

A SURVEY ON CANCER MODELLING

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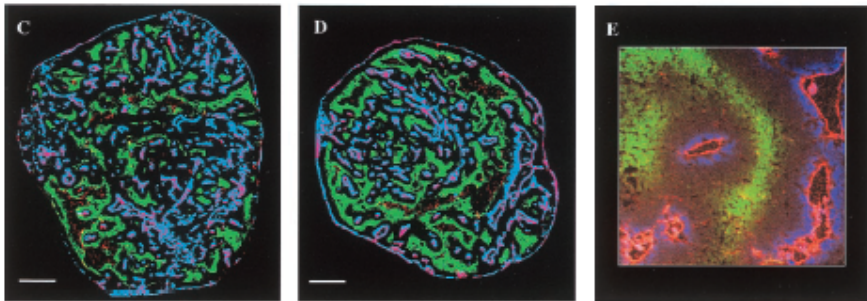
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Cancer originates from the derangement of the normal cellular machinery that controls cell replication. The main characters of tumour biology may be stated as follows (Hanahan & Weinberg, Cell 2000):

- Self-sufficiency in growth signals, insensitivity to anti-growth signals, capacity to evade apoptosis
- Unlimited proliferation of transformed cells
- Ability to stimulate angiogenesis to form a new vascular network that supplies oxygen and nutrients to tumour cells
- Ability to invade the surrounding normal tissues and to promote the formation of distant metastases by dissemination of tumour cells via blood and lymphatic vessels.

An important point is that genetic changes as well as microenvironmental influences occur during tumour growth. The transformed genome may exhibit thousands and even more of genetic mutations. These factors lead to a remarkable *heterogeneity* in a wide variety of the properties of the individual tumour cells. Many aspects of tumour development are affected, including the resistance to therapeutic agents and the invasiveness.

Tumour sections from a human glioma xenograft (E106) Rijken et al., 2000



Vessel endothelium (red), perfusion (blue), hypoxia (green)

The distribution and extent of perfusion and hypoxia in the tumour mass may be evaluated by means of molecular markers. We note that there is a chronic or diffusion-limited hypoxia and an acute or perfusion-limited hypoxia related to irregularity of blood flow.

The simplest way to describe the dynamics of the tumour is to write an equation for the number N of tumour cells. For instance, the (generalized) logistic equation:

$$\frac{dN}{dt} = \alpha N \left[1 - \left(\frac{N}{K} \right)^\delta \right] - \mu N, \quad N(0) = N_0,$$

where the second term in the rhs may represent cell death with rate coefficient μ . Often the Gompertz equation has also been used.

The basic population model can be improved by accounting for the distinction between proliferating (P) cells and non-proliferating quiescent (Q) cells. In an advanced stage of tumour growth, a large fraction of cells is indeed quiescent, and this fact has been suggested to be a cause of the observed saturating behaviour of the growth curve. Gyllenberg and Webb (1987) proposed:

$$\begin{aligned} \dot{P} &= (\alpha - \mu_P)P - \lambda(N)P + \gamma(N)Q, & P(0) &= P_0 \\ \dot{Q} &= -\mu_Q Q + \lambda(N)P - \gamma(N)Q, & Q(0) &= Q_0, \end{aligned}$$

where $N(t) = P(t) + Q(t)$. The rate coefficient of $P \rightarrow Q$ transition, $\lambda(N)$, is a nonnegative non-decreasing function of N and the rate of Q cells recruitment into proliferation, $\gamma(N)$, is a nonnegative non-increasing function of N .

Cell populations models: age structure

A further refinement of the population model consists in the subdivision of proliferating cells according to their position in the cell cycle. This can be done by introducing the cell age, a , and the cell density with respect to age, $n(a, t)$, such that the integral of n over a gives the number of proliferating cells at time t . We have:

$$\begin{aligned}\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} &= -[\beta(a) + \mu_P(a)]n(a, t) \\ n(0, t) &= 2\theta \int_0^\infty \beta(a)n(a, t) da \\ \dot{Q}(t) &= 2(1 - \theta) \int_0^\infty \beta(a)n(a, t) da - \mu_Q Q,\end{aligned}$$

