\}, \{u = 1.162963907\ 10^{-17}, v = -4.782217803\ 10^{10}\}, \{u = 1.000000595, v = 6.915631257\ 10^{-24}\}, \{u = 1.000000595, v = -5.945972317\ 10^{-7}\}, \{u = 1.000000595, v = -4.782217803\ 10^{10}\}, \{u = -10107.07778, v = 6.915631257\ 10^{-24}\}, \{u = -10107.07778, v = -5.945972317\ 10^{-7}\}, \{u = -10107.07778, v = -4.782217803\ 10^{10}\} \quad \textbf{(29)}$$

We find one positive solutions with biological meaning, S_uv:

$soluv[1]$

$$\{u = 1.162963907\ 10^{-17}, v = 6.915631257\ 10^{-24}\} \quad \textbf{(30)}$$

$pointplot([[0.02411054445, 6.915614757\ 10^{-24}]])$



Evaluating the steady state S_uv

$A1 := simplify(subs(soluv[1], A))$

$$A1 := \begin{bmatrix} -0.9999010692 & 0.00003516454935 \\ 3.361139826\ 10^{-10} & -5.713333337 \end{bmatrix} \quad \textbf{(31)}$$

$Determinant(A1)$

$$5.712768112 \quad \textbf{(32)}$$

$Trace(A1)$

$$-6.713234406 \quad \textbf{(33)}$$

9.4 C2

```
restart
with(LinearAlgebra) :
with(plots) :
```

$$\alpha := 1.3 \cdot 10^{4} :$$

$$\varepsilon := \frac{1}{2.4 \cdot 10^{-2}} :$$

$$ax := 1.5 :$$

$$Kx := \frac{1}{2.17 \cdot 10^{-8}} :$$

$$rx := 0.14 :$$

$$px := 0.9997 :$$

$$dx := 0.12 :$$

$$\beta x := \frac{1}{1.3 \cdot 10^{-7}} :$$

$$Rx := \frac{1}{1 \cdot 10^{-7}} :$$

$$ay := 8.57 :$$

$$Ky := 10^{9} :$$

$$rypy := \frac{1}{4.88 \cdot 10^{-8}} :$$

$$dy := 0.65 :$$

$$\beta y := 1.26 \cdot 10^{5} :$$

$$Ry := \frac{1}{3 \cdot 10^{-7}} :$$

$$\varphi x := \frac{rx \cdot px \cdot \alpha}{dx \cdot ax}$$

$$\varphi x := 10108.07778 \quad (1)$$

$$wx := \frac{Rx \cdot Kx}{dx}$$

$$wx := 3.840245776\ 10^{15} \quad (2)$$

$$\varphi y := \frac{rypy \cdot \alpha \cdot \beta y \cdot Ky}{\beta x \cdot Kx \cdot dy \cdot ax}$$

$$\varphi y := 9.711639347\ 10^{10} \quad (3)$$

$$wy := \frac{Ry \cdot Ky}{dy}$$

$$wy := 5.128205128\ 10^{15} \quad (4)$$

$$\mu := \frac{\beta y \cdot Ky}{\beta x \cdot Kx}$$

$$\mu := 0.3554460000 \quad (5)$$

$\rho := \frac{ay}{ax}$

$$\rho := 5.713333333 \tag{6}$$

$\delta := \frac{\varepsilon}{\beta x \cdot Kx}$

$$\delta := 1.175416667\ 10^{-13} \tag{7}$$

We define the third degree equaiton for u as two equal functions:

$Hu1 := u^3 \cdot wx + u^2 \cdot (wx \cdot \delta + 1 - wx) - u \cdot (wx \cdot \delta + 1 - \delta) - \delta$

$$Hu1 := 3.840245776\ 10^{15}\ u^3 - 3.840245776\ 10^{15}\ u^2 - 452.3888890\ u - 1.175416667\ 10^{-13} \tag{8}$$

$Hu2 := -u \cdot \varphi x$

$$Hu2 := -10108.07778\ u \tag{9}$$

Solving these equations we find the values for u:

