A Reaction Diffusion Model of Acid Mediated Tumor Invasion with Chemotherapy Intervention

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Abstract

It has been studied that most cancer cells rely on aerobic glycolysis, a phenomenon termed the Warburg effect to generate energy needed for cellular purposes. The Warburg effect is a phenomenon wherein cells ferment glucose to lactic acid using glycolysis even in the presence of normal levels of oxygen. This altered metabolism results in an acidic extracellular tumor environment leading to destruction of normal tissue at the tumor-host interface, while promoting proliferation of cancer cells against normal cells. In this project, we will consider a four-component reaction diffusion system of equations describing the effect of chemotherapy intervention on the spatial distribution and temporal development of tumor tissue and excess H^+ ion concentration. Our model is an extension of the seminal work by Gatenby and Gawlinski (Cancer Res. 1996). We perform mathematical analysis and as well as numerical simulations to investigate how treatment affects the strength of the acid-mediated invasion and intervene the progression of cancer cells.

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1. Biological Background

1.1. **Glycolysis and the Warburg effect.** In this project, we analyze the interactions between normal and tumor cells in an acidic environment. This acidic environment is brought by a change in the standard cellular metabolism that prioritizes a process known as glycolysis in aerobic conditions: something that usually only occurs in anaerobic conditions. Termed the Warburg effect, it causes the tumor cells to produce and release acid into the surrounding environment, which in turn, kills off normal cells, creating empty space for the tumor to expand. Theorized by Dr. Otto Warburg, a german physiologist, the Warburg effects precise nature remains unclear, and is currently still under much study. Below is a pictorial interpretation of a healthy and cystic kidneys cell activities.

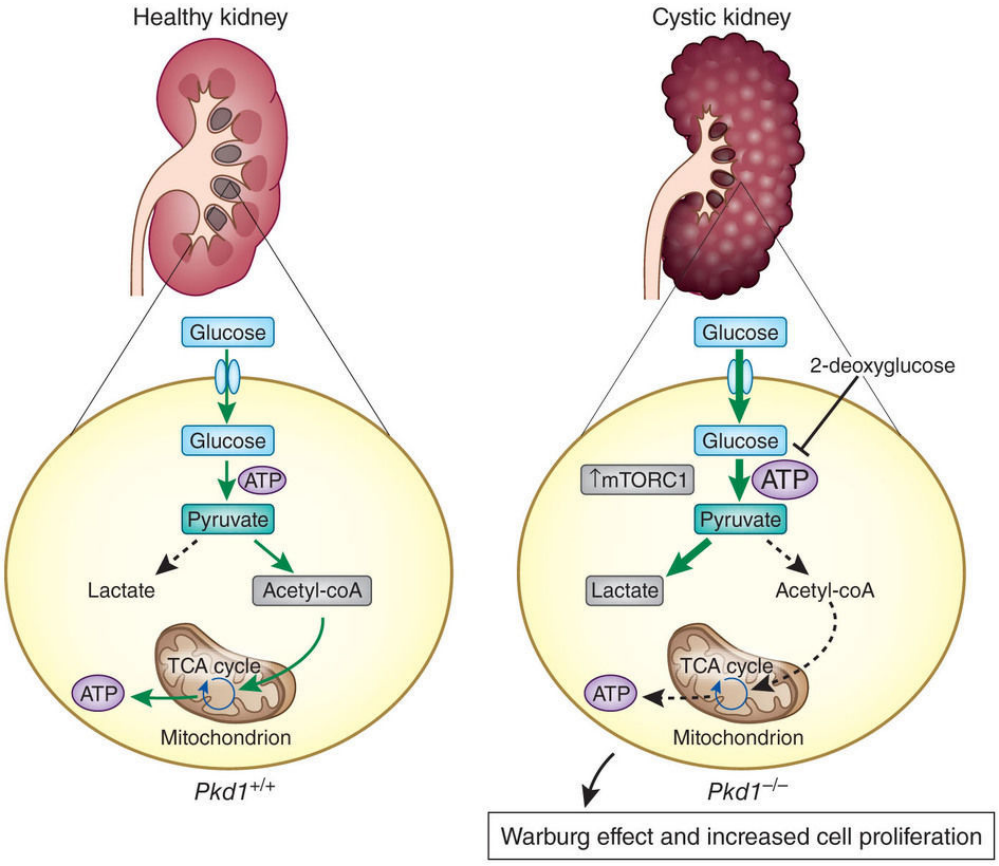


Figure 1. Metabolic reprogramming in polycystic kidney disease: Carmen Priolo, Elizabeth Henske, Nature Medicine

On the left is a healthy kidney. In a resting state, glucose enters the healthy cells of the kidney and will then undergo glycolysis. Glycolysis, or glucose lysis, is a metabolic pathway in which glucose is changed into pyruvate. In a resting state, oxygen will be present, so the pyruvate is converted into Acetyl coA. This chemical then travels to the mitochonria where it will undergo a process known as the Krebs cycle. In the Krebs cycle, Acetyl coA is oxidized into ATP with bi-products of carbon dioxide and water. ATP, or Adenosine triphosphate, is

a special chemical that can store energy which a cell need in order to survive. In total, this process will produce 36 ATP per glucose.

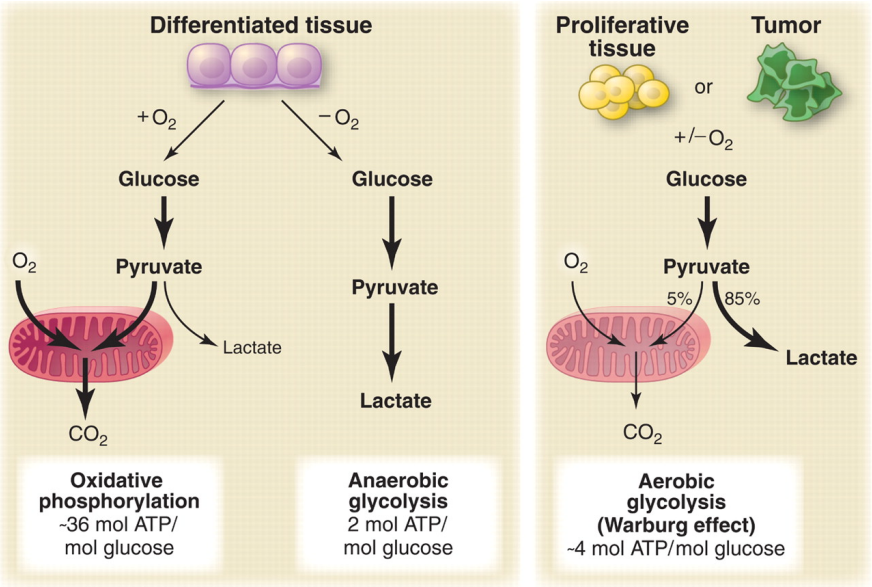


FIGURE 2. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation; Heiden, Cantley,Thompson

In a physically strenuous state, such as exercising, the normal cells in the healthy kidney are deprived of oxygen. The route that pyruvate takes through the mitochondria is highly dependent on oxygen, so this biological path is no longer usable. The cells will then use an alternative method for producing ATP. The glucose will undergo glycolysis to produce pyruvate, but instead of being broken down, the pyruvate will then ferment into lactic acid. We experience this lactic acid in the form of cramps when working out or performing physically strenuous activity. This method will produce a total of 2 ATP per glucose

On the right is a tumorous kidney,in which the cells are undergoing the Warburg effect. In the healthy cells, there were two pathways for energy production dependent on oxygen levels. In tumor cells, the Warburg effect will cause the cells to prioritize the anaerobic pathway even when oxygen is present. This means that the cells will produce ATP through only one pathway, which is also the least effective pathway.

The tumor cells then produce excess lactic acid, which spreads into the surrounding environment killing off normal cells, an occurance known as acidosis. Note that acidosis occurs around a pH of 7.2-7.4. The normal cells die off, making space in which the tumor cells can expand as these tumor cells are highly resistant to the lactic acid they produce. The tumor cells however are not greatly affected by the acid they produce, showing a high level of resistance.

In this project we are analyzing the interaction at the tumor-host interface. It has been found that a reaction-diffusion model is fairly accurate at mathematically modeling such scenarios, with diffusion being how used to explain how the normal, tumor cells, and the acid are spreading.

2. Mathematical Background

2.1. **Routh Hurwitz Criterion.** The purpose of this theorem is to assist in finding the signs of the roots of higher degree polynomials when it is not easy to solve the polynomial explicitly. This theorem states that given the polynomial,

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_{n-1}\lambda + a_n$$

where the coefficients a_i are real constants, $i = 1, ...n$, define the n Hurwitz matrix using the coefficients a_i of the characteristic polynomial:

$$H_1 = (a_1), H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, H_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix}, H_n = \begin{bmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_n \end{bmatrix}$$

where $a_j = 0$ if $j > n$. All of the roots of the polynomial $P(\lambda)$ are negative or have negative real parts iff the determinants of all Hurwitz matrices are positive.

2.2. **Linear System of ODE's.** We will discuss general solutions of a linear system of ODE's. Consider $\dot{y} = Ay$, a linear system of differential equations where

$$\dot{u} = au + bv,$$
$$\dot{v} = cu + dv,$$

and

$$\text{A}=\begin{bmatrix} a & b \\ c & d \end{bmatrix}, \mathbf{y}=\begin{bmatrix} u \\ v \end{bmatrix}.$$

In order to find solutions of the linear system, we solve the characteristic equation

$$det(A - \lambda I) = 0$$

where I is the 2×2 identity matrix and λ is a scalar. The roots of the characteristic equation are said to be the eigenvalues and the corresponding eigenvectors are said to be the eigensolutions to the linear system. Solving the characteristic equation will yield

$$\lambda^2 - \tau\lambda + \Delta = 0$$

where

$$\tau = trace(A),\ \Delta = det(A),$$

and the roots of the equation will be

$$\lambda_1 = \frac{\tau + \sqrt{\tau^2 - 4\Delta}}{2},$$
$$\lambda_2 = \frac{\tau - \sqrt{\tau^2 - 4\Delta}}{2}.$$

Suppose w and z are eigenvectors of the matrix A corresponding to the eigenvalues λ_1 and λ_2 respectively. A general solution to $\dot{y} = Ay$ is given by

$$\begin{bmatrix} u(t) \\ v(t) \end{bmatrix} = c_1 e^{\lambda_1 t} w + c_2 e^{\lambda_2 t} z$$

where c_1 and c_2 are constant and t is time. Note that a fixed point of this system is $(0, 0)$.

2.3. **Linearizing a System of ODE's.** To analyze a nonlinear system of ODE's, we must first linearize the system in order to analyze activity around the fixed points of the system. Given a system of four nonlinear differential equations

$$\begin{cases} \dot{u}_1 = f_1(u_1, u_2, u_3, u_4) \\ \dot{u}_2 = f_2(u_1, u_2, u_3, u_4) \\ \dot{u}_3 = f_3(u_1, u_2, u_3, u_4) \\ \dot{u}_4 = f_4(u_1, u_2, u_3, u_4) \end{cases}$$

we find a fixed point of the system, $(u_1^0, u_2^0, u_3^0, u_4^0)$, where $f_1(u_1^0, u_2^0, u_3^0, u_4^0) = 0$, $f_2(u_1^0, u_2^0, u_3^0, u_4^0) = 0$, $f_3(u_1^0, u_2^0, u_3^0, u_4^0) = 0$, and $f_4(u_1^0, u_2^0, u_3^0, u_4^0) = 0$. We then make a change of variables to translate the fixed point to the origin such that

$$\omega_1 = u_1 - u_1^0,\ \omega_2 = u_2 - u_2^0,\ \omega_3 = u_3 - u_3^0,\ \omega_4 = u_4 - u_4^0.$$

We can then expand the translated system using a Taylor series expansion, using the fact that $(u_1^0, u_2^0, u_3^0, u_4^0)$ is a fixed point. First, we will expand the ω_1-equation:

$$\begin{aligned} \dot{\omega}_1 &= \dot{u}_1 \\ &= f_1(u_1^0 + \omega_1, u_2^0 + \omega_2, u_3^0 + \omega_3, u_4^0 + \omega_4) \\ &= f_1(u_1^0, u_2^0, u_3^0, u_4^0) + \omega_1 \frac{\partial f_1}{\partial u_1}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_2 \frac{\partial f_1}{\partial u_2}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_3 \frac{\partial f_1}{\partial u_3}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \\ &\quad \omega_4 \frac{\partial f_1}{\partial u_4}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + O(2) \\ &= \omega_1 \frac{\partial f_1}{\partial u_1}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_2 \frac{\partial f_1}{\partial u_2}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_3 \frac{\partial f_1}{\partial u_3}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_4 \frac{\partial f_1}{\partial u_4}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + O(2) \end{aligned}$$

Similarly, the rest of the equations are as follows,

$$\dot{\omega}_2 = \omega_1 \frac{\partial f_2}{\partial u_1}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_2 \frac{\partial f_2}{\partial u_2}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_3 \frac{\partial f_2}{\partial u_3}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_4 \frac{\partial f_2}{\partial u_4}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + O(2),$$

$$\dot{\omega}_3 = \omega_1 \frac{\partial f_3}{\partial u_1}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_2 \frac{\partial f_3}{\partial u_2}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_3 \frac{\partial f_3}{\partial u_3}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_4 \frac{\partial f_3}{\partial u_4}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + O(2),$$

$$\dot{\omega}_4 = \omega_1 \frac{\partial f_4}{\partial u_1}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_2 \frac{\partial f_4}{\partial u_2}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_3 \frac{\partial f_4}{\partial u_3}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + \omega_4 \frac{\partial f_4}{\partial u_4}|_{(u_1^0, u_2^0, u_3^0, u_4^0)} + O(2).$$

Note that O(2) represents higher order terms. We will consider a small region around the fixed point,and we will only take the first order terms of the expansion. The higher order terms will also be truncated. Thus, it follows that the system will behave according to the linearized system:

$$\begin{bmatrix} \dot{\omega}_1 \\ \dot{\omega}_2 \\ \dot{\omega}_3 \\ \dot{\omega}_4 \end{bmatrix} = \begin{bmatrix} \frac{\partial f_1}{\partial u_1} & \frac{\partial f_1}{\partial u_2} & \frac{\partial f_1}{\partial u_3} & \frac{\partial f_1}{\partial u_4} \\ \frac{\partial f_2}{\partial u_1} & \frac{\partial f_2}{\partial u_2} & \frac{\partial f_2}{\partial u_3} & \frac{\partial f_2}{\partial u_4} \\ \frac{\partial f_3}{\partial u_1} & \frac{\partial f_3}{\partial u_2} & \frac{\partial f_3}{\partial u_3} & \frac{\partial f_3}{\partial u_4} \\ \frac{\partial f_4}{\partial u_1} & \frac{\partial f_4}{\partial u_2} & \frac{\partial f_4}{\partial u_3} & \frac{\partial f_4}{\partial u_4} \end{bmatrix} \Big|_{(u_1^0, u_2^0, u_3^0, u_4^0)} \begin{bmatrix} \omega_1 \\ \omega_2 \\ \omega_3 \\ \omega_4 \end{bmatrix}$$

We define the Jacobian to be:

$$\text{J}= \begin{bmatrix} \frac{\partial f_1}{\partial u_1} & \frac{\partial f_1}{\partial u_2} & \frac{\partial f_1}{\partial u_3} & \frac{\partial f_1}{\partial u_4} \\ \frac{\partial f_2}{\partial u_1} & \frac{\partial f_2}{\partial u_2} & \frac{\partial f_2}{\partial u_3} & \frac{\partial f_2}{\partial u_4} \\ \frac{\partial f_3}{\partial u_1} & \frac{\partial f_3}{\partial u_2} & \frac{\partial f_3}{\partial u_3} & \frac{\partial f_3}{\partial u_4} \\ \frac{\partial f_4}{\partial u_1} & \frac{\partial f_4}{\partial u_2} & \frac{\partial f_4}{\partial u_3} & \frac{\partial f_4}{\partial u_4} \end{bmatrix}$$

The eigenvalues of $J|_{(u_1^0, u_2^0, u_3^0, u_4^0)}$ will be used to determine the stability of the fixed point $(u_1^0, u_2^0, u_3^0, u_4^0)$. We can classify the stability of a fixed point based on the eigenvalues. If all the eigenvalues are negative, or have negative real parts, the fixed point is stable. If there is at least one positive eigenvalue, then the fixed point is unstable. This analysis can be extended to a set of partial differential equations with no-flux boundary conditions. This analysis can be extended for $n \times n$ matrices.

