

Report Assignment 1: A Cancer Model

The first report assignment concerns a mathematical model of cancer. It is based on an article by John D. Nagy [Competition and natural selection in a mathematical model of cancer. *Bulletin of Mathematical Biology* 66, pp. 663–687, 2004]. This article presents exciting new research in an area that crosses the boundaries of mathematical biology and medicine. For this reason, we believe that Nagy’s model is a nice combination of what you will be learning for the first four weeks of this course (and then some, but we will simplify the model so that it suits our curriculum).

A malignant tumour is a dynamic mishmash (amalgamation) of various groups of cells (cell phenotypes). We will consider two distinct cell population: cancer cells (parenchyma); and healthy cells that are controlled by the cancer cells (stroma). These cell populations compete over resources, but they also cooperate to maintain tumour viability. This makes the model quite complex. So let us handle it in small steps.

1 Blood and Oxygen as Limited Resources

All cells within a tumour compete for oxygen. The oxygen concentration C in a patient’s tissue is expressed as partial pressure (measured in mmHg). Under normal conditions, the maximum oxygen pressure C_{\max} is approximately 95 mmHg. Oxygen is supplied by blood and, therefore, the density v of blood microvessels in a cell population is what we may think of as the *nutrition* for the oxygen concentration. In other words, oxygen concentration $C(v)$ is constrained by blood microvessel density v .

Assignment 1 *Formulate a symbolic expression which describes how oxygen concentration $C(v)$ increases as a function of microvessel density v . The saturation level is C_{\max} .*

Assignment 2 *It has been estimated for a tumour in which $v = 1$ that the oxygen concentration $C(1)$ is about 40 mmHg. Use this information as well as $C_{\max} = 95$ mmHg to insert numeric values for the constants in the expression found in Assignment 1. Now, plot $C(v)$ in MATLAB and describe what it means.*

An expression for C as a function of v is important because blood microvessel density relates in a simple way to the mass x of parenchyma cells (measured in g). The relation is $v = z/x$, where z is a measure for the mass of microvessels in the tumour¹. The parenchyma mass x is a quantity that we are particularly interested in since the development of this mass over time tells us whether the tumour is growing or dying. We would like to express this relationship by a function $\Phi(v)$ that describes the *per capita growth rate*² of the parenchyma population

The function $\Phi(v)$ is expressible as a function of v because v determines C , and the oxygen concentration C is the resource that limits cell population growth. Cells both divide (proliferate) when oxygen is available and undergo programmed cell death (apoptosis) when oxygen is unavailable. Consequently, we will split $\Phi(v)$ into two terms:

$$\Phi(v) = A a(C(v)) - B[1 - b(C(v))] , \quad (1)$$

¹Technically z is the mean length of tumour microvessels divided by the the mean microvessel length in one gram of healthy tissue. The result is a measure for the mass of the tumour microvessels.

²This means the change in population size during a small time interval divided by the population size. In other words, the growth rate that each individual contributes to a population on average.

Cell line	A (g/day)	B (g/day)	k_a (mmHg)	k_b (mmHg)
wild-type	0.05385	0.05331	0.76	0.4
p53 mutant	0.05385	0.02667	0.53	0.095

Table 1: Parameters for the function $\Phi(v)$ which describes tumour parenchyma per capita growth rate.

where $Aa(C)$ describes cell proliferation and $B[1 - b(C)]$ describes cell apoptosis. As C increases, a increases until a saturation level A is reached while b decreases from a level B . The oxygen concentration C can be thought of as the *nutrition* for the cell population growth while k_a and k_b are the half-saturation constants for the a and b functions, respectively.

Assignment 3 Formulate symbolic expressions for $a(C)$ and $b(C)$ such that they both have the range $[0, 1]$. Use C^2 in these expressions (cf. **C**: Exercise 46 of Sec. 1.2.9). To make sure that $b(C)$ goes to 1 for C going to C_{\max} , introduce a saturation level σ into $b(C)$ which depends on C_{\max} and the half-saturation constant k_b . Insert your expressions for $a(C)$ and $b(C)$ into Equation 1 to get an expression for $\Phi(C)$.

Assignment 4 Write a MATLAB program that does the following: (a) constructs variables for the input parameters A , B , k_a , k_b , and C_{\max} , (b) computes σ , (c) computes a vector of C -values from a vector of v -values as in Assignment 2, (d) computes a vector of a -values and a vector of b -values, (e) computes a vector of Φ -values and plots them as a function of the v -values. Run the program with the input parameters for each of the cancer cell types in Table 1 and describe your plots.

