A Mathematical Model of Basal Cell Carcinoma

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About two years ago, a small tumor on my nose was diagnosed as basal cell carcinoma, the most common type of skin cancer. I was relieved to learn that this type of cancer is very slow growing, and it does not metastasize or spread to other parts of the body so it is usually not fatal. Surgical removal is advised, and as long as a good margin of healthy tissue is removed with it, the tumor usually does not come back. I had my tumor surgically excised, but I couldn't help wondering how large it would have grown (and how fast) otherwise!

For this project, I decided to research basal cell carcinoma and find a mathematical model that I could use to simulate the growth of a tumor. The only model I could find was developed by Tohya et al (1998) to study the processes of cell proliferation and spatial pattern formation of the skin tumor. Their model consists of a pair of non-dimensionalized, non-linear partial differential equations describing the relationship between tumor cells and nutrients.

The authors made three assumptions in developing the model:

1) The proliferation rate of tumor cells depends on the availability of nutrients, which diffuse out of capillaries;
2) Nutrients are consumed by active tumor cells;
3) The cell diffusion coefficient expressing tumor cell movement increases with the cell density and the nutrient availability.

The Model

The two-dimensional model indicates a vertical slice of skin, with the x-axis parallel to the skin and the y-axis vertical to the skin, where x ranges from 0 to L and y ranges from 0 to H. n(x,y,t) represents the nutrient concentration, and c(x,y,t) is the density of tumor cells.

The concentration of nutrients is given by:

$$\partial n/\partial t = \nabla\text{^}2\, n - nc$$

The first term indicates a simple diffusion of nutrients, and the second term expresses the consumption of the nutrients by tumor cells, the rate of which increases with the activity of tumor cells.

The density of tumor cells is given by:

$$\frac{\partial \boldsymbol{c}}{\partial \boldsymbol{t}} = \boldsymbol{\nabla} \cdot (\boldsymbol{\sigma n c \nabla c}) + \boldsymbol{nc}$$

The second term reflects the consumed nutrients that are used for the maintenance and proliferation of tumor cells, while the first term indicates the random movement of tumor cells. The diffusion coefficient of cells depends on a constant σ, as well as both n and c, because the general activity of the cell movement increases with the nutrient level as well as the tumor cell density.

The initial conditions for the model are:

$$c(x,y,0) = \begin{cases} c_0, & for\ 0 \le y \le y_0 \\ 0, & for\ y_0 < y \le H \end{cases}$$

$$n(x,y,0) = n_0,\ \ for\ 0 < x < L\ and\ 0 < y < H$$

The initial distribution of tumor cells is assumed to be smooth with cell density c_0, and the nutrients are uniformly distributed with a constant level n_0.

The boundary conditions are:

$$n(x,H,t) = n_o,\ \ for\ 0 < x < L$$

$$\frac{\partial}{\partial y} n(x,0,t) = \frac{\partial}{\partial y} c(x,0,t) = \frac{\partial}{\partial y} c(x,H,t) = 0,\ \ for\ 0 < x < L$$

$$\frac{\partial}{\partial x} n(0,y,t) = \frac{\partial}{\partial x} c(0,y,t) = \frac{\partial}{\partial x} n(L,y,t) = \frac{\partial}{\partial x} c(L,y,t) = 0,$$

$$for\ 0 < y < H$$

The concentration of nutrients is fixed at $n=n_0$ at $y=H$, because the nutrient is supplied by the capillary which exists at this layer.

Equilibrium States

I started by analyzing the equilibrium states of the one-dimensional version of the system:

$$\frac{\partial \boldsymbol{n}}{\partial \boldsymbol{t}} = \frac{\partial^2 \boldsymbol{n}}{\partial \boldsymbol{x}^2} - \boldsymbol{nc}$$

$$\frac{\partial \boldsymbol{c}}{\partial \boldsymbol{t}} = \boldsymbol{\sigma n c} \frac{\partial^2 \boldsymbol{c}}{\partial \boldsymbol{x}^2} + \boldsymbol{\sigma n} \left(\frac{\partial \boldsymbol{c}}{\partial \boldsymbol{x}}\right)^2 + \boldsymbol{\sigma c} \frac{\partial \boldsymbol{n}}{\partial \boldsymbol{x}} \frac{\partial \boldsymbol{c}}{\partial \boldsymbol{x}} + \boldsymbol{nc}$$