3. PDE Model

3.1. **Model Formulation.** From this biological understanding, as well as from previous works on the subject(Gatenby, Holder), we are able to develop a PDE model to represent the complex system of interactions between the normal cells, the tumor cells, the excess acid, and the chemotherapy intervention. Below are the basic assumptions for how the model works.

- Both normal and tumor cells are governed by logistic growth in the absence of any kind of intervention. Logistic growth occurs when the growth rate decreases as the population reaches carrying capacity.
- Both normal and tumor cells undergo cell diffusion. Furthermore, the diffusion coefficients may be dependent on the other respective cell density.
- There is a population competition relationship between the normal and the tumor cells.
- The tumor tissue produces H^+ ions as a result of aerobic glycolysis at a rate proportional to the tumor cell density.
- The normal tissue interacts with the excess H^+ ions, leading to a death rate proportional to the H^+ ion concentration.
- Excess H^+ ions diffuse chemically with a constant diffusion rate and are produced at a rate proportional to the tumor cell density. Moreover, an uptake term is included to take account of mechanisms for increasing pH. the acid production is capped by the carrying capacity of the tumor cells.
- The chemotherapy drug is infused equally across the system at a rate given by a function of time. A term is included for removal of drug from the system by metabolic processes and the drug is assumed to diffuse chemically with a constant rate of diffusion.
- The tumor tissue interacts with the chemotherapy drug leading to destruction of tumor tissue at a rate proportional to the concentration of the drug.
- The chemotherapy drug concentration is decreased as a result of interaction with the tumor tissue.

Let the populations at time s(in seconds) and position y(in cm) be denoted by:

- $N_1(y, s)$, normal cell density(in $cells\ cm^{-3}$);
- $N_2(y, s)$, tumor cell density(in $cells\ cm^{-3}$);

- $L(y,s)$, excess H^+ ion concentration(in M);
- $C(y,s)$, chemotherapy drug concentration(in M).

Consider the following model

$$\begin{cases} \frac{\partial N_1}{\partial s} = \underbrace{\nabla[D_{N_1}\nabla N_1]}_{\text{cell movement}} + \underbrace{r_1 N_1(1-\frac{N_1}{K_1}-\alpha_1\frac{N_2}{K_2})}_{\text{log. growth with cellular comp.}} - \underbrace{d_1 L N_1}_{\text{death by acid}} \\ \frac{\partial N_2}{\partial s} = \underbrace{\nabla[D_{N_2}\nabla N_2]}_{\text{cell movement}} + \underbrace{r_2 N_2(1-\frac{N_2}{K_2}-\alpha_2\frac{N_1}{K_1})}_{\text{log. growth with cellular comp.}} - \underbrace{d_2 C N_2}_{\text{death by drug}} \\ \frac{\partial L}{\partial s} = \underbrace{D_3\nabla^2 L}_{\text{acid diffusion}} + \underbrace{r_3 N_2(1-\frac{N_2}{K_2})}_{\text{acid production}} - \underbrace{m_3 L}_{\text{acid uptake}} \\ \frac{\partial C}{\partial s} = \underbrace{D_4\nabla^2 C}_{\text{drug diffusion}} + \underbrace{r_I(s)}_{\text{drug infusion}} - \underbrace{m_4 C}_{\text{drug decomp.}} - \underbrace{d_4 N_2 C}_{\text{drug tumor inter. removal}} \end{cases}$$

We have placed the parameters as well as their descriptions in the following table, excluding three; D_{N_1},D_{N_2}, and $r_I(s)$. For D_{N_1} and D_{N_2}, we will assume constant diffusion coefficients

$$D_{N_1} = D_1 \; and \; D_{N_2} = D_2$$

in order to approximate and account for any cellular movement.

Parameters	**Units**	**Description**	value
r_1	s^{-1}	normal cell growth rate	$O(10^{-6})$
r_2	s^{-1}	tumor cell growth rate	$O(10^{-6})$
r_3	$Mcm^3s^{-1}cells^{-1}$	H^+ ion production rate	$2.2*10^{-17}$
d_1	$M^{-1}s^{-1}$	fractional normal cell kill by H^+ ions	$O(1)$
d_2	$M^{-1}s^{-1}$	fractional tumor cell kill by chemotherapy	$9.3*10^{-6}$
d_4	$cells^{-1}s^{-1}$	fractional chemotherapy removal by tumor inter.	$O(10^{-13})$
m_3	s^{-1}	H^+ ion removal rate	$O(10^{-4})$
m_4	s^{-1}	chemotherapy removal rate	$O(10^{-5})$
K_1	$cellscm^{-3}$	normal cell carrying capacity	$5*10^7$
K_2	$cellscm^{-3}$	tumor cell carrying capacity	$5*10^7$
D_1	cm^2s^{-1}	cell diffusion coefficients	$O(10^{-10})$
D_2	cm^2s^{-1}	cell diffusion coefficients	$2*10^{-10}$
D_3	cm^2s^{-1}	ion diffusion coefficients	$5*10^{-6}$
D_4	cm^2s^{-1}	Chemo diffusion coefficients	$5*10^{-6}$
α_1	none	fractional normal cell death from tumor	$O(1)$
α_2	none	fractional tumor cell death from normal	$O(1)$

3.2. **Chemotherapy Drug Infusion.** The term $r_I(s)$ in the final equation pertains to the drug infusion and is a function in which there are several options depending on how the chemotherapy drug is introduced into the system. In this work we have analyzed two such options, one being continuous infusion where r_I is chosen to be constant, and the other in which we have periodic infusion as described by the weighted boxcar function

$$r_I(s) = r_4 \sum_{n=0}^{N-1} [H(s - nP) - H(s - nP - s_0)]$$

where P is the length of the treatment cycle, s_0 is the infusion time, N is the number of treatment cycles, and $H(s)$ is the Heaviside function. A graph of this function can be seen in chapter 7.

3.3. **Boundary and Initial Conditions.** We denote the spatial domain by Ω and we assume Ω is one dimensional. We then assume no flux boundary conditions

- $\frac{\partial u_1}{\partial \overrightarrow{n}} = \overrightarrow{\nabla u_1} \cdot \overrightarrow{n} = 0$ on $\partial\Omega \times [0, \infty)$,
- $\frac{\partial u_2}{\partial \overrightarrow{n}} = \overrightarrow{\nabla u_2} \cdot \overrightarrow{n} = 0$ on $\partial\Omega \times [0, \infty)$,
- $\frac{\partial u_3}{\partial \overrightarrow{n}} = \overrightarrow{\nabla u_3} \cdot \overrightarrow{n} = 0$ on $\partial\Omega \times [0, \infty)$,
- $\frac{\partial u_4}{\partial \overrightarrow{n}} = \overrightarrow{\nabla u_4} \cdot \overrightarrow{n} = 0$ on $\partial\Omega \times [0, \infty)$,

where $\overrightarrow{n}$ is the normal vector to Ω.
We then assume our initial conditions to be

- $u_1(\cdot, 0) = u_1^0(\cdot) \geq 0$
- $u_2(\cdot, 0) = u_2^0(\cdot) \geq 0$
- $u_3(\cdot, 0) = u_3^0(\cdot) \geq 0$
- $u_4(\cdot, 0) = u_4^0(\cdot) \geq 0$.

3.4. **Nondimensionalization.** Next we will nondimensionalize our system to decrease the number of parameters and eliminate the need for units of measurement. Considering the function $r_I(s)$ with period P we let

$$\bar{r} = \frac{1}{P} \int_0^P r_I(s) ds$$

where $\bar{r}$ is the average infusion rate, to nondimensionalize the system. We will define new variables and parameters as follows,

$$u_1 = \frac{N_1}{K_1}, \quad u_2 = \frac{N_2}{K_2}, \quad u_3 = \frac{d_1}{\alpha_1 r_1} L, \quad u_4 = \frac{m_4}{\bar{r}} C, \quad x = \sqrt{\frac{r_1}{D_3}} y, \quad t = r_1 s, \quad \beta_2 = \frac{r_2}{r_1},$$

$$\beta_3 = \frac{r_3 d_1 K_2}{\alpha_1 r_1^2}, \quad \beta_4 = \frac{m_4}{r_1}, \quad \eta_1 = \frac{D_1}{D_3}, \quad \eta_2 = \frac{D_2}{D_3}, \quad \eta_4 = \frac{D_4}{D_3}, \quad \delta_1 = \alpha_1, \quad \delta_2 = \frac{d_2 \bar{r}}{r_2 m_4},$$

$$\delta_3 = \frac{m_3}{r_1}, \quad \delta_4 = \frac{d_4 K_2}{m_4}, \quad i(t) = \frac{r_I(t/r_1)}{\bar{r}}, \quad \rho = r_1 P \ .$$

We then obtain the following system of nondimensionalized equations,

$$\begin{cases} \dfrac{\partial u_1}{\partial t} = \eta_1 \dfrac{\partial^2 u_1}{\partial x^2} + u_1(1 - u_1 - \alpha_1 u_2 - \delta_1 u_3) \\ \dfrac{\partial u_2}{\partial t} = \eta_2 \dfrac{\partial^2 u_2}{\partial x^2} + \beta_2 u_2(1 - u_2 - \alpha_2 u_1 - \delta_2 u_4) \\ \dfrac{\partial u_3}{\partial t} = \dfrac{\partial^2 u_3}{\partial x^2} + \beta_3 u_2(1 - u_2) - \delta_3 u_3 \\ \dfrac{\partial u_4}{\partial t} = \eta_4 \dfrac{\partial^2 u_4}{\partial x^2} + \beta_4(i(t) - u_4 - \delta_4 u_4 u_2) \end{cases}$$

where the meanings of our new parameters are found in the table below.

Parameters	**Interpretation**	**Value/Range**
α_1	fractional normal death	$O(1)$
α_2	fractional tumor death	$O(1)$
δ_1	tumor aggressiveness	$O(1)$
δ_2	chemotherapy aggressiveness	$O(10^{-1}) - O(1)$
δ_3	relative acid uptake	$O(10^2)$
δ_4	frac. removal from interaction str.	$O(10^{-1}) - O(1)$
β_2	relative tumor growth rate	1.0
β_3	relative H^+ ion production rate	$O(10^2)$
β_4	relative chemotherapy rate of inc.	$O(10)$
η_1	rel. normal-H^+ ion diff. rate	$4X10^{-5}$
η_2	rel. tumor-H^+ ion diff. rate	$O(10^{-5})$
η_4	rel. chemotherapy-H^+ ion diff. rate	$O(1)$

3.5. **Homogenous Steady State Solutions.** Homogenous steady state solutions are solutions that will satisfy the system in the absence of diffusion terms. Note that we still have $i(t)$ as a function of time for periodic infusion. The rate of infusion per unit time equals the average rate over each period. Without loss of generality, we will assume that this rate equals 1 and perform existence and stability analysis on the ODE system written below.

$$\begin{cases} \dfrac{du_1}{dt} = u_1(1 - u_1 - \alpha_1 u_2 - \delta_1 u_3) \\ \dfrac{du_2}{dt} = \beta_2 u_2(1 - u_2 - \alpha_2 u_1 - \delta_2 u_4) \\ \dfrac{du_3}{dt} = \beta_3 u_2(1 - u_2) - \delta_3 u_3) \\ \dfrac{du_4}{dt} = \beta_4(1 - u_4 - \delta_4 u_4 u_2) \end{cases}$$

3.6. **Fixed Points.** Fixed points are the solutions of the system that do not change across time. The ODE system when set to zero is as follows

$$\begin{cases} u_1(1-u_1-\alpha_1 u_2-\delta_1 u_3)=0 \\ \beta_2 u_2(1-u_2-\alpha_2 u_1-\delta_2 u_4)=0 \\ \beta_3 u_2(1-u_2)-\delta_3 u_3)=0 \\ \beta_4(1-u_4-\delta_4 u_4 u_2)=0 \end{cases}$$

and the system admits the following solutions

(1) $E_1=(0,0,0,1)$

(2) $E_2=(1,0,0,1)$

(3) $E_3^{\pm}=(0,\hat{u_2}^{\pm},\dfrac{\beta_3\hat{u_2}^{\pm}(1-\hat{u_2}^{\pm})}{\delta_3},\dfrac{1}{1+\delta_4\hat{u_2}^{\pm}})$, where

$$\hat{u_2}^{\pm}=\frac{(\delta_4-1)\pm\sqrt{(\delta_4+1)^2-4\delta_4\delta_2}}{2\delta_4}$$

(4) $E_4=(u_1^\star,u_2^\star,u_3^\star,u_4^\star)$, where

$$u_1^\star=\frac{1}{\alpha_2}(1-u_2^\star-\frac{\delta_2}{1+\delta_4 u_2^\star}),\ u_3^\star=\frac{\beta_3}{\delta_3}u_2^\star(1-u_2^\star),\ u_4^\star=\frac{1}{1+\delta_4 u_2^\star}$$

and $u_2^\star$ is a solution of the cubic equation

$$1-\frac{1}{\alpha_2}\left[(1-u_2^\star-\frac{\delta_2}{1+\delta_4 u_2^\star})-\alpha_1 u_2^\star-\frac{\beta_3\delta_1 u_2^\star(1-u_2^\star)}{\delta_3}\right]=0.$$

Note that E_1 is the trivial fixed point, E_2 is the tumor free state fixed point, E_3 is the tumor invasive state fixed point, and E_4 is the coexistence state fixed point. Also note that since E_3 is dependent on $\hat{u_2}^{\pm}$, there is a possibility of having two third fixed points. Note that $\hat{u_2}^{\pm}$ are roots of

$$\hat{u_2}^{\pm} = \frac{(\delta_4 - 1) \pm \sqrt{(\delta_4 + 1)^2 - 4\delta_4\delta_2}}{2\delta_4}.$$

- only one positive root if $\delta_2 < 1$
- two positive roots if $1 < \delta_2 \leq \dfrac{(1+\delta_2)^2}{4\delta_4}$
- no positive roots exist if $\delta_2 > 1$ and $\delta_2 > \dfrac{(1+\delta_4)^2}{4\delta_4}$ or if $1 < \delta_2 < \dfrac{(1+\delta_4)^2}{4\delta_4}$ and $\delta_4 < 1$

4. Existence and Stability Analysis of the trivial, tumor free state, and tumor invasive state fixed points

4.1. **Existence Conditions of the Fixed Points.** In order for us to do stability analysis of the fixed points, we must first find sufficient conditions in which the fixed points of the system exist. Below is a table that shows the necessary conditions for the fixed points to exist.