$solu := evalf(solve([Hu1 = Hu2], u), 15)$

$$solu := \{u = 1.21733660970390\ 10^{-17}\}, \{u = 2.51432921367962\ 10^{-12}\}, \{u = 0.999999999997486\} \tag{10}$$

We find three positive solutions corresponding to a steady states S_u1*, S_u2*, S_u3*

$solu[1]$

$$\{u = 1.21733660970390\ 10^{-17}\} \tag{11}$$

$solu[2]$

$$\{u = 2.51432921367962\ 10^{-12}\} \tag{12}$$

$solu[3]$

$$\{u = 0.999999999997486\} \tag{13}$$

We define the third degree equaiton for v as two equal functions:

$Hv1 := v^3 \cdot wy \cdot \rho \cdot \mu + v^2 \cdot (wy \cdot \delta \cdot \rho + \rho \cdot \mu - wy \cdot \rho \cdot \mu) - v \cdot (wy \cdot \delta \cdot \rho + \rho \cdot \mu - \delta \cdot \rho) - \delta \cdot \rho$

$$Hv1 := 1.041426400\ 10^{16}\ v^3 - 1.041426400\ 10^{16}\ v^2 - 3445.901152\ v - 6.715547224\ 10^{-13} \tag{14}$$

$Hv2 := -v \cdot \varphi y$

$$Hv2 := -9.711639347\ 10^{10}\ v \tag{15}$$

Solving these equations we find the values for v:

$solv := solve([Hv1 = Hv2], v)$

$$solv := \{v = 6.914947335\ 10^{-24}\}, \{v = 9.325411348\ 10^{-6}\}, \{v = 0.9999906746\} \tag{16}$$

We find three positive solutions, corresponding to the steady state S_v1*, S_v2*, S_v3*:

$solv[1]$

$$\{v = 6.914947335\ 10^{-24}\} \tag{17}$$

$solv[2]$

$$\{v = 9.325411348\ 10^{-6}\} \tag{18}$$

$solv[3]$

$$\{v = 0.9999906746\} \tag{19}$$

We define the functions where u>0 and v>0:

$gu := \frac{\varphi x \cdot u}{\mu \cdot (1 - u) \cdot (wx \cdot u + 1)} - \frac{(u + \delta)}{\mu}$

$$gu := \frac{28437.73113\,u}{(1-u)\left(3.840245776\,10^{15}\,u+1\right)} - 2.813366869\,u - 3.306878308\,10^{-13} \quad \textbf{(20)}$$

$$gv := \frac{\varphi y \cdot v}{\rho \cdot (1-v) \cdot (wy \cdot v + 1)} - (v \cdot \mu + \delta)$$

$$gv := \frac{1.699820189\,10^{10}\,v}{(1-v)\left(5.128205128\,10^{15}\,v+1\right)} - 0.3554460000\,v - 1.175416667\,10^{-13} \quad \textbf{(21)}$$

Solving these equations we find values for u and v:

$soluv := evalf(solve([gu = v, gv = u], \{u, v\}), 15)$

$$soluv := \{u = 1.21733660990414\,10^{-17}, v = 6.91566349183991\,10^{-24}\}, \{u = 2.51432921310802\,10^{-12}, v = 1.54832433844059\,10^{-22}\}, \{u = 0.999996972249663, v = -2.81335590505644\}, \{u = 0.999999999997368, v = -1.95000646366569\,10^{-16}\}, \{u = 0.999999999998058, v = 0.999997554567652\}, \{u = -0.177721486102873 + 99.6806066203542\,I, v = 0.499995740910938 - 280.438116147526\,I\}, \{u = -2.60399999983596\,10^{-16}, v = 0.999990674588322\}, \{u = -2.60400206762003\,10^{-16}, v = 9.32541134824728\,10^{-6}\}, \{u = -0.177721486102873 - 99.6806066203542\,I, v = 0.499995740910938 + 280.438116147526\,I\} \quad \textbf{(22)}$$

We find three positive steady state S_u*v*1, S_u*v*2, S_u*v*3

$soluv[1]$

$$\{u = 1.21733660990414\,10^{-17}, v = 6.91566349183991\,10^{-24}\} \quad \textbf{(23)}$$