Any $n_0, c_0 \in \mathbb{R}\ such\ that\ n_0 c_0 = 0\ satisfy\ both\ equations.$

To determine the stability of these states, consider perturbations

$$n(x,t) = n_0 + \hat{n}(x,t) \;\; and \;\; c(x,t) = c_0 + \hat{c}(x,t)$$

Then

$$\frac{\partial \hat{n}}{\partial t} = \frac{\partial^2 \hat{n}}{\partial x^2} - (n_0 + \hat{n})(c_0 + \hat{c})$$

$$\frac{\partial \hat{c}}{\partial t} = \sigma(n_0 + \hat{n})(c_0 + \hat{c})\frac{\partial^2 \hat{c}}{\partial x^2} + \sigma(n_0 + \hat{n})\left(\frac{\partial \hat{c}}{\partial x}\right)^2 + \sigma(c_0 + \hat{c})\frac{\partial \hat{n}}{\partial x}\frac{\partial \hat{c}}{\partial x} + (n_0 + \hat{n})(c_0 + \hat{c})$$

Multiplying the terms out yields

$$\frac{\partial \hat{n}}{\partial t} = \frac{\partial^2 \hat{n}}{\partial x^2} - n_0 c_0 - n_0 \hat{c} - c_0 \hat{n} - \hat{n}\hat{c}$$

$$\frac{\partial \hat{c}}{\partial t} = \sigma(n_0 c_0 + n_0 \hat{c} + c_0 \hat{n} + \hat{n}\hat{c})\frac{\partial^2 \hat{c}}{\partial x^2} + \sigma(n_0 + \hat{n})\left(\frac{\partial \hat{c}}{\partial x}\right)^2 + \sigma(c_0 + \hat{c})\frac{\partial \hat{n}}{\partial x}\frac{\partial \hat{c}}{\partial x} + n_0 c_0 + n_0 \hat{c} + c_0 \hat{n} + \hat{n}\hat{c}$$

Replacing n_0c_0 with zero and removing all non-linear terms gives the linearized system:

$$\frac{\partial \hat{n}}{\partial t} = \frac{\partial^2 \hat{n}}{\partial x^2} - n_0 \hat{c} - c_0 \hat{n}$$

$$\frac{\partial \hat{c}}{\partial t} = n_0 \hat{c} + c_0 \hat{n}$$

Next consider

$$\hat{n}(x,t) = C_1 \sin(qx)\, e^{\alpha t} \;\; and \;\; \hat{c}(x,t) = C_2 \sin(qx) e^{\alpha t}$$

Then the system can be written as

$$\alpha \hat{n} = -q^2 \hat{n} - n_0 \hat{c} - c_0 \hat{n}$$

$$\alpha \hat{c} = n_0 \hat{c} + c_0 \hat{n}$$

Or equivalently

$$\alpha C_1 = -q^2 C_1 - n_0 C_2 - c_0 C_1$$

$$\alpha C_2 = n_0 C_2 + c_0 C_1$$

Combining like terms gives:

$$(\alpha + q^2 + c_0)C_1 + n_0 C_2 = 0$$

$$-c_0 C_1 + (\alpha - n_0)C_2 = 0$$

To find non-trivial solutions we need

$$det\begin{bmatrix} \alpha + q^2 + c_0 & n_0 \\ -c_0 & \alpha - n_0 \end{bmatrix} = 0$$

So we have

$$(\alpha + q^2 + c_0)(\alpha - n_0) + n_0 c_0 = 0$$

Multiplying gives

$$\alpha^2 - n_0\alpha + q^2\alpha - q^2 n_0 + c_0\alpha - n_0 c_0 + n_0 c_0 = 0$$

$$\alpha^2 + (-n_0 + q^2 + c_0)\alpha - q^2 n_0 = 0$$

Using the Routh-Hurwitz stability criterion, $\alpha < 0\ if\ and\ only\ if\ -q^2 n_0 > 0$,

which would require that $n_0<0$. But n_0 can't be less than zero, so the equilibrium states are unconditionally unstable!