Fixed Points	**Feasibility Conditions**
E_1=(0,0,0,1)	always exists
E_2=(1,0,0,1)	always exists
E_3^+=$(0, \hat{u_2}^+, \frac{\beta_3 \hat{u_2}^+(1-\hat{u_2}^+)}{\delta_3}, \frac{1}{1+\delta_4 \hat{u_2}^+})$	$\delta_2 < 1$ or $1 < \delta_2 \leq \frac{(\delta_4+1)^2}{4\delta_4}$, $\delta_4 > 1$
E_3^-=$(0, \hat{u_2}^-, \frac{\beta_3 \hat{u_2}^-(1-\hat{u_2}^-)}{\delta_3}, \frac{1}{1+\delta_4 \hat{u_2}^-})$	$1 < \delta_2 \leq \frac{(\delta_4+1)^2}{4\delta_4}$, $\delta_4 > 1$
$E_4 = (u_1^*, u_2^*, u_3^*, u_4^*)$	to be covered in chapter 5

4.2. **Linear Stability Analysis.** Next do we linear stability analysis at the fixed points by studying the Jacobian at each fixed point. The signs of the eigenvalues of the Jacobian will determine the stability. If all the eigenvalues are negative, then the fixed point is stable. The Jacobian matrix is written below.

$$\text{J}=\begin{bmatrix} 1-2u_1-\alpha_1 u_2-\delta_1 u_3 & -\alpha_1 u_1 & -\delta_1 u_1 & 0 \\ -\beta_2\alpha_2 u_2 & \beta_2(1-2u_2-\alpha_2 u_1-\delta_2 u_4) & 0 & -\beta_4\delta_2 u_2 \\ 0 & \beta_3-2\beta_3 u_2 & -\delta_3 & 0 \\ 0 & -\beta_4\delta_4 u_4 & 0 & \beta_4(-1-\delta_4 u_2) \end{bmatrix}$$

Now that we have the Jacobian, we can evaluate it at each fixed point. We will first evaluate the Jacobian at the trivial fixed point, E_1.

$$\text{J}[0,0,0,1]=\begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & \beta_2-\beta_2\delta_2 & 0 & 0 \\ 0 & \beta_3 & -\delta_3 & 0 \\ 0 & -\beta_4\delta_4 & 0 & -\beta_4 \end{bmatrix}$$

Note that this matrix is in upper triangular form, meaning that the eigenvalues will be the diagonals of the matrix. The eigenvalues are $1, \beta_2-\beta_2\delta_2, -\delta_3, -\beta_4$. Note that since one of the eigenvalues is positive, the fixed point will always be unstable.

Next we will evaluate the Jacobian at our tumor free state fixed point, E_2.

$$\text{J}[1,0,0,1]=\begin{bmatrix} -1 & -\alpha_1 & -\delta_1 & 0 \\ 0 & \beta_2-\alpha_2\beta_2-\delta_2\beta_2 & 0 & 0 \\ 0 & \beta_3 & -\delta_3 & 0 \\ 0 & -\beta_4\delta_4 & 0 & -\beta_4 \end{bmatrix}$$

Upon doing row simplification we find that the eigenvalues are once again the diagonals of the matrix. The eigenvalues are $-1, \beta_2 - \alpha_2\beta_2 - \delta_2\beta_2, -\delta_3, -\beta_4$. Note that the eigenvalue $\beta_2 - \alpha_2\beta_2 - \delta_2\beta_2$ can switch between positive and negative values, which means that the stability for this fixed point depends on the values for β_2, α_2, and δ_2. In order for the fixed point to be stable, we need $1 - \alpha_2 - \delta_2 < 0$.

Thirdly, we will evaluate the Jacobian at our tumor invasive state, E_3.

$$\mathrm{J}[E_3]=\begin{bmatrix} 1-\alpha_1\hat{u_2}-\dfrac{\delta_1\beta_3\hat{u_2}(1-\hat{u_2})}{\delta_3} & 0 & 0 & 0 \\ -\beta_2\alpha_2\hat{u_2} & \beta_2(1-2\hat{u_2}-\dfrac{\delta_2}{1+\delta_4\hat{u_2}}) & 0 & -\beta_2\delta_2\hat{u_2} \\ 0 & \beta_3-2\beta_3\hat{u_2} & -\delta_3 & 0 \\ 0 & \dfrac{-\beta_4\delta_4}{1+\delta_4\hat{u_2}} & 0 & \beta_4(-1-\delta_4\hat{u_2}) \end{bmatrix}$$

The characteristic polynomial is as follows,

$$P(\lambda) = \Big[-\lambda + (1-\alpha_1\hat{u_2}^{\pm} - \frac{\delta_1\beta_3\hat{u_2}^{\pm}(1-\hat{u_2}^{\pm})}{\delta_3})\Big][(-\lambda-\delta_3)]$$

$$\left[\lambda^2+\lambda\Big[\beta_4(1+\delta_2^2\hat{u_2}^{\pm})-\beta_2(1-2\hat{u_2}^{\pm}-\frac{\delta_2}{1+\delta_4\hat{u_2}^{\pm}})\Big]-\beta_4\beta_2\Big[1+\hat{u_2}^{\pm}(\delta_4-2-2\delta_4\hat{u_2}^{\pm})-\frac{\delta_2}{1+\delta_4\hat{u_2}^{\pm}}\Big]\right] = 0.$$

Two of the eigenvalues will be

$$\lambda_1 = -\delta_3 \; and \; \lambda_4 = 1-\alpha_1\hat{u_2}^{\pm} - \frac{\delta_1\beta_3\hat{u_2}^{\pm}(1-\hat{u_2}^{\pm})}{\delta_3}$$

while the other two eigenvalues, λ_2, λ_3, are roots of

$$\lambda^2 + \lambda\Big[\beta_4(1+\delta_2^2\hat{u_2}^{\pm}) - \beta_2(1-2\hat{u_2}^{\pm} - \frac{\delta_2}{1+\delta_4\hat{u_2}^{\pm}})\Big] - \beta_4\beta_2\Big[1+\hat{u_2}^{\pm}(\delta_4-2-2\delta_4\hat{u_2}^{\pm}) - \frac{\delta_2}{1+\delta_4\hat{u_2}^{\pm}}\Big] = 0.$$

4.3. **Stability Summarized.** Below is a table summarizing the trivial, tumor free state, and the tumor invasive states fixed points stability conditions.

Fixed Points	**Eigenvalues**	**stability conditions**
E_1	$1, \beta_2 - \beta_2\delta_2, -\delta_3, -\beta_4$	always unstable
E_2	$-1, \beta_2 - \alpha_2\beta_2 - \delta_2\beta_2,$ $-\delta_3, -\beta_4$	stable if $1 - \alpha_2 - \delta_2 < 0$
$E_3^{\pm}$	$-\delta_3, \lambda_2, \lambda_3, \lambda_4$	stable if $Re(\lambda_2), Re(\lambda_3), Re(\lambda_4) < 0$
E_4	to be covered in chapter 5	to be in chapter 5

5. Existence and Stability of the Coexistence Equilibrium Fixed Point

5.1. **Existence of Coexistence Equilibrium Fixed Point.** We denote the coexistence fixed point $E_4 = (u_1^\star, u_2^\star, u_3^\star, u_4^\star)$, where

$$u_1^\star = \frac{1}{\alpha_2}(1 - u_2^\star - \frac{\delta_2}{1+\delta_4 u_2^\star}),\ u_3^\star = \frac{\beta_3}{\delta_3}u_2^\star(1-u_2^\star),\ u_4^\star = \frac{1}{1+\delta_4 u_2^\star}$$

and $u_2^\star$ is a solution of the cubic equation

$$G(u_2^\star) = 1 - \frac{1}{\alpha_2}\left[(1 - u_2^\star - \frac{\delta_2}{1+\delta_4 u_2^\star}) - \alpha_1 u_2^\star - \frac{\beta_3\delta_1 u_2^\star(1-u_2^\star)}{\delta_3}\right] = 0.$$

For biological feasibility, $0 < u_2^\star < \hat{u_2}^+$. If $u_2^\star$ is outside of this range, since the other values depend on this value, the other values may become unrealistic, such as negative values. So we need to find conditions for $G(u_2^\star)$ to have roots in $(0, \hat{u_2})$. To this end, we compute $G(0)$ and $G(\hat{u_2})$, which we find to be

$$G(0) = \frac{\alpha_2 + \delta_2 - 1}{\alpha_2}$$

$$G(\hat{u_2}^+) = 1 - \alpha_1\hat{u_2}^+ - \frac{\delta_1\beta_3\hat{u_2}^+(1-\hat{u_2}^+)}{\delta_3}.$$

Note that the numerator of $G(0)$ is actually one of the eigenvalues for the tumor free state fixed point, while $G(\hat{u_2}^+)$ is one of the eigenvalues for the tumor invasive state fixed point. If these two values are opposite in sign, then by the Intermediate Value Theorem, we will have a sufficient set of conditions on the parameters that will allow at least one crossing of the X-axis, which means that $u_2^\star$ will be in the necessary range. Thus, the coexistence fixed point will exist.

One such set of conditions that will guarantee positive roots of $G(u_2^\star) = 0$ in that boundary is where we choose δ_2, δ_4 such that the equation holds if

$$\alpha_2 < 1 - \delta_2,$$
$$\delta_3 > \frac{1 - \alpha_1\hat{u}_2^+}{\delta_1\beta_3\hat{u}_2^+(1-\hat{u}_2^+)}.$$

5.2. **Stability of the Coexistence Fixed Point.** First we find the Jacobian evaluated at the coexistence fixed point to be

$$\mathrm{J}[E_4]=\begin{bmatrix} -u_1^\star & -\alpha_1 u_1^\star & -\delta_1 u_1^\star & 0 \\ -\beta_2\alpha_2 u_2^\star & -\beta_2 u_2^\star & 0 & -\beta_2\delta_2 u_2^\star \\ 0 & \beta_3 - 2\beta_3 u_2^\star & -\delta_3 & 0 \\ 0 & -\beta_4\delta_4 u_4^\star & 0 & -\dfrac{\beta_4}{u_4^\star} \end{bmatrix}$$

In order to analyze the eigenvalues of this Jacobain, we must analyze its characteristic equation. The characteristic equation for this Jacobian is as follows

$$P(\lambda) = \lambda^4 + A\lambda^3 + B\lambda^2 + C\lambda + D$$

where

$$A = \frac{\beta_4}{u_4^\star} + \beta_2 u_2 \star + u_1^\star + \delta_3$$

$$B = \frac{\beta_4}{u_4^\star}(\beta_4 u_2^\star + u_1^\star + \delta_3) + (\beta_2 u_2^\star u_1^\star - \beta_2\alpha_2 u_2^\star\alpha_1 u_1^\star + \delta_3(\beta_2 u_2^\star + u_1^\star)) + \beta_4\delta_2 u_4^\star\beta_2\delta_2 u_2^\star$$

$$C = \beta_2 u_1^\star u_2^\star(\alpha_2\alpha_1\delta_3 - \delta_3 - \beta_3\alpha_2\delta_1(-1+2u_2^\star)) - \frac{\beta_4}{u_4^\star}(\beta_2 u_2^\star u_1^\star - \beta_2\alpha_2 u_2^\star\alpha_1 u_1^\star + \delta_3(\beta_2 u_2^\star + u_1^\star)) - \beta_4\delta_4 u_4^\star\beta_2\delta_2 u_2^\star(u_1^\star + \delta_3)$$

$$D = \beta_4\beta_2 u_1^\star u_2^\star(\frac{1}{u_4^\star}(\alpha_1\alpha_2\delta_3 - \delta_3 - \beta_3\alpha_2\delta_1(-1+2u_2^\star)) - \delta_2\delta_3\delta_4 u_4^*)$$

This is, however, a very complicated fourth degree characteristic equation polynomial so we will use the Routh Hurwitz criterion(see chapter 2), to create the Hurwitz matrices and find the signs of the roots. We find our Hurwitz matrices to be

$$H_1 = (A), H_2 = \begin{bmatrix} A & 1 \\ C & B \end{bmatrix}, H_3 = \begin{bmatrix} A & 1 & 0 \\ C & B & A \\ 0 & D & C \end{bmatrix}, H_4 = \begin{bmatrix} A & 1 & 0 & 0 \\ C & B & A & 1 \\ 0 & D & C & B \\ 0 & 0 & 0 & D \end{bmatrix}.$$

Upon analysis of the determinants, we find that in order for us to have all negative roots, meaning all negative eigenvalues, we must have the following conditions for our coefficients met

- $A > 0$,
- $C > 0$,
- $D > 0$,
- $ABC > C^2 + A^2 D$.

If these conditions are met then we will have negative roots or negative real parts, and thus eigenvalues with negative real parts. This will give us stability of the coexistence equilibrium point.

6. Numerical Simulations(continuous)

6.1. **Initial Conditions Graphs.** Our normal cells and tumor cells will have the following initial conditions, while our excess ion concentration and the chemotherapy drug concentration start at zero. We are considering a 1-dimensional cross-section at the host-tumor interface. We denote the cross-section by Ω and let $\Omega = [-2, 2]$. Also note that $x = 0$ is the center of the tumor.

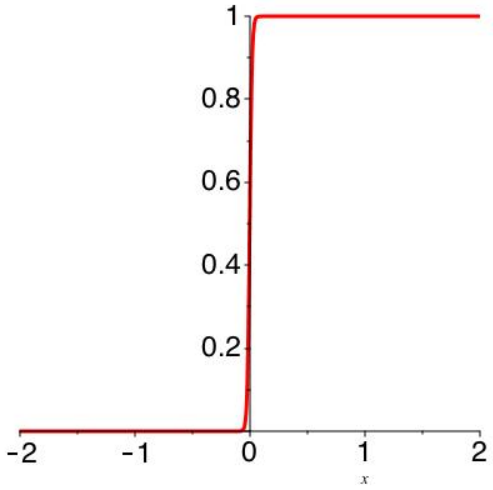


Figure 3. Initial normal cell density

The normal cells are at their carrying capacity on the interval $[0, 2]$.

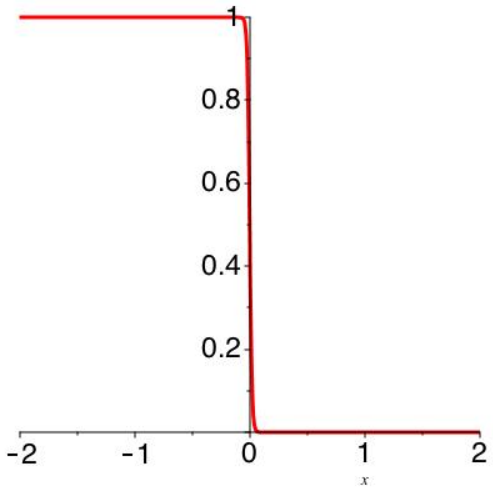


Figure 4. Initial tumor cell density

The tumor cells are at thier carrying capacity on the interval$[-2, 0]$.

6.2. **Continuous graph information.** In this chapter is the numerical simulations for continuous infusion of the chemotherapy drug, that is, where $i(t) = 1$.Below is a table that contains the parameter values we have chosen, as well as those parameter sets stabilities and existence and the graphs that pertain to these parameter sets.

Note that these specific parameter values remain the same for all parameter sets, $\alpha_1 = 1,\ \alpha_2 = .5,\ \beta_2 = 1.$

Parameter Values	**Stability/Existence**	**Figures**
$\beta_3 = 60,\ \beta_4 = 10, \delta_1 = 1.5,$ $\delta_2 = 1.1,\ \delta_3 = 10,\ \delta_4 = 1.1$	E_1 unstable, E_2 stable, E_3 DNE, E_4 DNE	figures 5-8
$\beta_3 = 60,\ \beta_4 = 10, \delta_1 = 1.5,$ $\delta_2 = .8,\ \delta_3 = 10,\ \delta_4 = 1.1$	E_1 unstable, E_2 stable, E_3 stable, E_4 unstable	figures 9-12
$\beta_3 = 50,\ \beta_4 = 10, \delta_1 = 0.5,$ $\delta_2 = .8,\ \delta_3 = 15,\ \delta_4 = 2$	E_1 unstable, E_2 stable, E_3 stable, E_4 unstable	figures 13-16
$\beta_3 = 90,\ \beta_4 = 10, \delta_1 = 0.5,$ $\delta_2 = .4,\ \delta_3 = 15,\ \delta_4 = 1$	E_1 unstable, E_2 unstable, E_3 stable, E_4 DNE	figures 17-20
$\beta_3 = 90,\ \beta_4 = 10, \delta_1 = 0.5,$ $\delta_2 = .55,\ \delta_3 = 35,\ \delta_4 = 1$	E_1 unstable, E_2 stable, E_3 unstable, E_4 stable	figures 21-24

We have drawn contour plots representing the densities of the normal cells, the tumor cells, the excess H^+ ion concentration, and the chemotherapy drug conentration, as a function of time and space. The x-axis represents the space in which the normal cells, tumor cells, excess acid, or the chemotherapy drug are occupying. The y-axis represents the non dimensionalized time. The color bar on the right of the contour plots represent the density for tumor and normal cells and the concentration for the excess acid and chemotherapy drug.