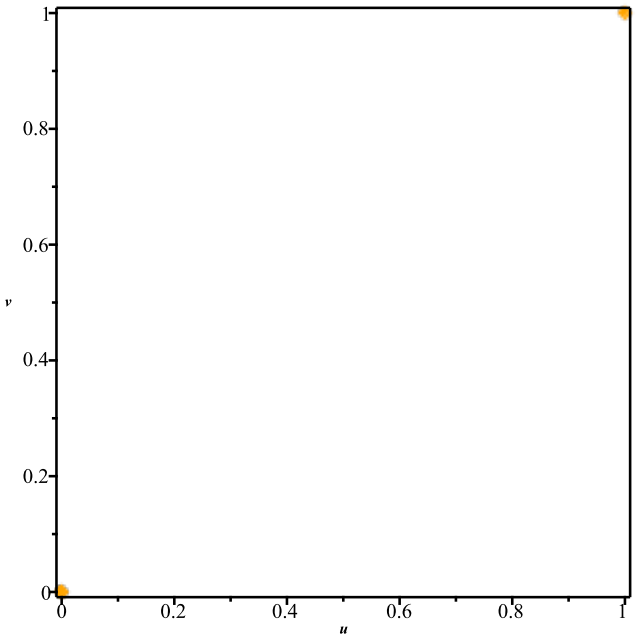
$soluv[2]$

$$\{u = 2.51432921310802\,10^{-12}, v = 1.54832433844059\,10^{-22}\} \quad \textbf{(24)}$$

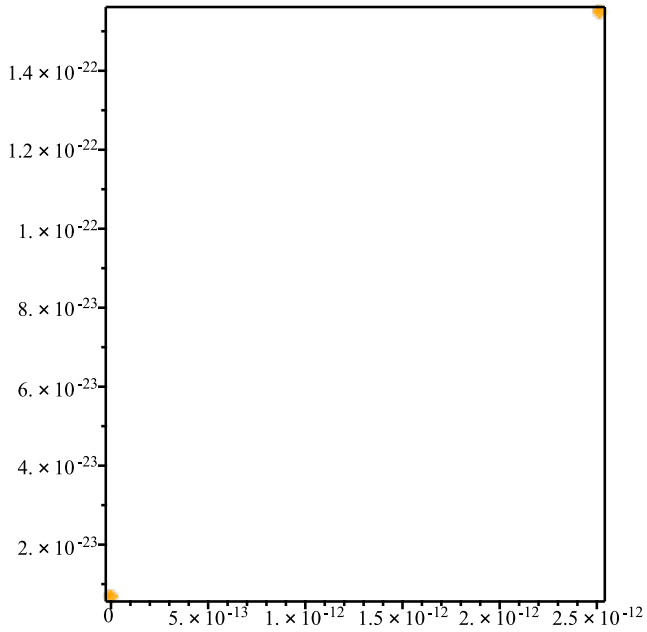
$soluv[5]$

$$\{u = 0.999999999998058, v = 0.999997554567652\} \quad \textbf{(25)}$$

$pointplot([[1.21733660990414\,10^{-17}, 6.91566349183991\,10^{-24}], [2.51432921310802\,10^{-12}, 1.54832433844059\,10^{-22}], [0.999999999998058, 0.999997554567652]])$



$$pointplot([[1.21733660990414\ 10^{-17}, 6.91566349183991\ 10^{-24}], [2.51432921310802\ 10^{-12}, 1.54832433844059\ 10^{-22}]])$$



For determine the stability of the steady states we find the Jacobian matrix of the system given by

$$dup := u\cdot(1-u) - \frac{\varphi x\cdot u^2}{(u+\mu\cdot v+\delta)\cdot(wx\cdot u+1)}$$

$$dup := u\,(1-u) - \frac{10108.07778\,u^2}{(u+0.3554460000\,v+1.175416667\ 10^{-13})\,(3.840245776\ 10^{15}\,u+1)} \quad \textbf{(26)}$$

$$dvp := \rho\cdot v\cdot(1-v) - \frac{\varphi y\cdot v^2}{(u+\mu\cdot v+\delta)\cdot(wy\cdot v+1)}$$

$$dvp := 5.713333333\,v\,(1-v) \quad \textbf{(27)}$$
$$- \frac{9.711639347\ 10^{10}\,v^2}{(u+0.3554460000\,v+1.175416667\ 10^{-13})\,(5.128205128\ 10^{15}\,v+1)}$$