Simulations

To simulate the one dimensional model, I devised a finite difference method using a uniform space-time discretization, and forward in time and central in space approximations.

$$Let\ x_i = i\Delta x,\ \ for\ i = 0, \dots, I$$

$$and\ t_k = k\Delta t,\ \ for\ t = 0, \dots, K$$

$$where\ \Delta x = \frac{L}{I}\ and\ \Delta t = \frac{T}{K}$$

The nutrient equation

$$\frac{\partial n}{\partial t} = \frac{\partial^2 n}{\partial x^2} - nc$$

Can be approximated by

$$\frac{n_i^{k+1} - n_i^k}{\Delta t} = \frac{n_{i+1}^k - 2n_i^k + n_{i-1}^k}{(\Delta x)^2} - n_i^k c_i^k$$

$$i = 1, \dots, I-1 \quad and\ k = 0, \dots, K-1$$

Where $n_i^k \approx n(x_i, t_k)$.

Likewise the tumor equation

$$\frac{\partial c}{\partial t} = \sigma nc \frac{\partial^2 c}{\partial x^2} + \sigma n \left(\frac{\partial c}{\partial x}\right)^2 + \sigma c \frac{\partial n}{\partial x}\frac{\partial c}{\partial x} + nc$$

Can be approximated by

$$\frac{c_i^{k+1} - c_i^k}{\Delta t} = \sigma n_i^k c_i^k \left(\frac{c_{i+1}^k - 2c_i^k + c_{i-1}^k}{(\Delta x)^2}\right) + \sigma n_i^k \left(\frac{c_{i+1}^k - c_{i-1}^k}{2\Delta x}\right)^2$$

$$+\sigma c_i^k \left(\frac{n_{i+1}^k - n_{i-1}^k}{2\Delta x}\right)\left(\frac{c_{i+1}^k - c_{i-1}^k}{2\Delta x}\right) + n_i^k c_i^k$$

$$i = 1, \dots, I-1 \quad and\ k = 0, \dots, K-1$$

Where $c_i^k \approx c(x_i, t_k)$.

The initial conditions $n(x,0) = n_0,\ c(x,0) = c_0, \quad for\ 0 < x < L$

Yield $n_i^0 = n_0\ and\ \ c_i^0 = c_0, for\ i = 0, \dots, I.$

To enforce the boundary conditions

$$\frac{\partial}{\partial x} n(0,t) = \frac{\partial}{\partial x} c(0,t) = \frac{\partial}{\partial x} n(L,t) = \frac{\partial}{\partial x} c(L,t) = 0,$$

I simply set $n_0^k = n_1^k,\ n_I^k = n_{I-1}^k,\ c_0^k = c_1^k,\ and\ c_I^k = c_{I-1}^k, for\ k = 1, \dots, K.$

I used parameter values similar to those in the paper (Tohya et al, 1998). For simplicity, I used n_0=1, c_0=1, and σ=1 for all simulations, but these parameter values can easily be changed in my code for future experimentation.

My first MATLAB simulation solves the 1-D system in the x-direction using the initial and boundary conditions given above. I used L=300, Δx=0.5, and Δt=0.02.

The results show that the nutrient concentration decreases uniformly until it reaches zero, and the tumor density increases uniformly to approximately 2. When the nutrient level reaches zero, the tumor density stops increasing.

For my second simulation, I changed the initial conditions slightly to reflect a smaller interval with tumor density equal to one.

$$c(x,0) = \begin{cases} c_0, & for\ 140 \le x \le 160 \\ 0, & elsewhere \end{cases}$$

The results show that the tumor density reaches a maximum value in the initial region, then it spreads in the positive and negative x-direction, consuming the available nutrients as it moves along.

My third simulation solves the 1-D system in the y-direction. I used the same finite difference method in y instead of x, with initial and boundary conditions:

$$n(y,0) = n_0, \;\; for \;\; 0 < y < H$$

$$c(y,0) = \begin{cases} c_0, & for \; 0 \le y \le y_0 \\ 0, & for \; y_0 < y \le H \end{cases}$$

$$n(H,t) = n_o$$

$$\frac{\partial}{\partial y} n(0,t) = \frac{\partial}{\partial y} c(0,t) = \frac{\partial}{\partial y} c(H,t) = 0$$

Here I used H=150, y_0=5, Δy=0.5, and Δt=0.02.