Tumor free state graphs

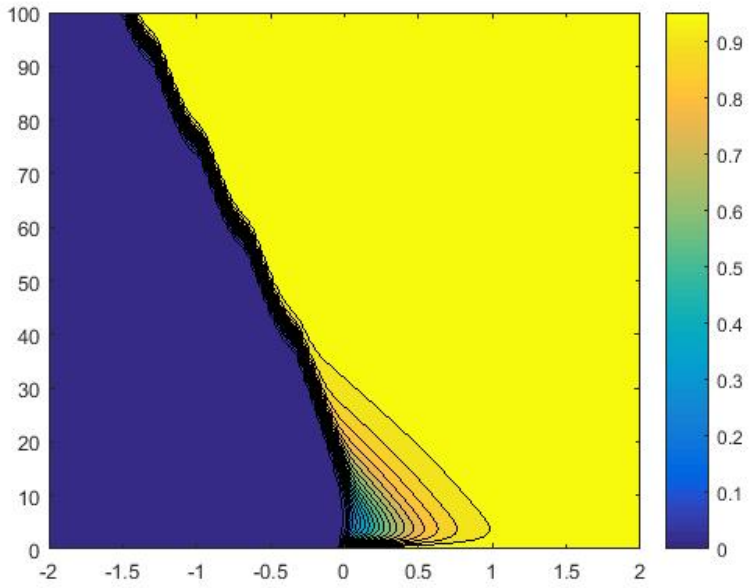


FIGURE 5. Normal cell density

The normal cells are growing into space not previously occupied by normal cells.

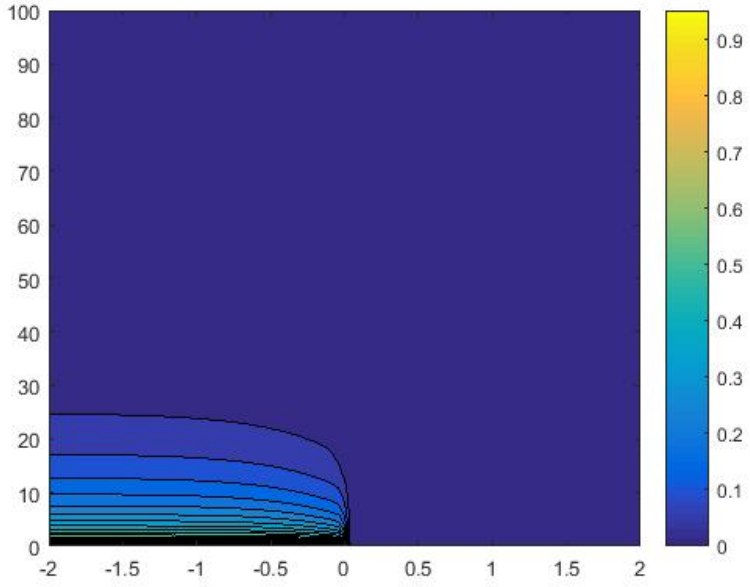


FIGURE 6. Tumor cell density

The tumor cells are dying off rapidly.

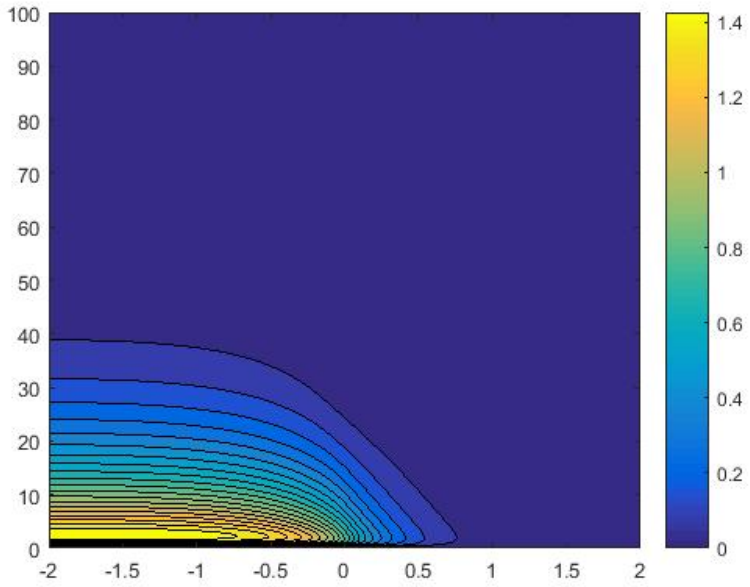


FIGURE 7. Excess H^+ ion concentration

The acid is quickly dispersing from the system.

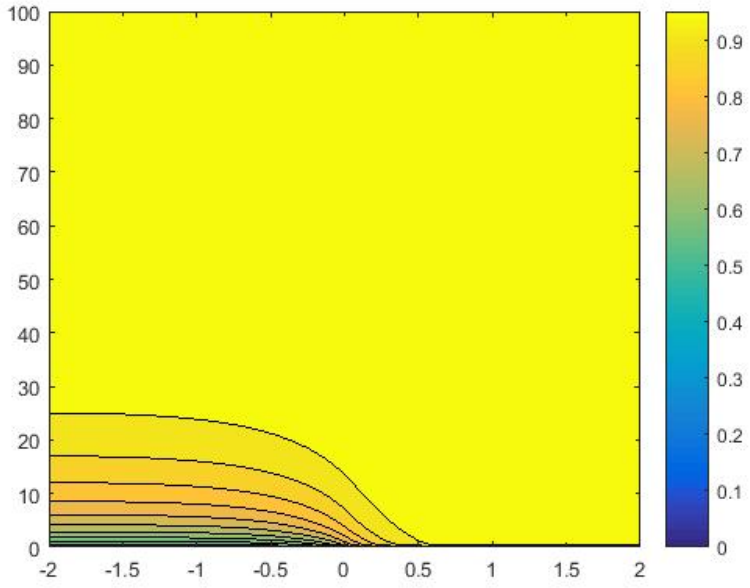


FIGURE 8. Chemo drug concentration

The chemotherapy drug is prevalent in the system.

Eventual tumor invasion graphs

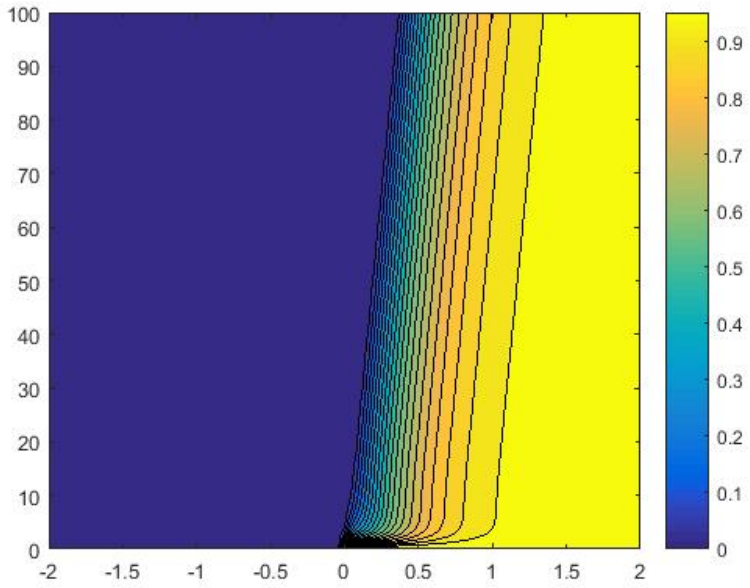


FIGURE 9. Normal cell density

The normal cells are slowly dying off.

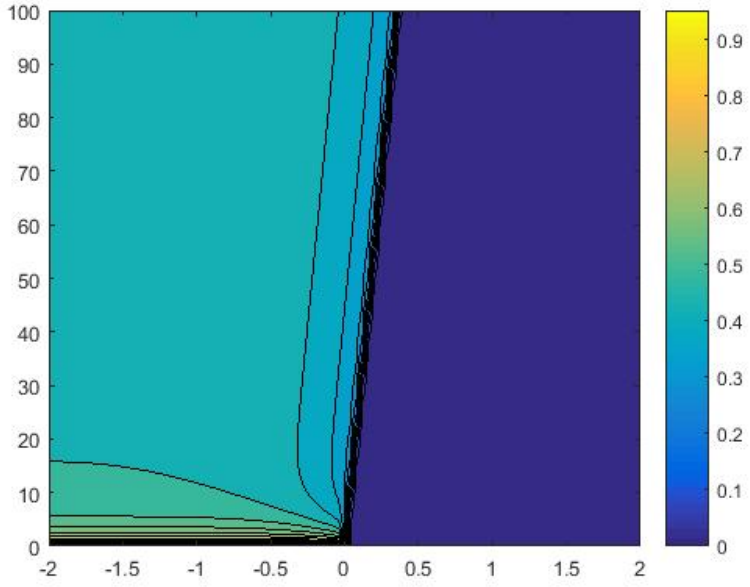


FIGURE 10. Tumor cell density

The tumor cells are slowly multiplying.

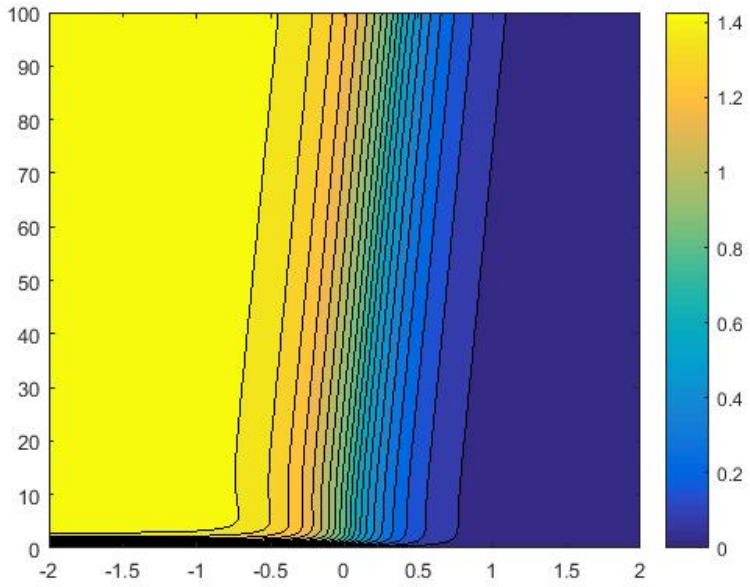


FIGURE 11. Excess H^+ ion concentration

The acid is gradually increasing.

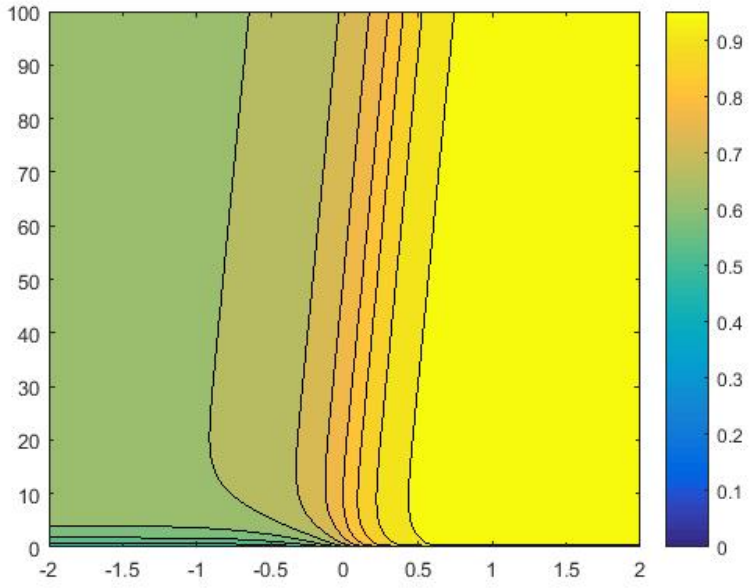


FIGURE 12. Chemo drug concentration

The chemotherapy drug is being used up.

Eventual tumor clearance graphs

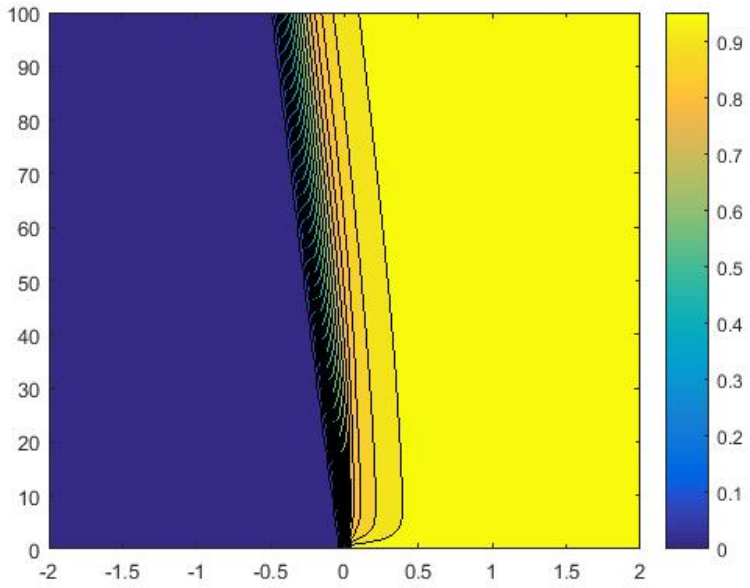


FIGURE 13. Normal cell density

The normal cells are very gradually increasing and expanding.

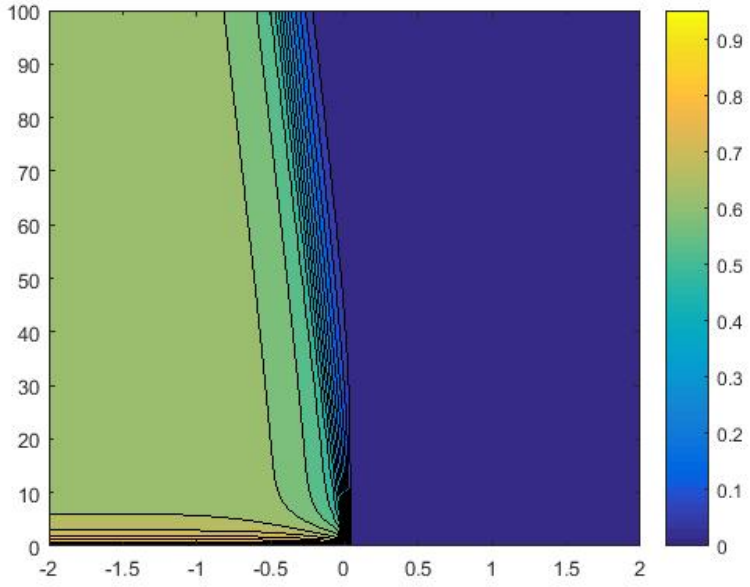


FIGURE 14. Tumor cell density

The tumor cells are very gradually decreasing.

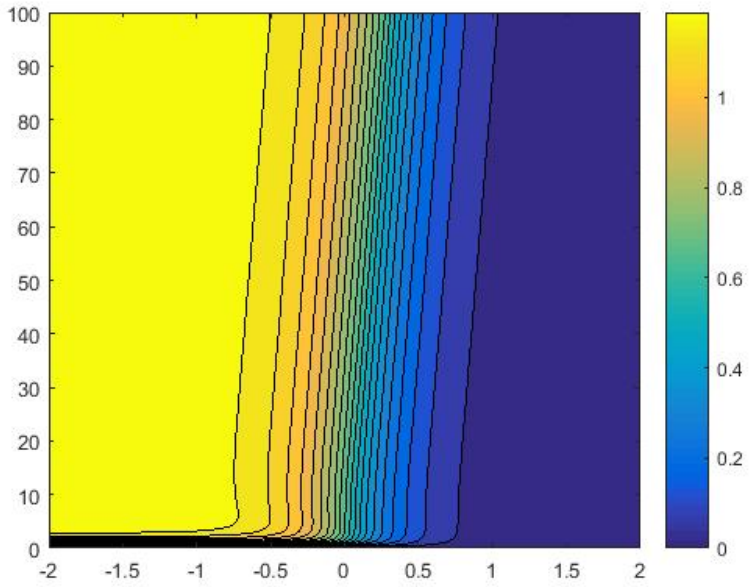


FIGURE 15. Excess H^+ ion concentration

The excess acid remains in the system.