The solutions to this system corresponds to the solutions found above:

$$sol := evalf(solve([dup=0, dvp=0], \{u, v\}), 12)$$

$$sol := \{u=0., v=0.\}, \{u=0., v=6.91494733491\ 10^{-24}\}, \{u=0., v=9.32541134855\ 10^{-6}\}, \quad \textbf{(28)}$$
$$\{u=0., v=0.999990674588\}, \{u=1.21733660971\ 10^{-17}, v=0.\}, \{u$$
$$=2.51432921367\ 10^{-12}, v=0.\}, \{u=0.999999999997, v=0.\}, \{u$$
$$=1.21733660974\ 10^{-17}, v=6.91566349107\ 10^{-24}\}, \{u=2.51432921361\ 10^{-12}, v$$
$$=1.54832433857\ 10^{-22}\}, \{u=0.999996971837, v=-2.81335590389\}, \{u$$
$$=0.999999999997, v=-1.95000646367\ 10^{-16}\}, \{u=0.999999999998, v$$
$$=0.999997554568\}, \{u=-2.60399999984\ 10^{-16}, v=0.999990674588\}, \{u$$
$$=-2.60400206762\ 10^{-16}, v=9.32541134928\ 10^{-6}\}$$

$$sol[5]$$

$$\{u=1.21733660971\ 10^{-17}, v=0.\} \quad \textbf{(29)}$$

$sol[6]$

$$\{u = 2.51432921367\ 10^{-12},\ v = 0.\} \tag{30}$$

$sol[7]$

$$\{u = 0.999999999997,\ v = 0.\} \tag{31}$$

$sol[2]$

$$\{u = 0.,\ v = 6.91494733491\ 10^{-24}\} \tag{32}$$

$sol[3]$

$$\{u = 0.,\ v = 9.32541134855\ 10^{-6}\} \tag{33}$$

$sol[4]$

$$\{u = 0.,\ v = 0.999990674588\} \tag{34}$$

$sol[8]$

$$\{u = 1.21733660974\ 10^{-17},\ v = 6.91566349107\ 10^{-24}\} \tag{35}$$

$sol[9]$

$$\{u = 2.51432921361\ 10^{-12},\ v = 1.54832433857\ 10^{-22}\} \tag{36}$$

$sol[12]$

$$\{u = 0.999999999998,\ v = 0.999997554568\} \tag{37}$$

For determination of the stability of the steady states we calculate the Jacobian matrix of dup and dvp:

$A := VectorCalculus[Jacobian]([dup, dvp], [u, v])$

$$A := \left[\left[1 - 2\,u - \frac{20216.15556\,u}{(u + 0.3554460000\,v + 1.175416667\ 10^{-13})\,(3.840245776\ 10^{15}\,u + 1)} + \frac{10108.07778\,u^2}{(u + 0.3554460000\,v + 1.175416667\ 10^{-13})^2\,(3.840245776\ 10^{15}\,u + 1)} + \frac{3.881750300\ 10^{19}\,u^2}{(u + 0.3554460000\,v + 1.175416667\ 10^{-13})\,(3.840245776\ 10^{15}\,u + 1)^2}, \frac{3592.875815\,u^2}{(u + 0.3554460000\,v + 1.175416667\ 10^{-13})^2\,(3.840245776\ 10^{15}\,u + 1)}\right], \left[\frac{9.711639347\ 10^{10}\,v^2}{(u + 0.3554460000\,v + 1.175416667\ 10^{-13})^2\,(5.128205128\ 10^{15}\,v + 1)}, 5.713333333 - 11.42666667\,v - \frac{1.942327869\ 10^{11}\,v}{(u + 0.3554460000\,v + 1.175416667\ 10^{-13})\,(5.128205128\ 10^{15}\,v + 1)} + \frac{3.451963359\ 10^{10}\,v^2}{(u + 0.3554460000\,v + 1.175416667\ 10^{-13})^2\,(5.128205128\ 10^{15}\,v + 1)} + \frac{4.980327870\ 10^{26}\,v^2}{(u + 0.3554460000\,v + 1.175416667\ 10^{-13})\,(5.128205128\ 10^{15}\,v + 1)^2}\right]\right] \tag{38}$$