The results show that the tumor density reaches a maximum value in the initial region, then it spreads in the positive y-direction, consuming the available nutrients as it moves along. When the 'wave' reaches the boundary, it appears to bounce back with a higher density.

Stability Analysis

I tried using larger values for Δt to speed up the simulations, but this caused the solutions to 'blow up'. In order to investigate the stability of the finite difference scheme, consider

$$n_j^k = \alpha^k e^{i\beta j} \; and \; c_j^k = \rho^k e^{i\gamma j}$$

$$where \; \beta, \gamma \in \mathbb{R} \; and \; \alpha(\beta), \rho(\gamma) \in \mathbb{C}.$$

Then the finite difference schemes

$$\frac{n_i^{k+1} - n_i^k}{\Delta t} = \frac{n_{i+1}^k - 2n_i^k + n_{i-1}^k}{(\Delta y)^2} - n_i^k c_i^k$$

$$\frac{c_i^{k+1} - c_i^k}{\Delta t} = \sigma n_i^k c_i^k \left(\frac{c_{i+1}^k - 2c_i^k + c_{i-1}^k}{(\Delta y)^2} \right) + \sigma n_i^k \left(\frac{c_{i+1}^k - c_{i-1}^k}{2\Delta y} \right)^2$$

$$+ \sigma c_i^k \left(\frac{n_{i+1}^k - n_{i-1}^k}{2\Delta y} \right) \left(\frac{c_{i+1}^k - c_{i-1}^k}{2\Delta y} \right) + n_i^k c_i^k$$

Can be written as

$$(1)\ \alpha^{k+1}e^{i\beta j}-\alpha^k e^{i\beta j}=\frac{\Delta t}{(\Delta y)^2}\left(\alpha^k e^{i\beta(j+1)}-2\alpha^k e^{i\beta j}+\alpha^k e^{i\beta(j-1)}\right)-\Delta t\alpha^k e^{i\beta j}\rho^k e^{i\gamma j}$$

$$\begin{aligned}(2)\ \rho^{k+1}e^{i\gamma j}-\rho^k e^{i\gamma j}\\ &=\sigma\alpha^k e^{i\beta j}\rho^k e^{i\gamma j}\frac{\Delta t}{(\Delta y)^2}\left(\rho^k e^{i\gamma(j+1)}-2\rho^k e^{i\gamma j}+\rho^k e^{i\gamma(j-1)}\right)\\ &+\sigma\alpha^k e^{i\beta j}\frac{\Delta t}{4(\Delta y)^2}\left(\rho^k e^{i\gamma(j+1)}-\rho^k e^{i\gamma(j-1)}\right)^2\\ &+\sigma\rho^k e^{i\gamma j}\frac{\Delta t}{4(\Delta y)^2}\left(\alpha^k e^{i\beta(j+1)}-\alpha^k e^{i\beta(j-1)}\right)\left(\rho^k e^{i\gamma(j+1)}-\rho^k e^{i\gamma(j-1)}\right)\\ &+\Delta t\alpha^k e^{i\beta j}\rho^k e^{i\gamma j}\end{aligned}$$

Dividing (1) by $\alpha^k e^{i\beta j}$ and (2) by $\rho^k e^{i\gamma j}$ gives

$$(1)\ \alpha-1=\frac{\Delta t}{(\Delta y)^2}\left(e^{i\beta}-2+e^{-i\beta}\right)-\Delta t\rho^k e^{i\gamma j}$$

$$\begin{aligned}(2)\ \rho-1=&\ \sigma\alpha^k e^{i\beta j}\rho^k e^{i\gamma j}\frac{\Delta t}{(\Delta y)^2}\left(e^{i\gamma}-2+e^{-i\gamma}\right)+\sigma\alpha^k e^{i\beta j}\frac{\Delta t}{4(\Delta y)^2}\rho^k e^{i\gamma j}\left(e^{i\gamma}-e^{-i\gamma}\right)^2\\ &+\sigma\rho^k e^{i\gamma j}\frac{\Delta t}{4(\Delta y)^2}\alpha^k e^{i\beta j}\left(e^{i\beta}-e^{-i\beta}\right)\left(e^{i\gamma}-e^{-i\gamma}\right)+\Delta t\alpha^k e^{i\beta j}\end{aligned}$$