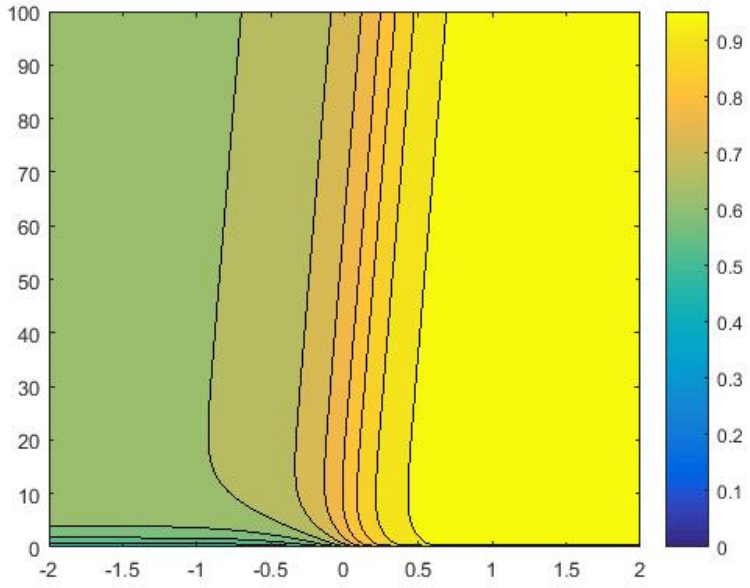


FIGURE 16. Chemo drug concentration

The chemotherapy drug is being used up.

Tumor Invasive State

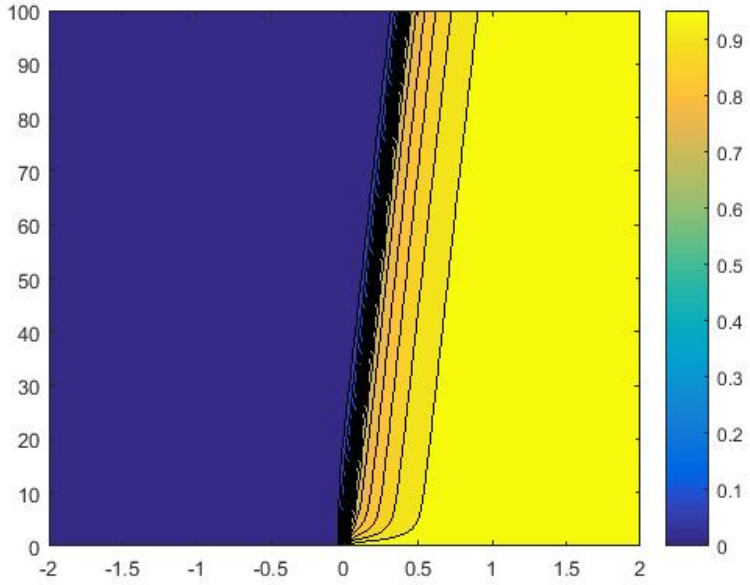


FIGURE 17. Normal cell density

The normal cells are dying off slowly.

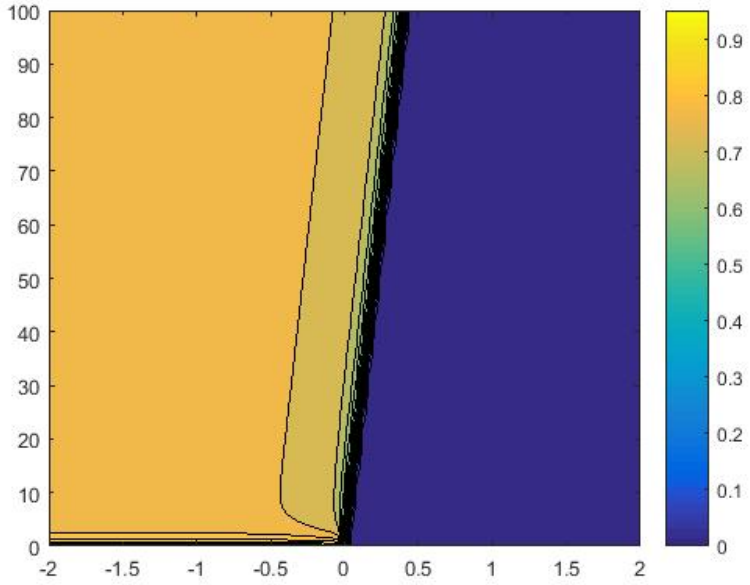


FIGURE 18. Tumor cell density

The tumor cells are multiplying.

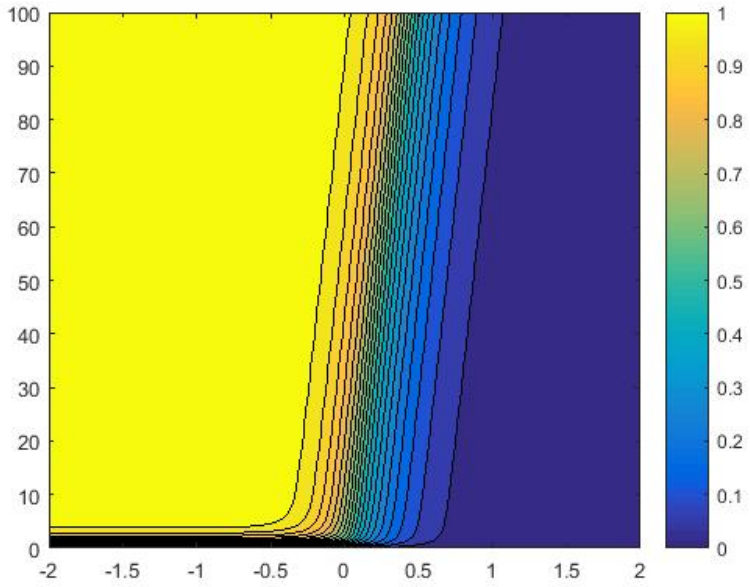


FIGURE 19. Excess H^+ ion concentration

Excess acid is pervading the system.

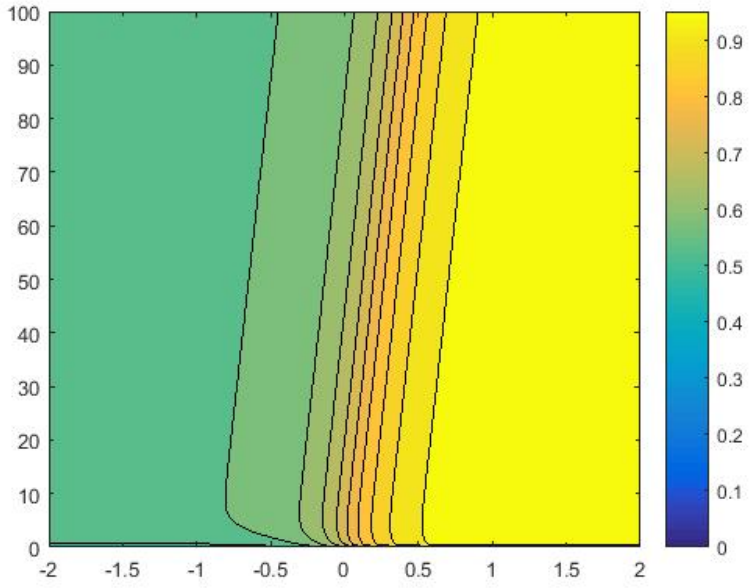


FIGURE 20. Chemo drug Concentration

The chemotherapy drug is being used up.

Competition between E_2 and E_4

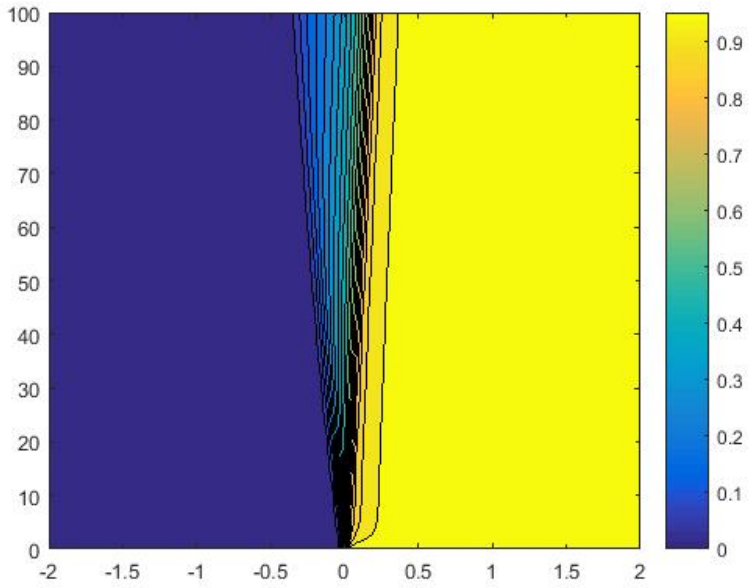


FIGURE 21. Normal cell density

The normal cells are neither increasing nor decreasing drastically.

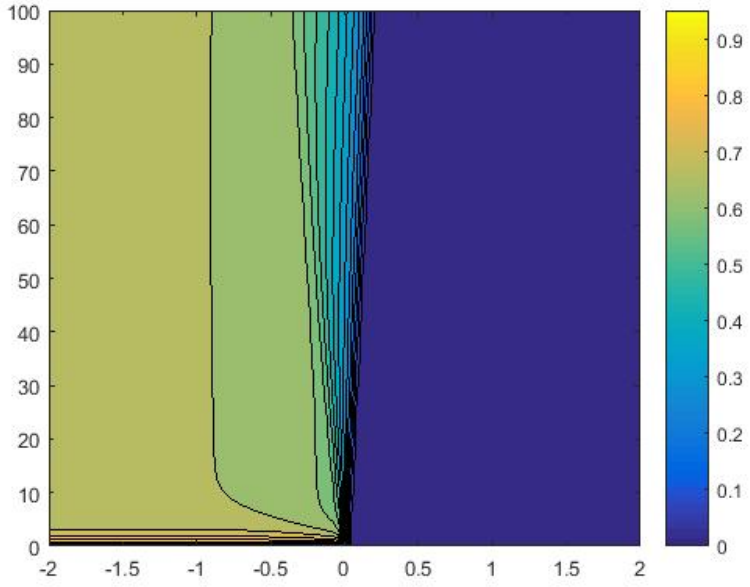


FIGURE 22. Tumor cell density

The tumor cells are neither increasing or decreasing drastically.

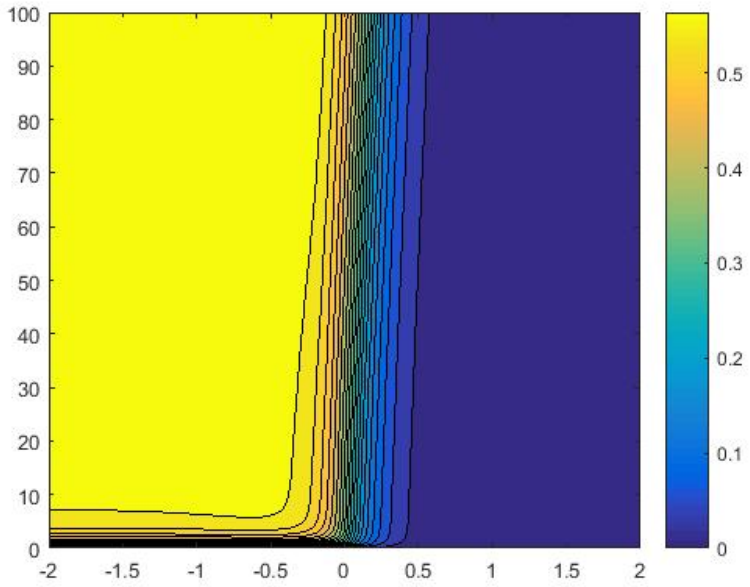


FIGURE 23. Excess h^+ ion concentration

Excess acid remains in the system.

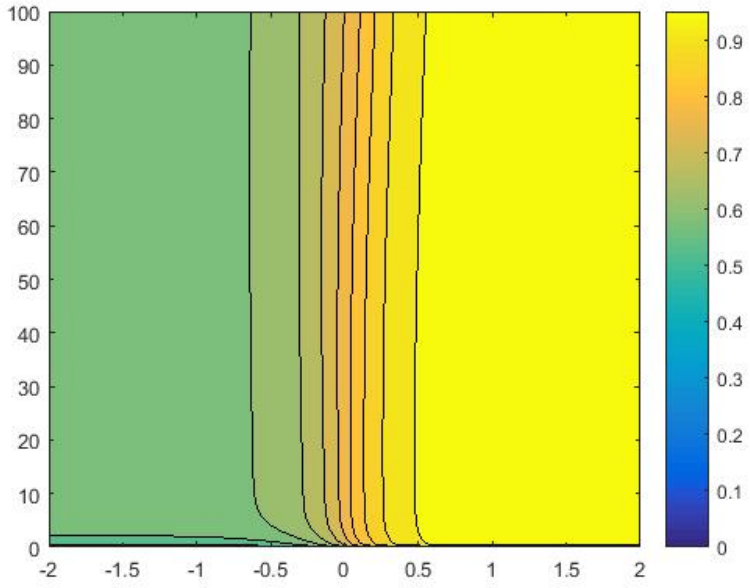


FIGURE 24. Chemo drug concentration

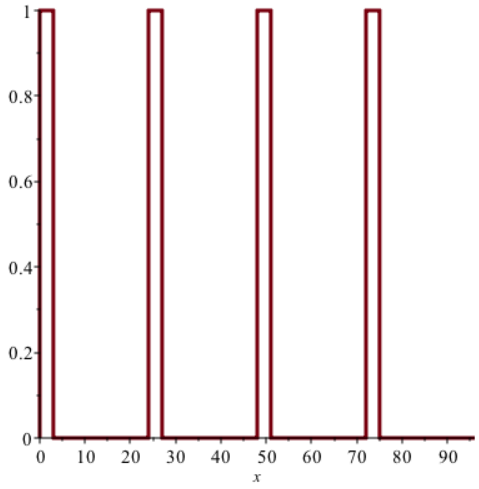
The chemotherapy drug is being used up.

7. Periodic Infusion

In this chapter is the numerical simulations for periodic infusion of the chemotherapy drug, that is, where we use the weighted boxcar function in chapter 3. Below is a graphical interpretation of this function. Note that the below picture only represents four cycle where as the actual function has N cycles. In this project we considered a 24 day cycle, 3 of which we infuse chemotherapy drugs, and 21 of which we do not infuse chemotherapy drugs. We chose the number of treatment cycles, N=10. It is also important to note that we are using deparameterized time in which

$$t = r_1 s,$$

where r_1 is of $O(10^{-}6)$, t is dimensionalized time, and s is nondimensionalized time.
Note that the x-axis is nondimensionalized time.



These specific parameter values remain the same for all parameter sets,
$\alpha_1 = 1,\ \alpha_2 = .5,\ \beta_2 = 1.$

Parameter Values	**Stability/Existence**	**Figures**
$\beta_3 = 60,\ \beta_4 = 10, \delta_1 = 1.5,$ $\delta_2 = 1.1,\ \delta_3 = 10,\ \delta_4 = 1.1$	E_1 unstable, E_2 stable, E_3 DNE, E_4 DNE	figures 25-30
$\beta_3 = 60,\ \beta_4 = 10, \delta_1 = 1.5,$ $\delta_2 = .8,\ \delta_3 = 10,\ \delta_4 = 1.1$	E_1 unstable, E_2 stable, E_3 stable, E_4 unstable	figures 31-36
$\beta_3 = 50,\ \beta_4 = 10, \delta_1 = 0.5,$ $\delta_2 = .8,\ \delta_3 = 15,\ \delta_4 = 2$	E_1 unstable, E_2 stable, E_3 stable, E_4 unstable	figures 37-42
$\beta_3 = 90,\ \beta_4 = 10, \delta_1 = 0.5,$ $\delta_2 = .4,\ \delta_3 = 15,\ \delta_4 = 1$	E_1 unstable, E_2 unstable, E_3 stable, E_4 DNE	figures 43-48
$\beta_3 = 90,\ \beta_4 = 10, \delta_1 = 0.5,$ $\delta_2 = .55,\ \delta_3 = 35,\ \delta_4 = 1$	E_1 unstable, E_2 stable, E_3 unstable, E_4 stable	figures 49-54

We have again drawn contour plots to represent the densities and concentrations. We also produce snapshots of the densities of the normal and tumro cells for every 50 days over the

interval of 250 days. For the snapshots, we chose $t_0 \equiv 0$ days, $t_1 \equiv 50$ days, $t_2 \equiv 100$ days, $t_3 \equiv 150$ days, $t_4 \equiv 200$ days, and $t_5 \equiv 250$ days.