2 Tumour Growth

While we have encountered no exponential functions so far in this mathematical model of cancer, tumour growth is indeed exponential when oxygen resources are available.

The previous section was about finding a mathematical expression for the per capita growth rate Φ of the parenchyma population. The per capita growth rate describes the development of a population over time. In particular, it means that the population growth follows the autonomous differential equation:

$$\frac{1}{x} \frac{dx}{dt} = \Phi(v) = \Phi(z/x) . \quad (2)$$

Assignment 5 For a moment let us assume that microvessel density is constant such that $v = \hat{v}$ (this happens when microvessels grow at the same rate as the parenchyma population such that z/x is constant). Under this assumption, where $\Phi(\hat{v})$ is independent of x , show that tumour growth is exponential by finding a function $x(t)$ which satisfies the differential equation (2).

As mentioned introductorily, the stroma population is controlled by the parenchyma population. This works as follows: The parenchyma population produces a signal (angiogenesis signal) which controls the *per capita growth rate* of VECs (vascular endothelial cells) in the stroma. Like blood microvessels in the parenchyma, the VECs are cells that help the blood supply in the stroma. Let us call the tumour VEC per capita growth rate Ψ . There is a *linear* relationship between the angiogenesis signal h and Ψ . The angiogenesis signal is again a function of $C(v)$.

Assignment 6 Write down $\Psi(v)$ as a function of the angiogenesis signal h . Use α as slope and $-\beta$ as initial per capita growth rate. Look up α and β in Table 2 and determine whether the stroma population always grows or whether it can also decay given that $h \geq 0$.

α	β	r	ξ
0.06	0.04	0.28	0.06

Table 2: Parameters for the function $\Psi(v)$ which describes tumour VEC per capita growth rate.

It remains to model the angiogenesis signal $h(C)$ as a function of oxygen concentration C . The signal is 0 when C is 0. As long as C is small, the signal increases with increasing C . However, as C grows large, cells will be flushed with oxygen, and they will stop producing the signal. This means that h will start decreasing as C increases after the function has reached a maximum. We model this by writing $h(C)$ as a product of two functions:

$$h(C) = h_1(C)h_2(C) .$$

The increase is modelled by $h_1(C)$ and it is *proportional* to C . The decrease is modelled by $h_2(C)$ and it *decays exponentially* with C .

Assignment 7 *Formulate symbolic expressions for $h_1(C)$ and $h_2(C)$. Use H_1 as the proportionality factor of $h_1(C)$. Use H_2 as the initial value and ξ as the decay rate of $h_2(C)$. Combine $h_1(C)$ and $h_2(C)$ into $h(C)$. To obtain $h(C)$ in its final form, use the following simplifying relation $r = H_1H_2$.*

Assignment 8 *Use MATLAB to plot the tumour VEC per capita growth rate $\Psi(v)$ as a function of v . To do this, use your expressions for $h(C)$ and $C(v)$ as well as the parameter values in Table 2. Describe the plot. Where is the maximum?*

3 Tumour Dynamics

The differential equation (2) for the per capita growth rate of the parenchyma population provides some information about how the parenchyma population develops over time. Using the per capita growth rate of VECs $\Psi(v)$, we can formulate a similar differential equation to describe the development of the VECs in the tumour over time. Letting y denote the mass (in g) of VECs in the tumour, we have

$$\frac{1}{y} \frac{dy}{dt} = \Psi(v) . \quad (3)$$

This means that both x and y grow or decay exponentially (cf. Assignment 5). However, since v is in general not constant, we do not know the growth (or decay) rate. What we need is yet another differential equation to describe how v develops over time. And it turns out that the development of v depends on the density of VECs $w = y/x$ in the tumour. This means that we also need a differential equation to describe how w develops over time. In conclusion, the dynamics of our model is described by the following system of differential equations (the first two of which are equivalent to Equations 2 and 3):

$$\frac{dx}{dt} = \Phi(v)x \quad (4)$$

$$\frac{dy}{dt} = \Psi(v)y \quad (5)$$

$$\frac{dv}{dt} = -(\Phi(v) + \delta v)v + \gamma w \quad (6)$$

$$\frac{dw}{dt} = (\Psi(v) - \Phi(v))w . \quad (7)$$

Two new parameters appear in this set of equations, namely δ and γ . According to Nagy [2004], we can set $\delta = 0.004$ and $\gamma = 3$.

