Mathematical models of tumor growth

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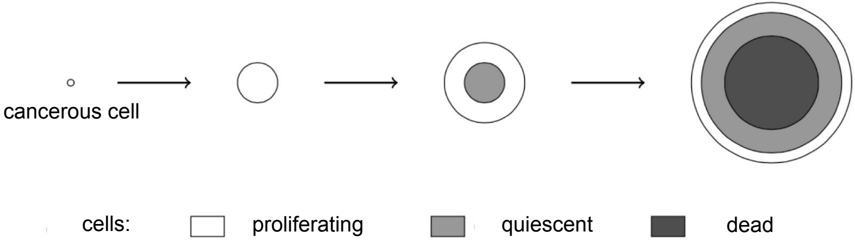
Biological background

Definition: A cancer or a malignant tumor is a group of cells involving abnormal cell growth that tend to invade surrounding tissue or spread to other parts of the body.

Types of cells in a tumor:



The reaction-diffusion equation

We consider the population number density $u(x,t)$ at position $x \in \mathbb{R}^d$ and at time $t \geq 0$.

$$\frac{\partial u(x,t)}{\partial t} = \underbrace{\nabla \cdot (D(x)\nabla u(x,t))}_{\text{diffusion term: cells motion}} + \overbrace{R(u(x,t))}^{\text{reaction term: population growth}}$$

We assume that $u \in [0;1]$:

➤ $u = 0$: No invasive cell - healthy cells only;

➤ $u = 1$: Invasive cells have arrived to their maximum number density.

We model the reaction by:

$$R(u) = \underbrace{\rho(x,t)}_{\text{proliferation rate}} \times u$$

Resolution of the equation

We assume that:

- D is constant;
- the model is bidimensional;
- the tumor has a circular geometry.

Reaction-diffusion equation: $\dfrac{\partial u}{\partial t} = D\nabla^2 u + \rho u$

Solution: $u(x,t) = \dfrac{N_0}{4\pi Dt} e^{\rho t} e^{-x^2/4Dt}$

Caracterisation of the tumor growth: the relation $\dfrac{\rho}{D}$

Fisher-Kolmogorov approximation: $D \approx \dfrac{v^2}{4\rho}$

where v is the linear speed of the tumor front.

Analysis of a simple biological model

We consider:

- P density of proliferating cells;
- Q density of quiescent cells;
- $\overrightarrow{v}$ speed of cells;
- α rate between birth and death cells.

Conservation of mass on P and Q:

$$\begin{cases} \dfrac{\partial P}{\partial t} + \nabla \cdot (\overrightarrow{v_P} P) = \alpha_P \\ \\ \dfrac{\partial Q}{\partial t} + \nabla \cdot (\overrightarrow{v_Q} Q) = \alpha_Q \end{cases}$$

We assume that:

☞ cells are incompressible: $P + Q = 1$.

☞ Same speed: $\overrightarrow{v}_P = \overrightarrow{v}_Q = \overrightarrow{v}$.

We obtain:

$$\nabla \cdot \overrightarrow{v} = \alpha_P + \alpha_Q.$$

Darcy's law through a porous medium:
$\overrightarrow{v} = -k\nabla p$ (k is a constant)

So:

$$-k\Delta p = \alpha_P + \alpha_Q \qquad \textit{(Poisson equation)}$$

Hele-Shaw model and free boundary formulation

We define G a function which represents the cells birth/death rate.
We assume that:

- G is lipschitz;
- $G'(\cdot) < 0$;
- $G(0) := G_M = \max G(\cdot)$;
- $\exists P_M > 0$ with the property that $G(P_M) = 0$.

We have:
$$\begin{cases} -\Delta p(x,t) = G(p(x,t)) & \text{if } x \in \Omega(t); \\ p(x,t) = 0 & \text{if } x \in \partial\Omega(t). \end{cases}$$

The tumor grows with a normal speed: $v(x,t) = -\nabla p(x,t)$ with $x \in \partial\Omega(t)$ (Darcy's law).

So: $\dot{X}(t) = v(X(t),t)$ if $X(t) \in \partial\Omega(t)$ with v the normal speed.

Fluid mechanical model

We consider the system of equations:

$$(S) \begin{cases} \dfrac{\partial n}{\partial t} + div(n\vec{v}) = nG(p(x,t)); \\ \vec{v} = -\nabla p(x,t) \quad \text{(Darcy's law)}; \\ p(x,t) = \Pi(n) = n(x,t)^{\gamma} \quad \text{with } \gamma > 1. \end{cases}$$

We assume that the initials conditions satisfy:

❒ $n(x, t=0) := n^0(x) \geq 0$ is a $L^1(\mathbb{R}^d)$ and a compact support function;

❒ $p(n^0) := p^0 \leq P_M$;

❒ $\nabla n^0 \in L^1(\mathbb{R}^d)$.

Hele-Shaw's limit

Let (n_γ, p_γ) be the unique bounded weak solution to (S). We can prove that, along some subsequence, there is a weak limit as $\gamma \longrightarrow \infty$ which turns out to be a solution of (S).

Theorem 1: Hele-Shaw's limit

When $\gamma \to +\infty$ in (S), we have:

1.
   1. $n_\gamma \to n_\infty \leq 1, p_\gamma \to p_\infty \leq P_M$ a.s in $\mathbb{R}^d \times]0; +\infty[$;
   2. $\nabla p_\gamma \rightharpoonup \nabla p_\infty$ in $L^2(\mathbb{R}^d \times]0, T[) \quad \forall T > 0$.
2. The weak limit of (S) is:

$$\begin{cases} \dfrac{\partial n_\infty}{\partial t} - div(n_\infty \nabla p_\infty) = n_\infty G(p_\infty) \\ n_\infty(x, t = 0) = n_\infty^0(x) \geq 0 \\ p_\infty(1 - n_\infty) = 0 \quad \text{avec} \quad 0 \leq n_\infty \leq 1. \end{cases}$$

Complementary formula

Theorem 2: Complementary relation

We have equivalence between:

1. $\nabla p_\gamma \longrightarrow \nabla p_\infty$ in $L^2_{loc}(\mathbb{R}^d \times]0, +\infty[)$;
2. $p_\infty(\Delta p_\infty + G(p_\infty)) = 0.$

Equivalence between Hele-Shaw's limit and the fluid mechanical model

Theorem 3:

We have equivalence between:

1. Hele-Shaw's limit

$$\begin{cases} -\Delta p_\infty = G(p_\infty) & \text{if } x \in \Omega(t) \\ p_\infty = 0 & \text{on } \partial\Omega(t) \end{cases}$$

$$\dot{X}(t) = v(X(t), t) \quad \text{if} \quad X(t) \in \partial\Omega(t).$$

2. Fluid mechanical model

$$p_\infty(\Delta p_\infty + G(p_\infty)) = 0$$

$$\begin{cases} \dfrac{\partial n_\infty}{\partial t} - div(n_\infty \nabla p_\infty) = n_\infty G(p_\infty) \\ p_\infty = 0 \quad \text{for } n_\infty < 1. \end{cases}$$