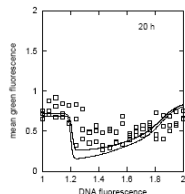
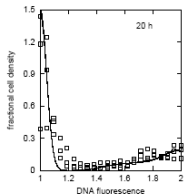
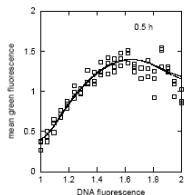
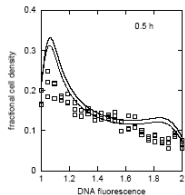
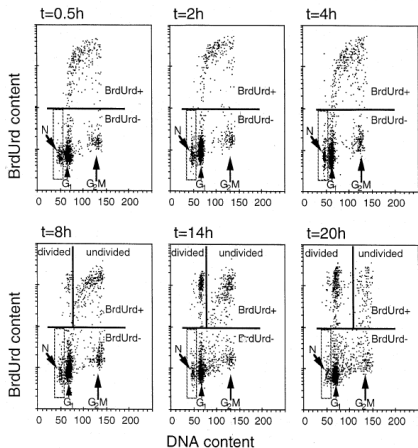
where $\beta(a)$ is the age-dependent mitotic rate and θ the fraction of newborn cells that enter the proliferative cycle. Note that the model represents here an irreversible quiescence. The integral of n between selected ages may identify the cells in a given cell cycle phase. Following this line, the phases G1, S, G2 and M may be represented by different densities (Chuang and Lloyd, 1975):

$$\begin{aligned}\frac{\partial n_i}{\partial t} + \frac{\partial n_i}{\partial a_i} &= -[\beta_i(a_i) + \mu_i]n_i(a_i, t), \quad i = 1, \dots, 4 \\ n_1(0, t) &= 2 \int_0^\infty \beta_4(a)n_4(a, t) da \quad \text{cell division} \\ n_i(0, t) &= \int_0^\infty \beta_{i-1}(a)n_{i-1}(a, t) da, \quad i = 2, 3, 4,\end{aligned}$$

where β_i , $i = 1, 2, 3$, is the rate of transition from phase i to phase $i + 1$.

Cell kinetics estimation from FCM data

Cell population models with age structure are useful for estimating cell kinetic parameters (e.g., cell-cycle phase durations) from flow cytometry data. A largely used technique is the measurement of a sequence of DNA-BrdUrd distributions after BrdUrd pulse labelling (Bertuzzi et al., Bull Math Biol 2002). The distributions predicted by the model refer to the BrdUrd(+) cells.

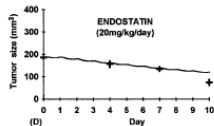
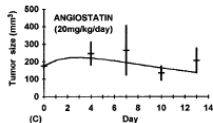
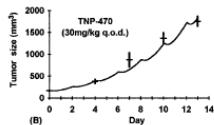
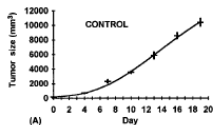


Tumour growth control by angiogenesis

In the logistic (or Gompertz) growth law, the carrying capacity K is constant. Hahnfeldt et al., Cancer Res (1999) proposed a model in which the carrying capacity represents the extent of tumour vasculature and evolves in time under stimuli generated by the tumour itself. The model is given by

$$\begin{aligned}\dot{N} &= \alpha N[1 - (N/K)], & N(0) &= N_0 \\ \dot{K} &= bN - (dN^{2/3} + \mu)K - \eta g(t)K, & K(0) &= K_0,\end{aligned}$$

where the first term in the rhs of the equation for K represents the stimulatory signal from the tumour cells, the second the inhibitory signal plus a spontaneous cell loss, and the third the action of an antiangiogenic drug of concentration $g(t)$. The tumour growth saturates because the vasculature growth ceases when the inhibitory signal balances the stimulatory one.



Diffusion models

Let $n(\mathbf{x}, t)$ be the cell density (number of cell per unit volume) at position \mathbf{x} and time t . Assuming that cell motion is governed by diffusion, we can write:

$$\frac{\partial n}{\partial t} + \nabla \cdot (-D(\mathbf{x})\nabla n) = \alpha n \left(1 - \frac{n}{k}\right) - \mu(t)n,$$

where D is the diffusivity of tumour cells. $\mu(t)$ represents the action of an anticancer agent.

- Application: Evolution of glioma after treatment (Swanson et al., Cell Prolif 2000).

Diffusion + chemotaxis/haptotaxis

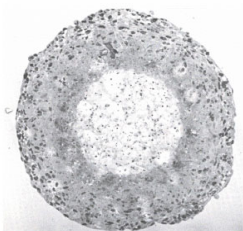
$$\frac{\partial n}{\partial t} + \nabla \cdot (-D\nabla n) + \nabla \cdot (nh(n, c)\nabla c) = \Gamma(n, t).$$

In the case of chemotaxis, $c(\mathbf{x}, t)$ is the concentration of the chemotactic attractant. Since, in general, the chemoattractant is a diffusible chemical the model must be coupled to an equation for c . In the case of haptotaxis (active movement of cells in the direction of the gradient of extracellular matrix concentration), c is the concentration of fibronectin.

- Application: Models of tumour invasion (Anderson et al., J Theor Med 2000; Gerisch & Chaplain, JTB 2008).