So far, our analysis of this cancer model has been abstract. In the following, our intension is to simulate tumour growth on a computer. This makes it possible for us to compute how a tumour of specific proportions would develop. For computer simulation, it is much more practical to work with vectors and matrices. And a system of differential equations can be formulated as a matrix equation of the form (C: pp. 702–704):

$$\frac{d\mathbf{u}}{dt} = \mathbf{A} \mathbf{u} . \quad (8)$$

Assignment 9 Rewrite Equations 4–7 as a matrix equation (8) where you specify the contents of the involved vector (\mathbf{u}) and matrix (\mathbf{A}). Note that $\mathbf{A}(v)$ has only one off-diagonal element which is nonzero. Try to give a biological explanation for the part of your matrix $\mathbf{A}(v)$ which is due to Equations 6–7. What names would you attach to the parameters δ and γ ?

Equations 4–7 is a rather complicated set of *nonlinear, first-order* differential equations. Finding an analytical solution is not at all straight forward. So what we would like to do is to make a *piecewise linear approximation* of the dynamics in our cancer model. We can do this using a *discrete time model* (cf. C: Sec. 2.1). But how do we rewrite the differential equations as *recurrence relations*? To solve this problem, we need to brush up on the theory of *derivatives*. As you probably know, the derivative of a function $f(t)$ with respect to t is defined by (C: Sec. 4.1)

$$f'(t) = \frac{df}{dt} = \lim_{\Delta t \rightarrow 0} \frac{f(t + \Delta t) - f(t)}{\Delta t} .$$

To make a piecewise linear approximation (with length of the line segments equal to Δt), we do as follows (C: Sec. 4.8):

$$\frac{df}{dt} \approx \frac{f(t + \Delta t) - f(t)}{\Delta t} . \quad (9)$$

This is all we need in order to rewrite a first-order differential equation as a recurrence relation that approximates the development over time piecewise linearly.

The anatomy of a first-order differential equation is

$$\frac{df}{dt} = g(t, f) .$$

If we use this with the approximation given by Equation 9, we have

$$f(t + \Delta t) \approx g(t, f(t))\Delta t + f(t) ,$$

where $g(t, f(t))$ is the right-hand side of the first-order differential equation which describes how the quantity f develops over time. This way of finding a piecewise linear approximation to the solution of a first order differential equation is called the *Euler method*. We can think of it as an approximative discrete time model with time steps of length Δt .

In matrix notation, the approximative discrete time version of our model is

$$\mathbf{u}(t + \Delta t) = (\mathbf{A}(v)\Delta t + \mathbf{I})\mathbf{u}(t) , \quad (10)$$

where $\mathbf{A}(v)$ is the matrix and $\mathbf{u}(t)$ is the vector constructed in Assignment 9 while \mathbf{I} is the 4×4 identity matrix. Note that v is an element of the \mathbf{u} -vector.

Assignment 10 Write a MATLAB program which constructs a variable $Dt = 10$ to denote the time step Δt and the vector $\mathbf{u}(0)$ from one of the sets of initial values given in Table 3. Then write two programs which, given the vector $\mathbf{u}(t)$, (a) retrieves v by indexing into $\mathbf{u}(t)$, (b) computes $\Phi(v)$ and $\Psi(v)$ using v , (c) constructs $\mathbf{A}(v)$ using Φ , Ψ , and v , and (d) takes a step in time by computing $\mathbf{u}(t + \Delta t)$ using Equation 10. When constructing $\mathbf{A}(v)$, use $\delta = 0.004$, $\gamma = 3$. The reason why you need two programs taking a step in time is that $\Phi(v)$ is different for the two different cell types in Table 1.

	x_0	y_0	v_0	w_0
Tumour 1	0.01	0.001	0.0	0.1
Tumour 2	0.01	10^{-5}	0.0	10^{-3}

Table 3: Initial parenchyma mass (x_0), VEC mass (y_0), microvessel density (v_0), and VEC density ($w_0 = y_0/x_0$) for two different tumours.