Tumor free state graphs

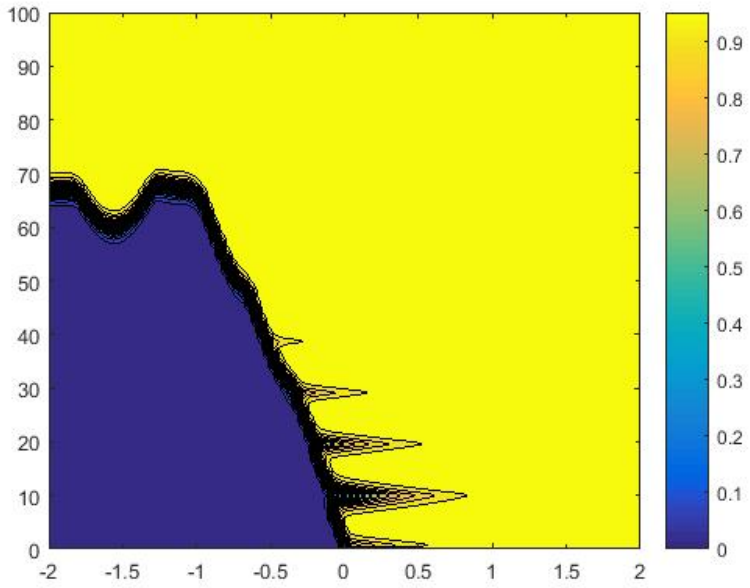


FIGURE 25. Normal cell density

The normal cells are increasing rapidly.

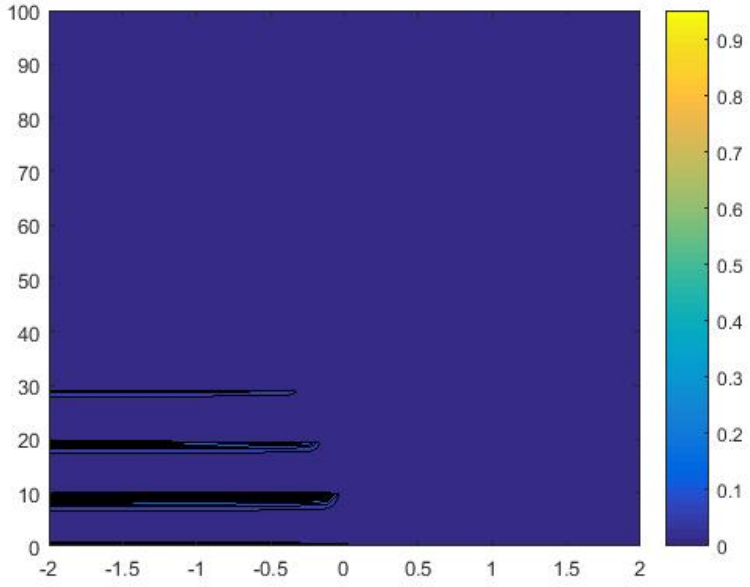


FIGURE 26. Tumor cell density

The tumor cells are dying off rapidly.

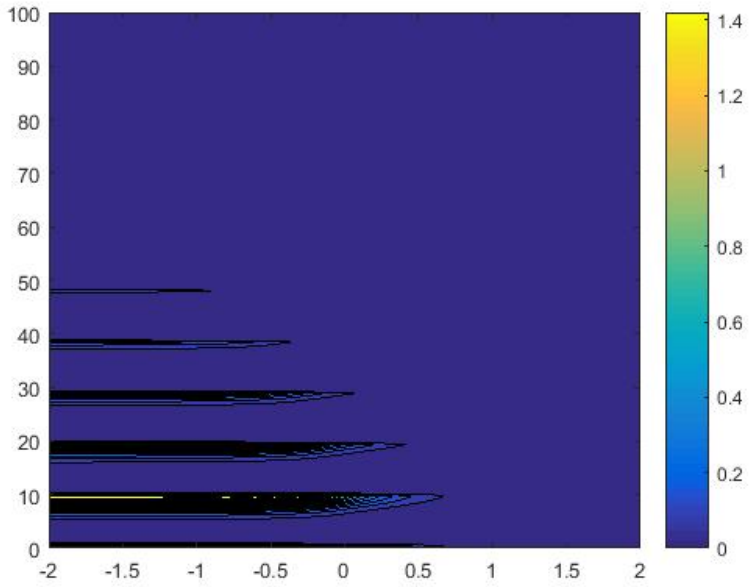


FIGURE 27. Excess H^+ ion concentration

The excess acid is leaving the system rapidly.

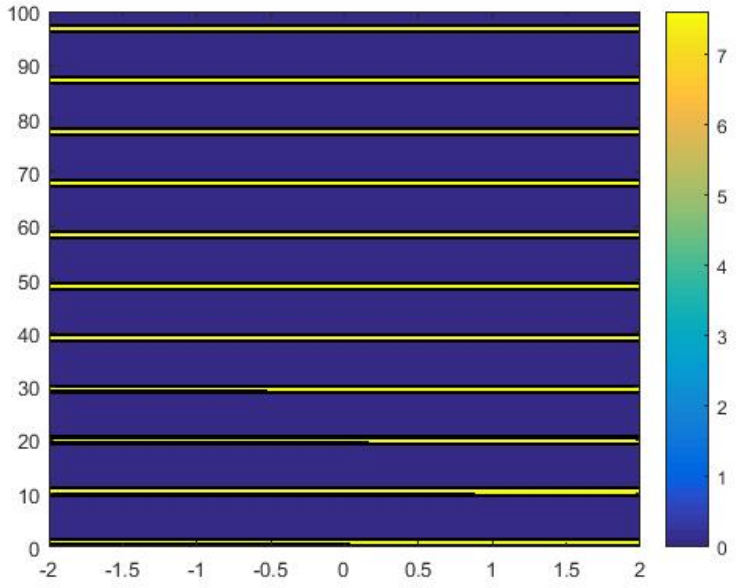


FIGURE 28. Chemo drug concentration

The chemotherapy drug is prevalent.

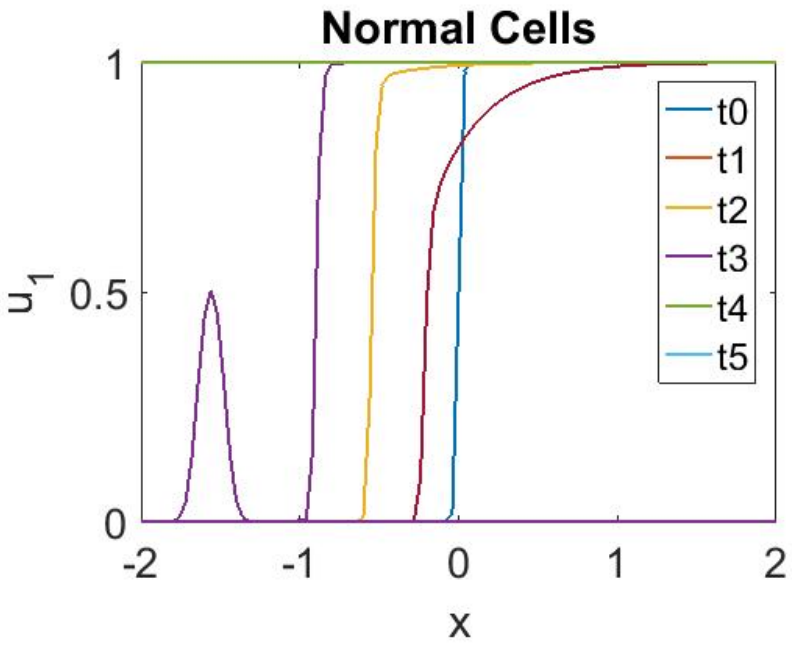


FIGURE 29. Snapshots of densities of normal cells

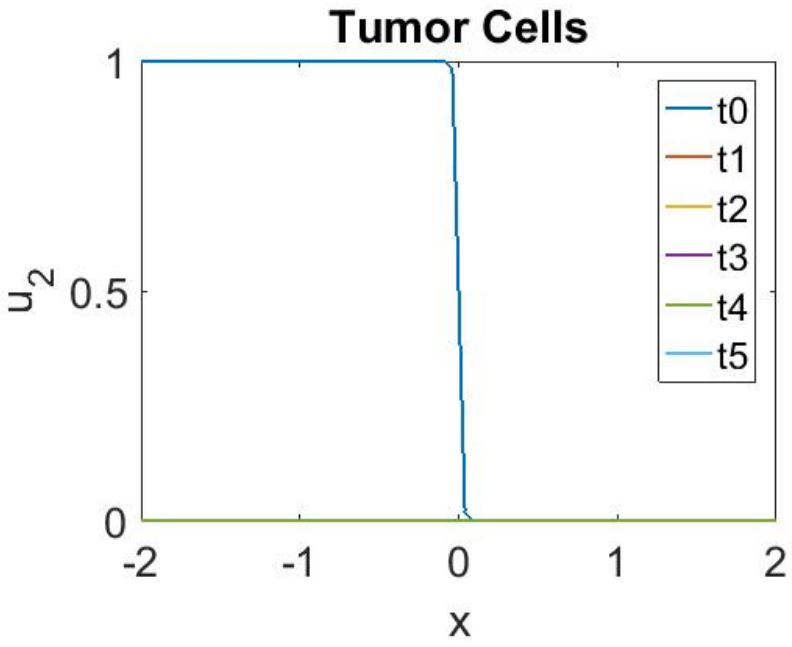


FIGURE 30. Snapshots of densities of tumor cells

Eventual tumor invasion state

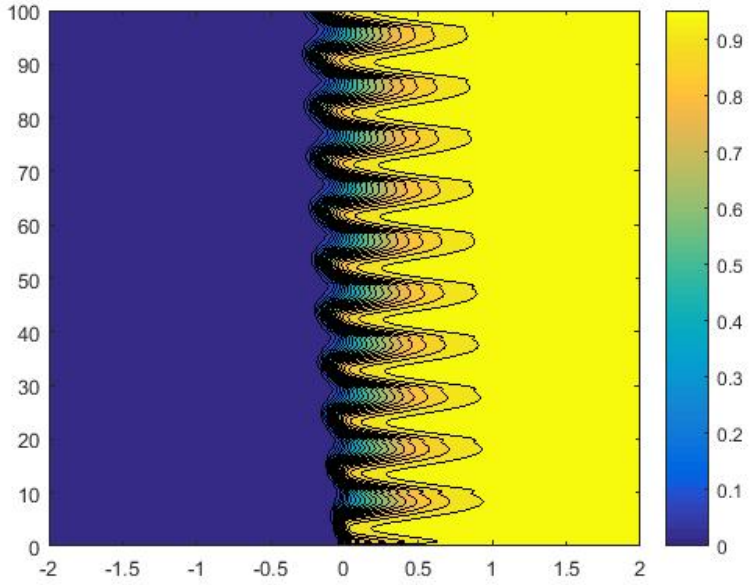


FIGURE 31. Normal cell density

The normal cells are neither dying off nor growing.

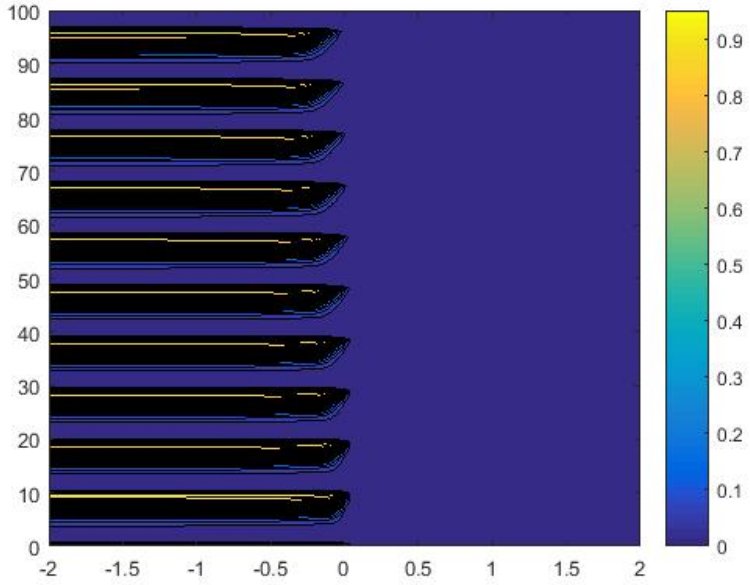


FIGURE 32. Tumor cell density

The tumor cells are neither increasing nor decreasing.

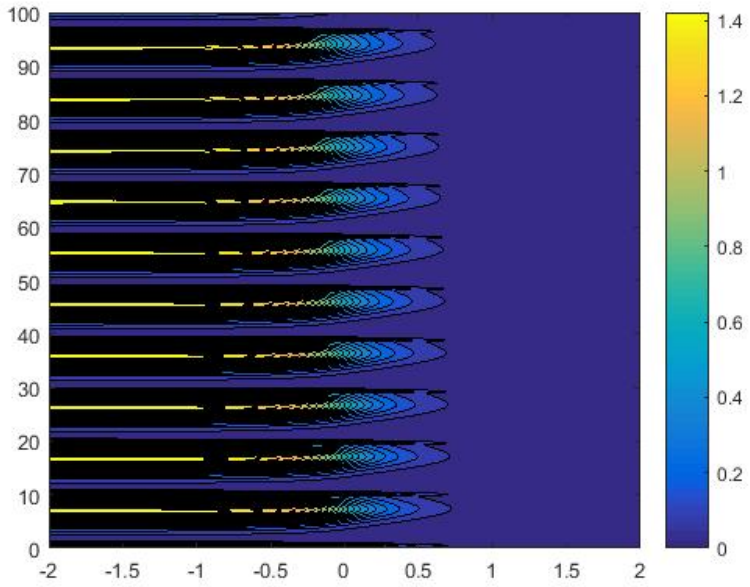


FIGURE 33. ExcessH^+ ion concentration

Excess acid is still present in the system.

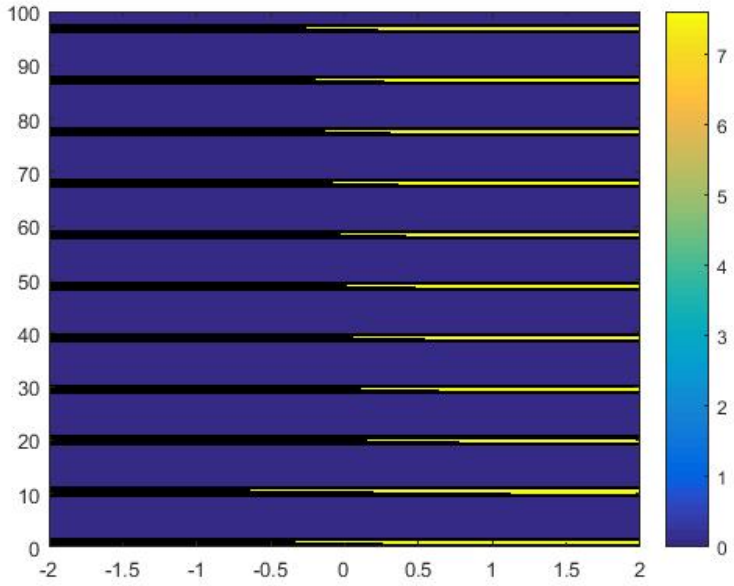


FIGURE 34. Chemo drug concentration

The chemotherapy drug is being used up.