Tumour as a continuum with boundary

The state variable, $\nu(\mathbf{x}, t)$, is the fraction of volume occupied *locally* by the cells. We have $0 < \nu < 1$ for $\mathbf{x} \in \Omega(t)$, with Ω being a bounded spatial domain that represents the volume occupied by the whole tumour (e.g., a multicellular tumour spheroid with the proliferating rim, a quiescent band and the necrotic core).



From the mass balance we have:

$$\frac{\partial \nu}{\partial t} + \nabla \cdot (\mathbf{u} \nu) = \Gamma(\nu, \sigma, t) \quad \text{in } \Omega(t),$$

where $\mathbf{u}(\mathbf{x}, t)$ is the cell velocity field. σ denotes the concentration of a diffusible nutrient that affects cell proliferation and cell death. The model can be refined by subdividing ν into ν_P, ν_Q, ν_N (proliferating, quiescent and necrotic cells).

How can the cell velocity \mathbf{u} be determined?

Determination of cell velocity \mathbf{u}

A. ν constant

Let us assume $\nu(\mathbf{x}, t) = \nu^*$. From the mass balance equation we obtain:

$$\nabla \cdot \mathbf{u} = \frac{1}{\nu^*} \Gamma(\nu^*, \sigma, t).$$

Thus \mathbf{u} can be determined if the geometry is 1D. In a sphere, assuming radial symmetry, we have for the scalar velocity field $u(r, t)$ the equation

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u \right) = \frac{1}{\nu^*} \Gamma(\nu^*, \sigma, t), \quad u(0, t) = 0.$$

Cells move as a result of a convective velocity field created by cell proliferation and death.

B. ν constant + Darcy-like closure

We assume

$$\mathbf{u} = -\nabla P,$$

where $P(\mathbf{x}, t)$ is a scalar field that can be denoted as "cell pressure". This assumption is made in analogy with the Darcy law for the motion of liquids in porous media (Darcy-like closure). Since $\nu = \nu^*$ and then $\nabla \cdot \mathbf{u} = \Gamma/\nu^*$, we obtain for P the equation

$$\Delta P = -\frac{1}{\nu^*} \Gamma(\nu^*, \sigma, t) \quad \text{in } \Omega(t)$$

with P prescribed on $\partial\Omega(t)$.

Determination of cell velocity \mathbf{u}

The domain Ω (actually, the shape of the external boundary of the tumour mass) evolves according to

$$\mathbf{u}_n = -\mathbf{n} \cdot \nabla P \quad \text{on } \partial\Omega(t),$$

where \mathbf{n} is the unit outward normal vector in the generic $\mathbf{x} \in \partial\Omega$ and u_n is the normal velocity.

The boundary condition for P has been assumed (Vasaliy & Friedman, Indiana Univ Math 2003; Cristini et al., J Math Biol 2003) of the form

$$P = -\gamma\kappa \quad \text{on } \partial\Omega(t),$$

where κ is the curvature and γ is a coefficient. This assumption arises from the consideration of a "surface tension" at the tumour boundary.

The problem for P is coupled to the problem for the nutrient concentration, σ , that under the assumption of quasi-steady state diffusion has the form

$$\Delta\sigma = f(\nu^*, \sigma) \quad \text{in } \Omega(t)$$

$$\sigma = \sigma^* \quad \text{on } \partial\Omega(t).$$

We remark that this approach allows the description of the tumour evolution from an arbitrary shape in 2D and 3D.

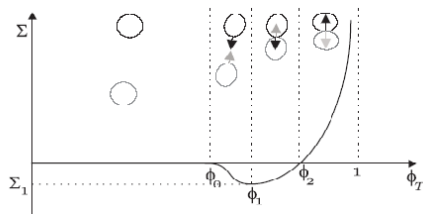
Determination of the cell velocity \mathbf{u}

C. ν non-constant: "avoiding crowd" approach

In this approach (Ambrosi & Preziosi, M3AS 2002) the velocity \mathbf{u} is assumed as:

$$\mathbf{u} = -k\nabla\Sigma(\nu),$$

where Σ can be interpreted as a stress of the cellular component. Σ is zero at $\nu = \nu_2$ (stress-free state) and increases for $\nu > \nu_2$ going to infinity for $\nu \rightarrow 1$. This increase reflects the compression of the cellular material.



The equation for ν becomes a nonlinear diffusion equation:

$$\frac{\partial \nu}{\partial t} + \nabla \cdot (-k\nu \Sigma'(\nu) \nabla \nu) = \Gamma(\nu, \sigma, t) \quad \text{in } \Omega(t)$$

$$\Sigma(\nu) = \Psi \quad \text{on } \partial\Omega(t)$$

with nonlinear diffusivity given by $k\nu \Sigma'(\nu)$. Ψ represents the interaction of the tumour with environment.