- Assignment 11 *Write a MATLAB program that step-by-step stores the result of a time step into two vectors of results: one \mathbf{u} -vector result and one time ($t + \Delta t$) result for each step. Take 15 steps in your discrete time model where you store results after each step. Plot x as a function of time by extracting the x -row from the \mathbf{u} -vector result. How do the two different tumours behave over time for each of the two cancer cell types?*
- Assignment 12 *Use your single-step MATLAB program to write a for-loop that takes N steps of length Δt . Decrease your step length Δt and increase N correspondingly to obtain a better piecewise linear approximation of the tumour dynamics. Finally, choose N and Δt such that you get smooth curves illustrating tumour development over 250 days. How good was the choice in Assignments 10 and 11 of $\Delta t = 10$ and $N = 15$. Describe what the curves tell you about the different cancer types.*

4 Tumour Viability

Tumour viability is qualitatively not different for the two cancer types. So, for this last part of the report, we will only consider cancer of the wild-type cell line.

The matrix $\mathbf{A}(v)$, which we encountered in the previous section, tells us something about how the tumour will behave in the nearest future. As is stated explicitly, \mathbf{A} is a function of the blood microvessel density v . And if we consider Equation 6, we see that the development of v is dependent on the VEC density w . This means that microvessel density and VEC density (v and w) are highly determinant for the development of the tumour. A *direction field* (cf. C: Sec. 11.1.1) is one way to determine the dynamics of v and w .

- Assignment 13 *Use the MATLAB command `quiver` to draw a direction field that shows the dynamics of $v \in]0, 1[$ and $w \in]0, 0.02[$ (use Equations 6 and 7). Note that to get a decent looking plot you need to scale the w -axis after computing the $(\frac{dv}{dt}, \frac{dw}{dt})$ -vectors. Write the scale you used in the plot-description of the w -axis. What does the direction field tell you? (Close-ups may be necessary to analyse the direction field properly.)*
- Assignment 14 *Use your plot from Assignment 4 to determine how small v needs to be for the tumour to decay. Suppose v is initially 0. Use your direction field to determine how small w needs to be initially for the tumour to decay eventually. Is your result consistent with your plots of tumour development from Assignment 12?*

We can use the concept of *eigenvalues* (LA: Chap. 3 and C: Sec. 11.1) to determine tumour viability. If all the eigenvalues of the matrix $\mathbf{A}(v)$ are negative (or zero), we can assume that the tumour will eventually die. If all the eigenvalues of $\mathbf{A}(v)$ are positive (or zero), we can assume that the tumour is viable, and that it will eventually kill the body it resides in. However, we must be careful. Our system of differential equations is not linear. This means that the eigenvalues are not constant. Thus we have to simulate the development of our eigenvalues over time to see if they approach a constant value.

Assignment 15 Use the MATLAB command `eig` to compute the eigenvalues of $A(v(t))$ for both Tumour 1 and Tumour 2. Get $v(t)$ by extracting the v -row from the u -vector result computed for each of the two different tumours in Assignment 12. Plot the eigenvalues as a function of time (one plot for each tumour). Do the eigenvalues converge toward constant values? Do they tell you whether the tumours are viable or not?

When you conclude your report, please summarise what you learned about cancer, mathematical modelling, and MATLAB as a result of working with Assignments 1–15.

List of Words

amalgamation	a merger of two or more things such that they form one (a mishmash)
angiogenesis	the formation of new blood vessels
apoptosis	a natural process of self-destruction in certain cells
endothelial cells	flat cells that cover the inside of vessels such as blood vessels
malignant	that cannot be controlled and is likely to cause death
parenchyma	the primary tissue of an organism
partial pressure	the pressure that one component of a mixture of gases would exert if it were alone in a container
perfusion	the injection of fluid into a blood vessel in order to reach an organ or tissues, usually to supply nutrients and oxygen
phenotype	an individual or a group of organisms exhibiting a particular set of physical or biochemical characteristics
proliferate	to increase rapidly in number or amount
stroma	the connective tissue framework of an organism
substrate	a substance on which something happens, a substrate may serve as a source of food for an organism or simply provide support
tumour	a mass of cells growing in or on a part of the body
vascular	of or containing veins
vascularization	the formation of vessels, especially blood vessels
viability	capability of growth and development

List of Quantities

x	mass (in g) of paranchyma cells
y	mass (in g) of VECs in the tumour
z	the mean length of tumour microvessels divided by the the mean microvessel length in one gram of healthy tissue (a measure for the mass of the tumour microvessels)
$v = z/x$	tumour vascularization (perfusion) measured in microvessel units per gram of parenchyma, also called tumour microvessel density
$w = y/x$	tumour VEC density (VECs are vascular endothelial cells contained in the stroma)
Φ	per capita growth rate of the paranchyma cells
Ψ	per capita growth rate of the VECs