Using trig identities and letting $\mu=\frac{\Delta t}{(\Delta y)^2}$ gives

$$(1)\ \alpha-1=2\mu(cos\beta-1)-\Delta t\rho^k e^{i\gamma j}$$

$$\begin{aligned}(2)\ \rho-1=&\ 2\sigma\alpha^k e^{i\beta j}\rho^k e^{i\gamma j}\mu(cos\gamma-1)-\sigma\alpha^k e^{i\beta j}\rho^k e^{i\gamma j}\mu sin^2\gamma\\ &-\sigma\alpha^k e^{i\beta j}\rho^k e^{i\gamma j}\mu sin\beta sin\gamma+\Delta t\alpha^k e^{i\beta j}\end{aligned}$$

Or equivalently

$$(1)\ \alpha=2\mu(cos\beta-1)-\Delta t\rho^k e^{i\gamma j}+1$$

$$(2)\ \rho=\sigma\alpha^k e^{i\beta j}\rho^k e^{i\gamma j}\mu(2cos\gamma-2-sin^2\gamma-sin\beta sin\gamma)+\Delta t\alpha^k e^{i\beta j}+1$$

And finally

$$(1)\ \alpha=2\mu(cos\beta-1)-\Delta t\rho^k(\cos(\gamma j)+i\sin(\gamma j))+1$$

$$\begin{aligned}(2)\ \rho=&\ \sigma\alpha^k\rho^k\mu(\cos(\beta j)+i\sin(\beta j))(\cos(\gamma j)+i\sin(\gamma j))(2cos\gamma-2-sin^2\gamma-sin\beta sin\gamma)\\ &+\Delta t\alpha^k(\cos(\beta j)+i\sin(\beta j))+1\end{aligned}$$

This is as far as I got; due to the non-linearity of the system, I do not know how to find the conditions that ensure $|\alpha|\leq 1\ and\ |\rho|\leq 1$.

Two-Dimensional Simulation

Next I wrote the 2-D system in derivative form

$$\boldsymbol{\frac{\partial n}{\partial t} = \frac{\partial^2 n}{\partial x^2} + \frac{\partial^2 n}{\partial y^2} - nc}$$

$$\boldsymbol{\frac{\partial c}{\partial t} = \sigma nc\frac{\partial^2 c}{\partial x^2} + \sigma\left(n\frac{\partial c}{\partial x} + c\frac{\partial n}{\partial x}\right)\frac{\partial c}{\partial x}}$$

$$\boldsymbol{+\sigma nc\frac{\partial^2 c}{\partial y^2} + \sigma\left(n\frac{\partial c}{\partial y} + c\frac{\partial n}{\partial y}\right)\frac{\partial c}{\partial y} + nc}$$

And devised a finite difference method similar to that for the 1-D system:

$$Let\ x_i = i\Delta x,\ \ for\ i = 0, \dots, I,$$

$$y_j = j\Delta y,\ \ for\ j = 0, \dots, J,$$

$$and\ t_k = k\Delta t,\ \ for\ t = 0, \dots, K$$

$$where\ \Delta x = \frac{L}{I}, \qquad \Delta y = \frac{H}{J}, \quad and\ \Delta t = \frac{T}{K}$$

$$\frac{n_{i,j}^{k+1} - n_{i,j}^k}{\Delta t} = \frac{n_{i+1,j}^k - 2n_{i,j}^k + n_{i-1,j}^k}{(\Delta x)^2} + \frac{n_{i,j+1}^k - 2n_{i,j}^k + n_{i,j-1}^k}{(\Delta y)^2} - n_{i,j}^k c_{i,j}^k$$