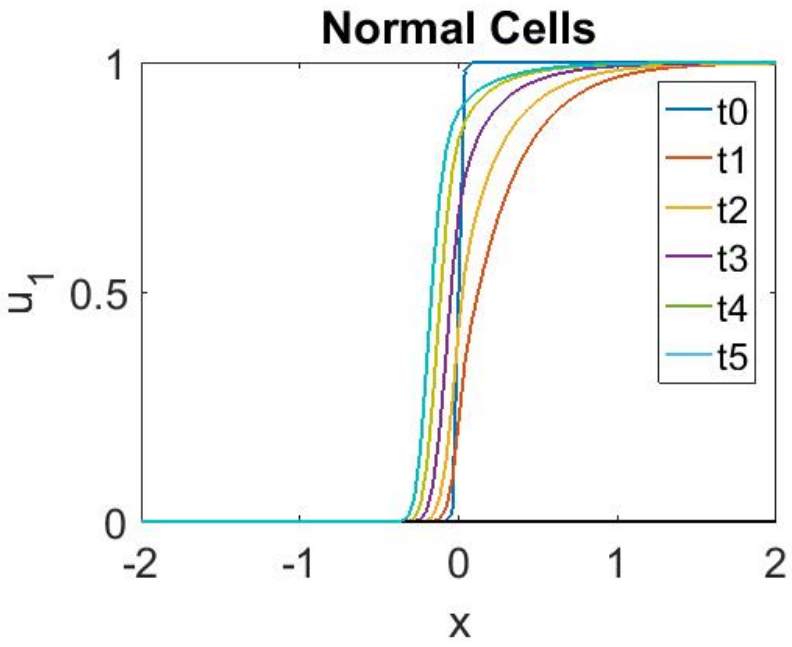


FIGURE 35. Snapshots of densities of normal cells

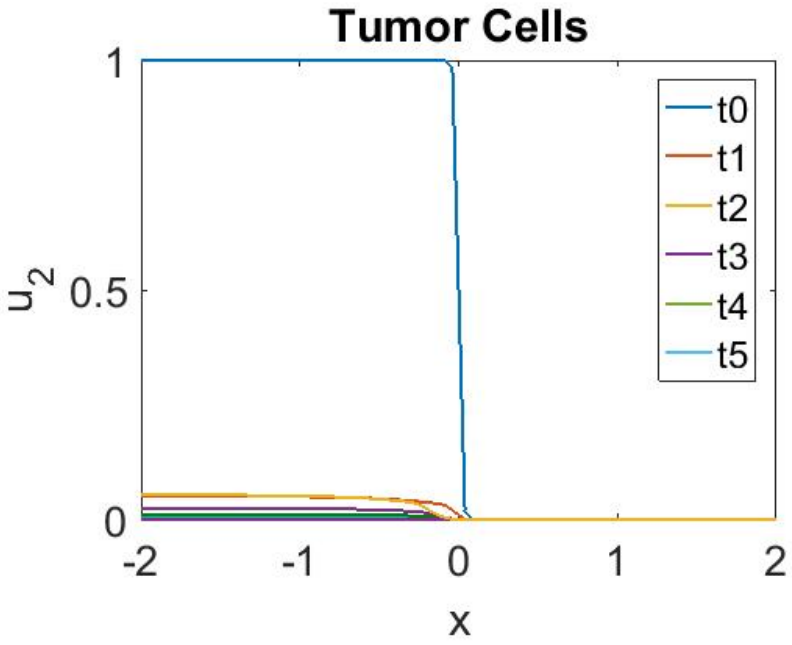


FIGURE 36. Snapshot of densities of tumor cells

Eventual tumor clearance state

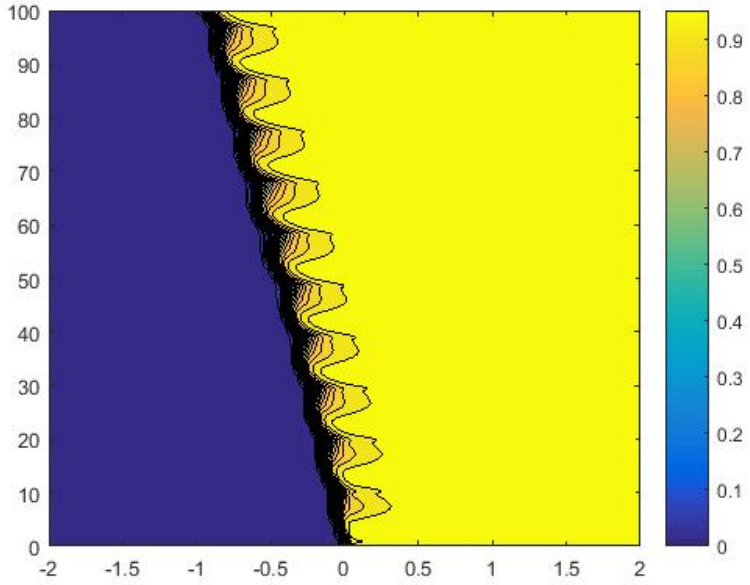


FIGURE 37. Normal cell density

The normal cells are gradually increasing.

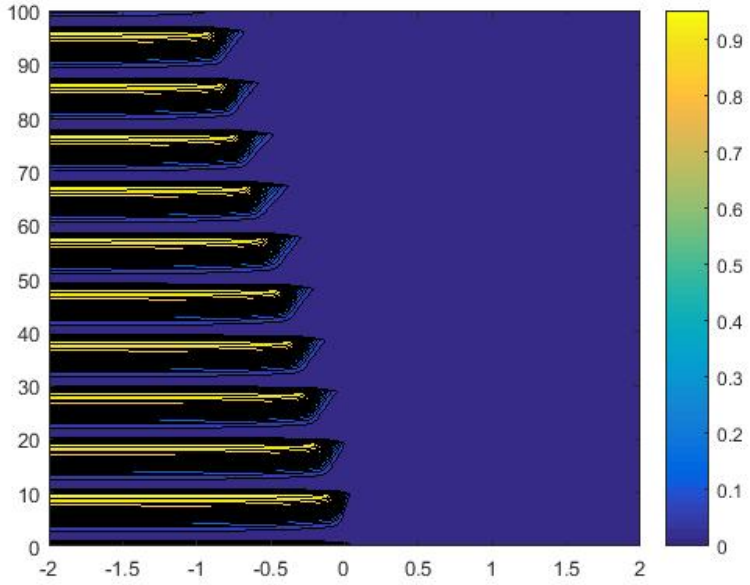


FIGURE 38. Tumor cell density

The tumor cells are dying off.

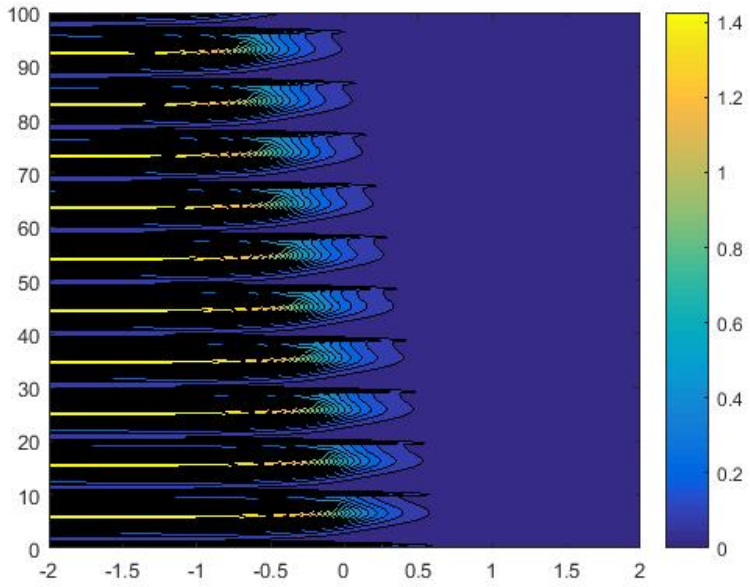


FIGURE 39. Excess h^+ ion concentration

Excess acid is slowly decreasing.

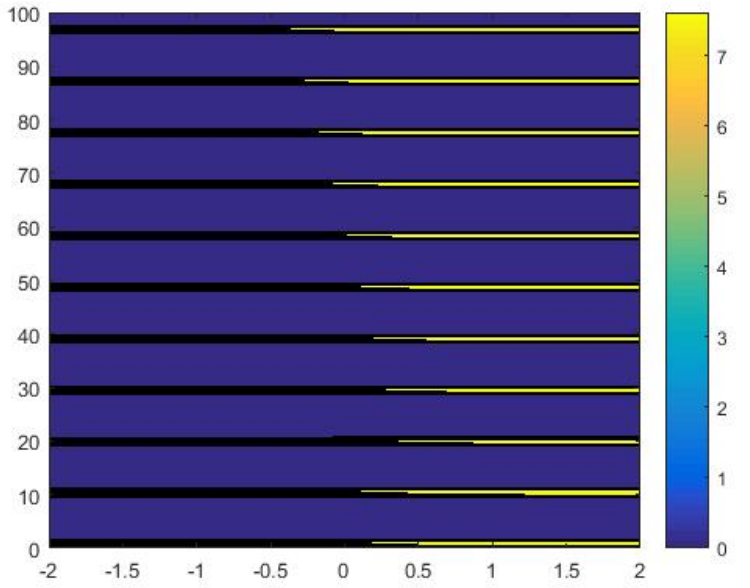


FIGURE 40. Chemo drug concentration

The chemotherapy drug is being used up.

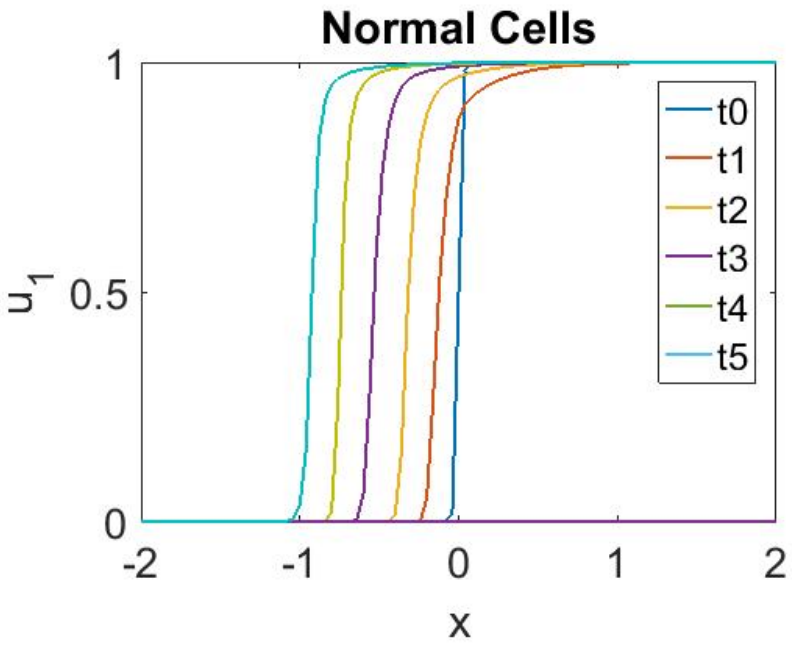


FIGURE 41. Snapshot of densities of normal cells

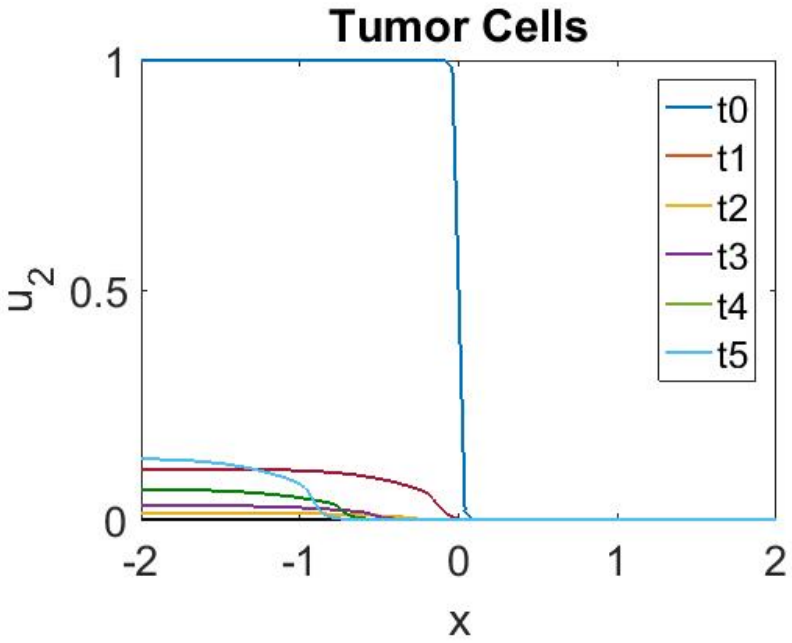


FIGURE 42. Snapshot of densities of tumor cells

Tumor invasive state graphs

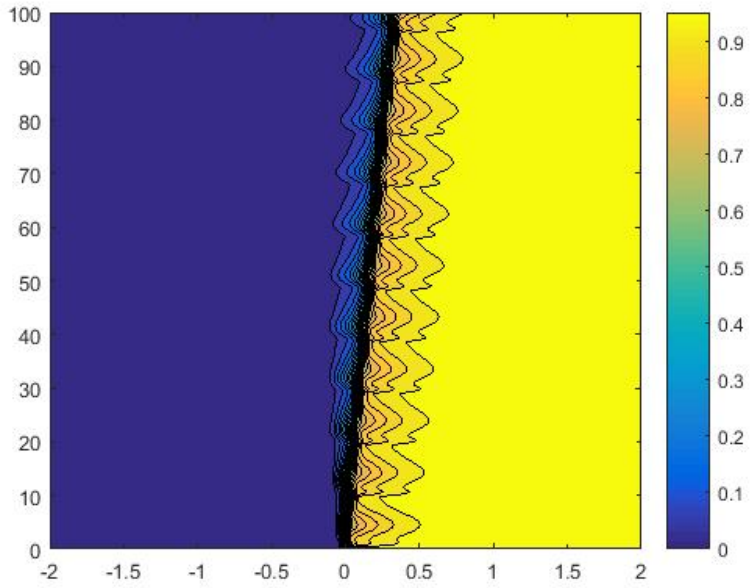


FIGURE 43. Normal cell density

The normal cells are gradually dying off.

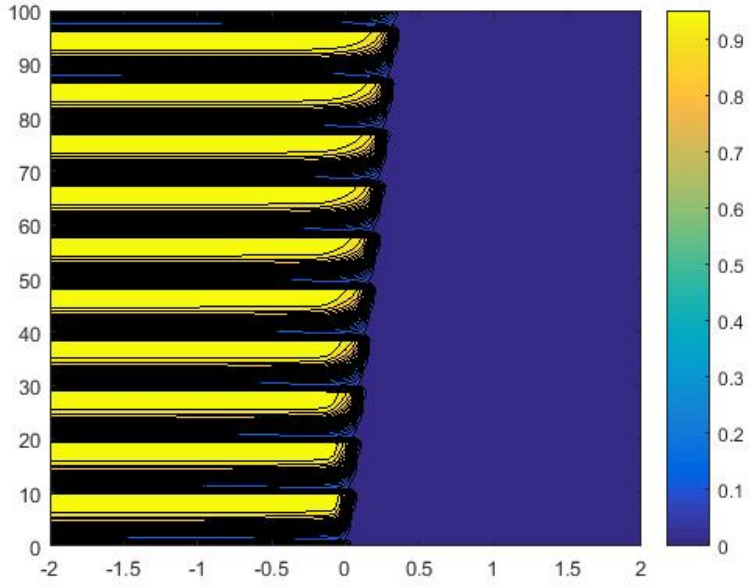


FIGURE 44. Tumor cell density

The tumor cells are gradually increasing.