We evaluate the steady states.
The steady state S_u1*:
$Au1 := simplify(subs(sol[5], A))$

$$Au1 := \begin{bmatrix} -0.9552355644 & 0.00003680844695 \\ 0. & 5.713333333 \end{bmatrix} \tag{39}$$

$Determinant(Au1)$

$$-5.457579191 \tag{40}$$

$Trace(Au1)$

$$4.758097769 \tag{41}$$

The steady state S_u2*
$Au2 := simplify(subs(sol[6], A))$

$$Au2 := \begin{bmatrix} 0.9552355646 & 0.3395714691 \\ 0. & 5.713333333 \end{bmatrix} \tag{42}$$

$Determinant(Au2)$

$$5.457579192 \tag{43}$$

$Trace(Au2)$

$$6.668568898 \tag{44}$$

Teh steady state S_u3*
$Au3 := simplify(subs(sol[7], A))$

$$Au3 := \begin{bmatrix} -1.000000000 & 9.355848622\ 10^{-13} \\ 0. & 5.713333333 \end{bmatrix} \tag{45}$$

$Determinant(Au3)$

$$-5.713333333 \tag{46}$$

$Trace(Au3)$

$$4.713333333 \tag{47}$$

The steady state S_v1*
$Av1 := simplify(subs(sol[2], A))$

$$Av1 := \begin{bmatrix} 1. & 0. \\ 3.361139946\ 10^{-10} & -5.713333134 \end{bmatrix} \tag{48}$$

$Determinant(Av1)$

$$-5.713333134 \tag{49}$$

$Trace(Av1)$

$$-4.713333134 \tag{50}$$

The steady state S_v2*
$Av2 := simplify(subs(sol[3], A))$

$$Av2 := \begin{bmatrix} 1. & 0. \\ 16.07355224 & 5.713226566 \end{bmatrix} \tag{51}$$

$Determinant(Av2)$

$$5.713226566 \tag{52}$$

$Trace(Av2)$

$$6.713226566 \tag{53}$$

The steady state S_v3*

$Av3 := simplify(subs(sol[4], A))$

$$Av3 := \begin{bmatrix} 1. & 0. \\ 0.0001498938951 & -5.713226777 \end{bmatrix} \tag{54}$$

$Determinant(Av3)$

$$-5.713226777 \tag{55}$$

$Trace(Av3)$

$$-4.713226777 \tag{56}$$

The steady state S_u*v*1

$Auv1 := simplify(subs(sol[8], A))$

$$Auv1 := \begin{bmatrix} -0.9552355644 & 0.00003680844695 \\ 3.361139944\ 10^{-10} & -5.713333134 \end{bmatrix} \tag{57}$$

$Determinant(Auv1)$

$$5.457579001 \tag{58}$$

$Trace(Auv1)$

$$-6.668568698 \tag{59}$$

The steady state S_u*v*2

$Auv2 := simplify(subs(sol[9], A))$

$$Auv2 := \begin{bmatrix} 0.9552355646 & 0.3395714691 \\ 3.361142494\ 10^{-10} & -5.713328791 \end{bmatrix} \tag{60}$$

$Determinant(Auv2)$

$$-5.457574853 \tag{61}$$

$Trace(Auv2)$

$$-4.758093226 \tag{62}$$

The steady state S_u*v*3

$Auv3 := simplify(subs(sol[12], A))$

$$Auv3 := \begin{bmatrix} -1.000000000 & 5.092362396\ 10^{-13} \\ 0.00001030771048 & -5.713315704 \end{bmatrix} \tag{63}$$

$Determinant(Auv3)$

$$5.713315704 \tag{64}$$

$Trace(Auv3)$

$$-6.713315704 \tag{65}$$