$$\begin{aligned}\frac{c_{i,j}^{k+1} - c_{i,j}^k}{\Delta t} = {} & \sigma n_{i,j}^k c_{i,j}^k\left(\frac{c_{i+1,j}^k - 2c_{i,j}^k + c_{i-1,j}^k}{(\Delta x)^2}\right) \\ & + \sigma\left(n_{i,j}^k\frac{c_{i+1,j}^k - c_{i-1,j}^k}{2\Delta x} + c_{i,j}^k\frac{n_{i+1,j}^k - n_{i-1,j}^k}{2\Delta x}\right)\left(\frac{c_{i+1,j}^k - c_{i-1,j}^k}{2\Delta x}\right) \\ & + \sigma n_{i,j}^k c_{i,j}^k\left(\frac{c_{i,j+1}^k - 2c_{i,j}^k + c_{i,j-1}^k}{(\Delta y)^2}\right) \\ & + \sigma\left(n_{i,j}^k\frac{c_{i,j+1}^k - c_{i,j-1}^k}{2\Delta y} + c_{i,j}^k\frac{n_{i,j+1}^k - n_{i,j-1}^k}{2\Delta y}\right)\left(\frac{c_{i,j+1}^k - c_{i,j-1}^k}{2\Delta y}\right) + n_{i,j}^k c_{i,j}^k\end{aligned}$$

$$i = 1, \dots, I-1, \qquad j = 1, \dots, J-1, \quad and\ k = 0, \dots, K-1$$

Where $n_{i,j}^k \approx n(x_i, y_j, t_k)$ *and* $c_{i,j}^k \approx c(x_i, y_j, t_k)$.

Using the initial and boundary conditions stated at the beginning of this paper, I set

$$n_{i,j}^{0} = n_0, \qquad for\ i = 0, \dots, I\ \ and\ j = 0, \dots, J$$

$$and\ \ c_{i,j}^{0} = \begin{cases} c_0, & for\ 0 \le j \le \dfrac{y_0}{\Delta t} \\ 0, & for\ \dfrac{y_0}{\Delta t} < j \le J \end{cases}, \qquad for\ i = 0, \dots, I$$

And let

$$n_{0,j}^{k} = n_{1,j}^{k}, \qquad n_{I,j}^{k} = n_{I-1,j}^{k}, \qquad c_{0,j}^{k} = c_{1,j}^{k}, \qquad c_{I,j}^{k} = c_{I-1,j}^{k},$$

$$n_{i,J}^{k} = n_o, \qquad n_{i,0}^{k} = n_{i,1}^{k}, \qquad c_{i,0}^{k} = c_{i,1}^{k}, \qquad c_{i,J}^{k} = c_{i,J-1}^{k}.$$

For the 2-D simulation I used L=300, y_0=5, H=150, Δx=Δy=0.5, and Δt=0.012 (I had to use a smaller Δt than before to get stability).

The results are surface plots of nutrient concentration over the x-y plane and tumor density over the x-y plane which behave similarly to the 1-D simulations. I was not able to go further than T=1200 due to the long computational times required!

Conclusion

Since the model I used is non-dimensionalized and the actual parameter values are unknown, I was not able to determine how big my tumor would have grown if left untreated. While my simulations show the general dynamics of tumor growth, more research and data is needed to make this model more useful.

I would also like to perform more simulations using varying parameter values and initial/boundary conditions, but the time required for the simulations is restrictive. I would like to devise an implicit finite difference method or a finite element method which would allow the use of a larger time step to overcome this difficulty, but at the present time I do not have the skills required to do this for a non-linear system of partial differential equations. Another future goal is to simulate this model in three dimensions, which Tohya et al (1998) were not able to accomplish.

References

Tohya S, Mochizuki A, Imayama S. On Rugged Shape of Skin Tumor (Basal Cell Carcinoma). J Theor Biol. 1998;194:65–78.

Eikenberry, Steffen, Craig Thalhauser, and Yang Kuang. "Tumor-Immune Interaction, Surgical Treatment, and Cancer Recurrence in a Mathematical Model of Melanoma." Ed. Carl T. Bergstrom. *PLoS Computational Biology* 5.4 (2009): e1000362. *PMC*. Web. 4 Mar. 2015.