MODELING BIOLOGICAL SYSTEMS

INSTRUCTIONS TP-TD6

Project 2 : a continuous model

Let us consider a cell density ρ of low grade glioma LGG (grade I/II brain tumors). General diffusion equations, as heat equation, follow:

$$\frac{\partial \rho}{\partial t} = D\Delta\rho$$

where D is a diffusion rate.
We want to apply this equation to glioma cell density, assuming the brain is homogeneous. For our biological application, D might depends on cell positions in the brain (diffusivity should be heterogeneous), but it will be assumed constant here. $\Delta\rho$ here denotes the Laplacian of the ρ function .

A. To introduce a proliferation term, it is generally accepted to add a proliferation rate κ of this cell density ρ . To limit an infinite number of cells due to an infinite proliferation, we will coupled it with a saturation term $1 - \rho$ to obtain finally a logistic function of ρ. Write the new equation for ρ.

B. What is the general shape of a low grade tumor? What spatial coordinates are you likely to use?

C. What symmetrical considerations could you make on ρ ? We assume ρ depending only on its radial distance r, (*i.e.* $\rho = \rho(r)$).
Show that ρ follows the Diffusion Proliferation Saturation DPS equation :

$$\frac{\partial \rho}{\partial t} = D\Big(\frac{\partial^2 \rho}{\partial r^2} + \frac{2}{r}\frac{\partial \rho}{\partial r}\Big) + \kappa\rho(1-\rho) \qquad \text{(E)}$$

D. Set $u = \rho \cdot r$ and find a new equation (E') depending on the variable u. We set $u(r = 0, t) = 0$ and $\frac{\partial u}{\partial r}(r = 0, t) = \rho(r = 0, t)$.

E. This equation (E') is not analytically solvable (because of the nonlinear proliferation saturation term). We will use a numerical approach to solve it. Instead of using a classical but unstable Euler's method, we will use a Crank-Nicolson method* that was first invented to solve the heat equation.

To avoid chaotic oscillations, we will assume that $(u_j^n)^2 \approx u_j^n u_j^{n+1}$ for $n > 1$. Starting from your equation (E') , show that the numerical scheme of the function u can be written as the following :

$$u_j^{n+1} = u_j^n\left(1 - 2\alpha + \kappa\Delta t - \kappa\frac{\Delta t}{r_j}u_j^{n+1}\right) + \alpha(u_{j+1}^n - u_{j-1}^n)$$

where $\alpha = \dfrac{D\Delta t}{(\Delta r^2)}$, $r_j = j\Delta r$ and $t_n = n\,\Delta t$, with $\rho_j^n = \dfrac{u_j^n}{r_j}$. Note that $u_j^n = u_{-j}^n$

This expression can be written only depending on u_j^{n+1} as the following :

$$u_j^{n+1} = \frac{1}{(1 + \frac{\kappa\Delta t u_j^n}{r_j})}\left[u_j^n(1 - 2\alpha \;\; + \kappa\Delta t) + \alpha(u_{j+1}^n + u_{j-1}^n)\right]$$

F. Use your numerical scheme to compute your solution in your favorite programming language. We want ρ with respect to t (in years).
This link could help you especially if you use Python :
https://levelup.gitconnected.com/solving-2d-heat-equation-numerically-using-python-3334004aa01a

For this part, you could use these informations :
- $\Delta r = 0.02$ mm, as the average size of a LGG cell ($\approx 20\,\mu$m) and will watch the evolution of ρ up to 100 mm;
- $\Delta t = 0.001$ year, up to a many years evolution;
- $\rho(r_0, t_0) = 1$;
- final tumor expected : between 10^3 and 10^4 cells for a small tumor;
- initial condition : one single mutated cell;
- in the case of a compact tumor, $\kappa = 10\text{year}^{-1}$ and $D = 0.01\text{mm}^2/\text{year}$;
- in the case of a diffuse tumor, $\kappa = 1.0\text{year}^{-1}$ and $D = 0.7\text{mm}^2/\text{year}$;
- edge growth velocity approximated : $v = 2\sqrt{\kappa D}$

Extra questions:

We define the radius of the tumor R :

$$R(\rho^*, t) = \sqrt{4D(t + t_0) \cdot \left[\kappa t - \frac{3}{2}\ln\left(\rho^* \frac{t + t_0}{t_0}\right)\right]}$$

where $\rho(r = R, t) = \rho^*$, the density at the edge of the tumor, and $t_0 = r_0^2/(4D)$

G. The detection threshold is known to be around $\rho_{\text{detected}} = 2$ %. Can you find the duration $t_{\text{detection}}$ before the glioma cells get detected ?

Appendix :

$$u(r, t) \leftrightarrow u_j(r_j, t_n)$$

$$\frac{\partial u}{\partial t} \leftrightarrow \frac{u_j^{n+1} - u_j^n}{\Delta t}$$

$$\frac{\partial^2 u}{\partial r^2} \leftrightarrow \frac{1}{(\Delta r)^2}\left[u_{j+1}^n - 2u_j^n + u_{j-1}^n\right]$$

Butcher's tableau of Crank-Nicoloson scheme:

$$\begin{array}{c|cc} 0 & 0 & 0 \\ 1 & 1/2 & 1/2 \\ \hline & 1/2 & 1/2 \end{array}$$