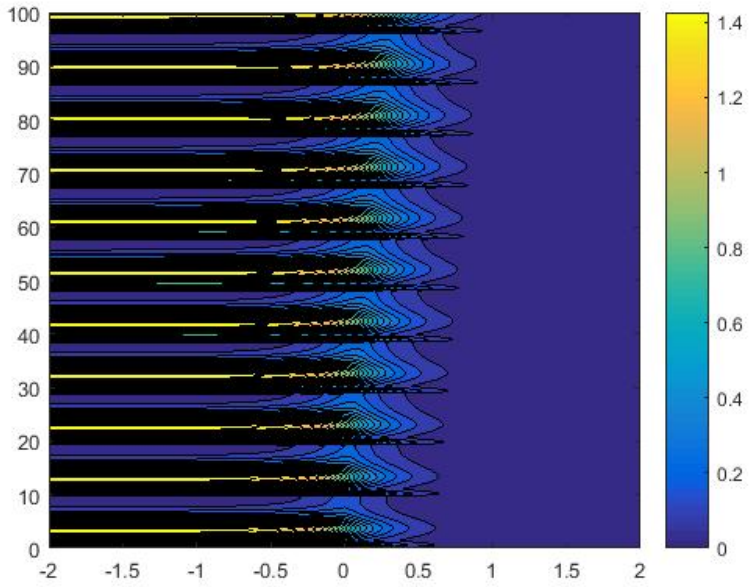


FIGURE 45. Excess H^+ ion concentration

Excess acid is increasing.

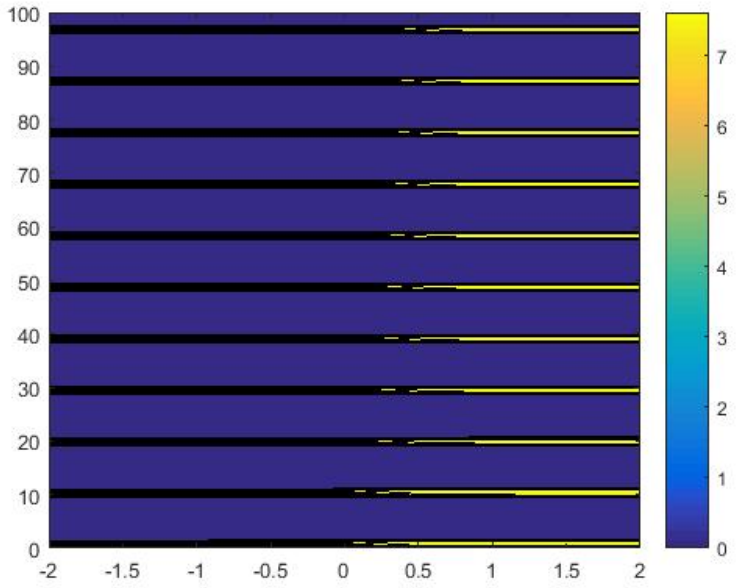


FIGURE 46. Chemo drug concentration

The chemotherapy drug is being used up.

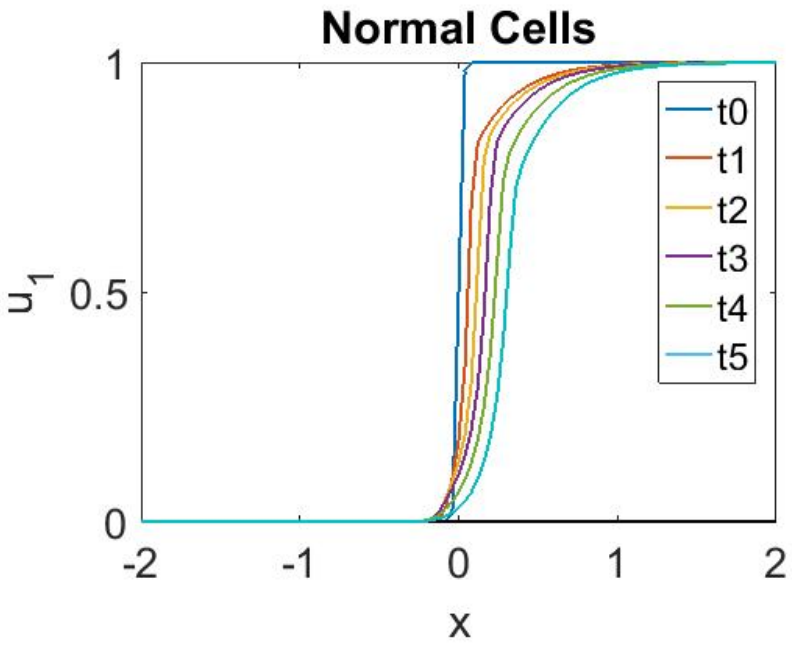


FIGURE 47. Snapshots of densities of normal cells

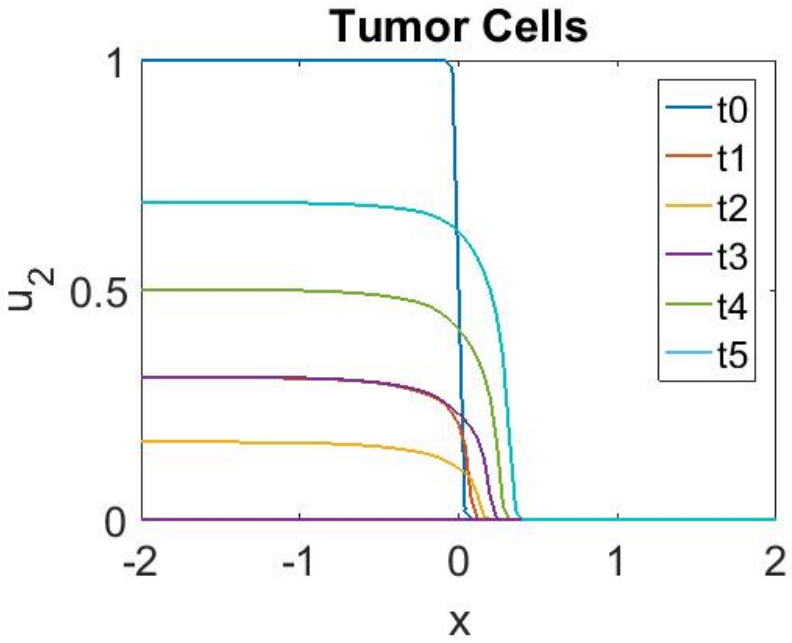


FIGURE 48. Snapshots of densities of tumor cells

Competition between E_2 and E_4

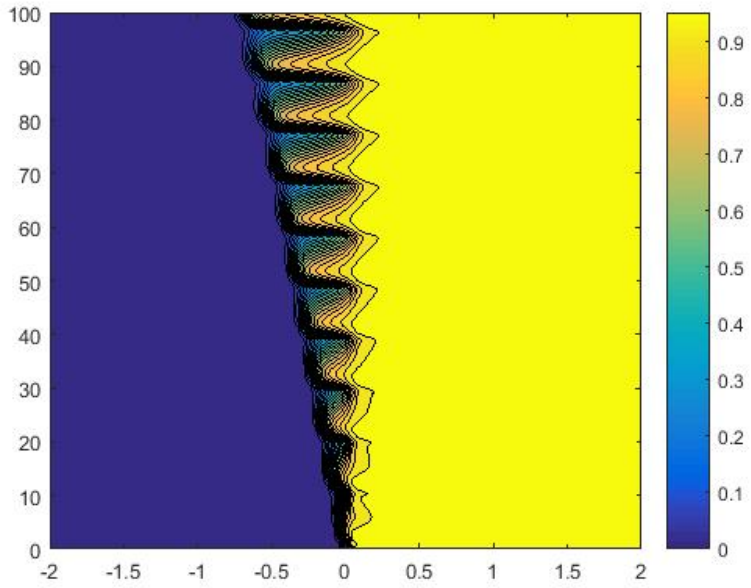


FIGURE 49. Normal cell density

The normal cells are very slowly increasing.

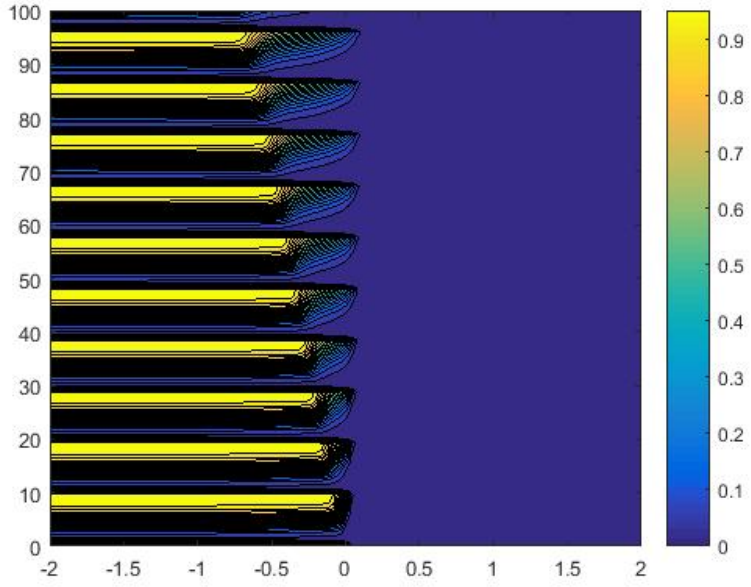


FIGURE 50. Tumor cell density

The tumor cells are very slowly dying off.

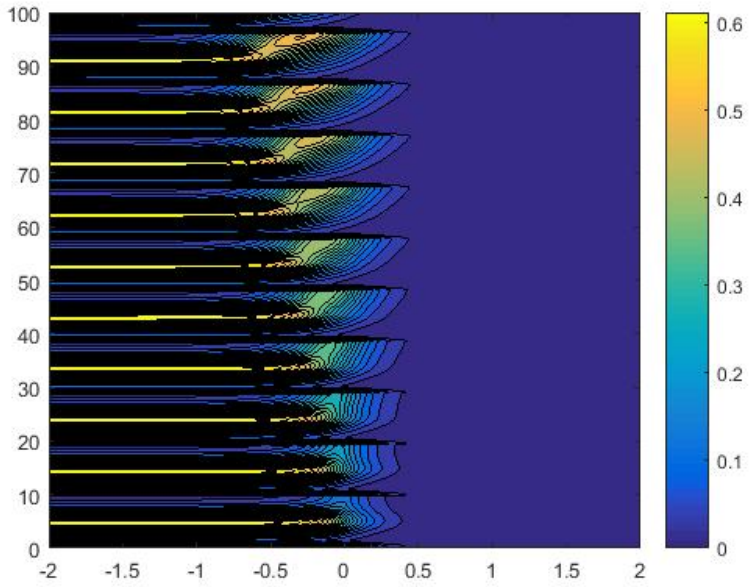


FIGURE 51. Excess H^+ ion concentration

Excess acid is still in the system.

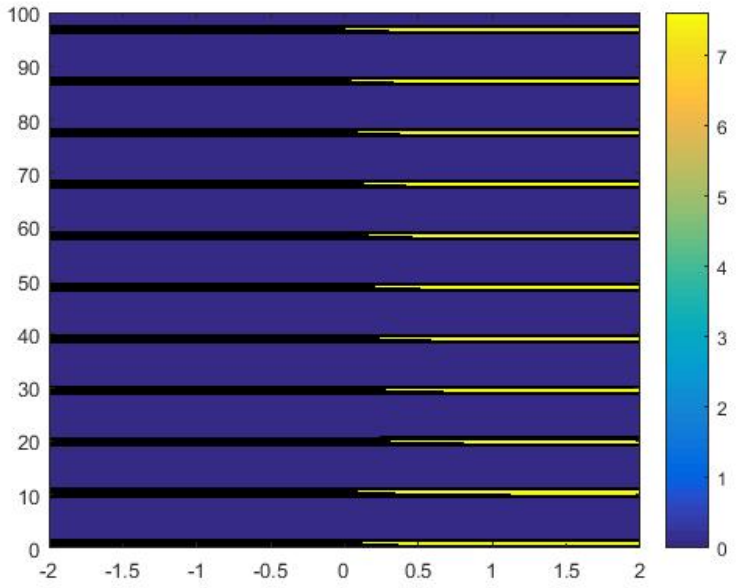


FIGURE 52. Chemo drug concentration

The chemotherapy drug is being used up.

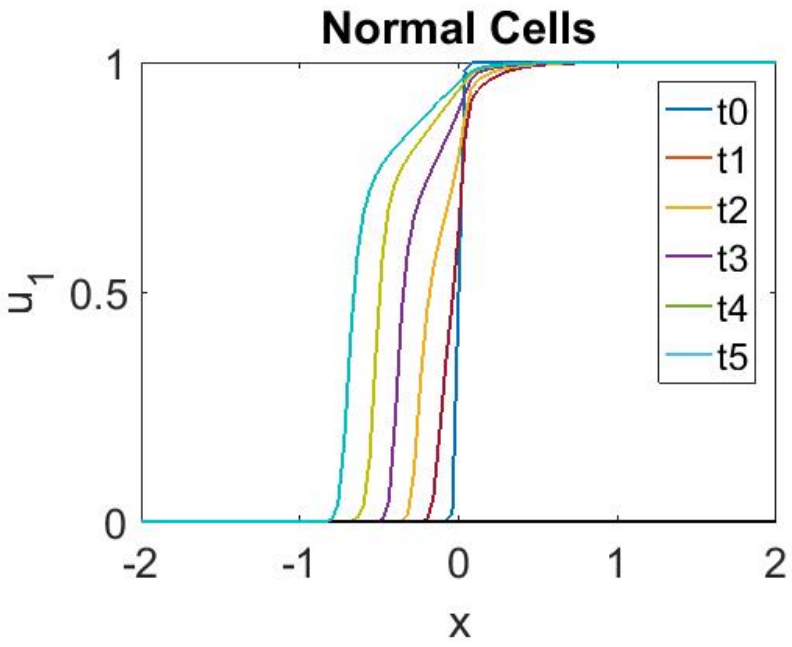


FIGURE 53. Snapshots of densities of normal cells

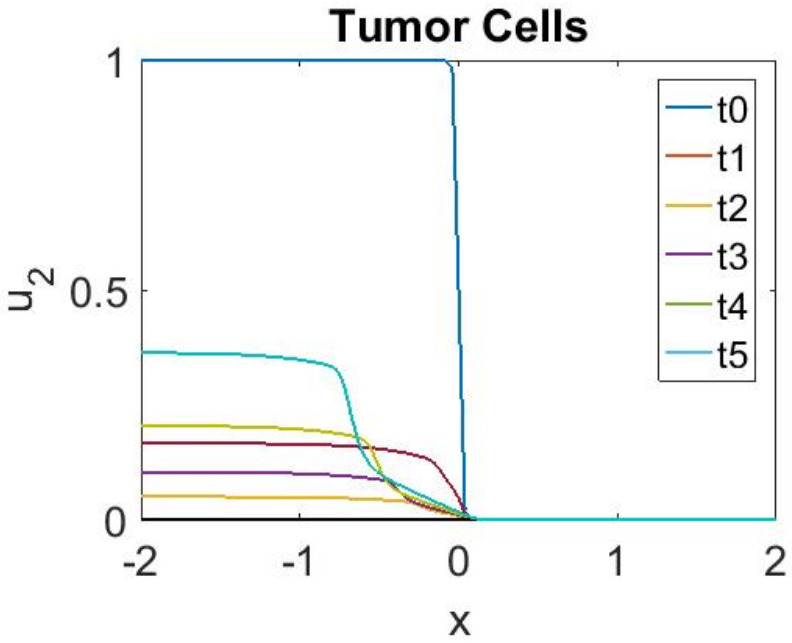


FIGURE 54. Snapshots of densities of tumor cells

8. Conclusion

Acid mediated tumor invasion as well as the Warburg Effect are still aspects of biology that are not very well understood. Our purpose was to analyze the complex interactions between normal and tumor cells in an acidic environment. In this work, we have contributed a mathematical model the we believe accurately describes these interactions in an acidic environment and acts as an extension of the previous work done by Gatenby and Gawlinski. Further research can be done either through modifying the system further, or by adjusting the time of the periodic infusion function, among other changes.

9. Works Cited

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(8) Schiesser, William E. Partial Differential Equation Analysis in Biomedical Engineering: Case Studies with MATLAB, Cambridge University Press, 2013.