Models including the mechanical interactions

The previous approach can be justified by restricting us to consider only the mechanical interaction between cells and extracellular matrix (ECM). Neglecting the inertia term, the linear momentum balance becomes:

$$0 = \nabla \cdot \mathbf{T}_c - m(\nu)(\mathbf{u} - \mathbf{v}_{\text{ECM}}),$$

where \mathbf{T}_c is the stress tensor, and the second term in the rhs represents the friction between cells and ECM, with \mathbf{v}_{ECM} being the ECM velocity. Assuming $\mathbf{v}_{\text{ECM}} = 0$ and the following form for the cell stress \mathbf{T}_c (cells act like an elastic liquid):

$$\mathbf{T}_c = -\Sigma(\nu)\mathbf{I},$$

with \mathbf{I} being the identity matrix, we get

$$\mathbf{u} = -\frac{1}{m(\nu)} \nabla \Sigma(\nu).$$

More advanced models based on the **mixture theory**:

- Biphasic model: cells plus interstitial liquid (Breward et al., J Math Biol 2002; Byrne & Preziosi, Math Med Biol 2003)
- Triphasic models: cells plus liquids plus ECM (Ambrosi & Preziosi, M3AS 2002; Lemon et al., J Math Biol 2006).

Assumptions:

- the cell volume fraction is constant and equal to ν^* in the whole spheroid
- cells die when the nutrient concentration, σ , falls to a critical value σ_N
- viable cells proliferate with rate constant $\chi(\sigma)$
- necrotic cells degrade with rate constant μ_N .

Let the initial radius, R_0 , be such that nutrient concentration is always above σ_N . Then

$$\frac{\partial \nu}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u \nu \right) = \chi(\sigma) \nu, \quad 0 < r < R(t),$$

where R is the tumour radius. Since $\nu = \nu^*$, we obtain

$$u(r, t) = \frac{1}{r^2} \int_0^r s^2 \chi(\sigma(s, t)) ds,$$
$$\dot{R} = u(R(t), t), \quad R(0) = R_0.$$

The concentration σ is the solution of

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \sigma}{\partial r} \right) = f(\sigma), \quad 0 < r < R(t),$$
$$\sigma(R(t), t) = \sigma^*,$$
$$\sigma_r(0, t) = 0.$$

A model for the spherical avascular tumour growth

As t increases, a time $t = t_N$ will be reached such that $\sigma(0, t_N) = \sigma_N$. For $t > t_N$, there exists a radius $\rho_N > 0$ such that $\sigma(r, t)$ and ρ_N are solution of the following problem

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \sigma}{\partial r} \right) = f(\sigma), \quad \rho_N(t) < r < R(t),$$

$$\sigma(R(t), t) = \sigma^*,$$

$$\sigma_r(\rho_N(t), t) = 0,$$

$$\sigma(\rho_N(t), t) = \sigma_N.$$

In this case, the mass balance reads

$$\frac{\partial \nu}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u \nu \right) = \chi(\sigma) \nu, \quad \rho_N(t) < r < R(t),$$

$$\frac{\partial \nu_N}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u \nu_N \right) = -\mu_N \nu_N, \quad 0 < r < \rho_N(t),$$

where ν_N is the volume fraction of necrotic cells. Imposing $\nu = \nu_N = \nu^*$, we obtain

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u \right) = \chi(\sigma), \quad \rho_N(t) < r < R(t),$$

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u \right) = -\mu_N, \quad 0 < r < \rho_N(t).$$

A model for the spherical avascular tumour growth

Thus we get for the velocity field the following expressions:

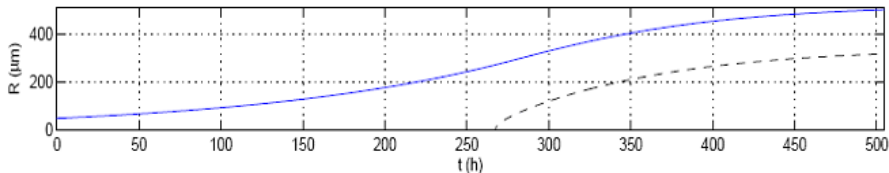
$$u(r, t) = -\frac{\mu_N}{3}r, \quad 0 < r \leq \rho_N(t)$$

$$u(r, t) = -\frac{\mu_N}{3} \frac{\rho_N^3}{r^2} + \frac{1}{r^2} \int_{\rho_N}^r s^2 \chi(\sigma(s, t)) ds, \quad \rho_N(t) < r \leq R(t).$$

Finally, we have

$$\dot{R}(t) = u(R(t), t).$$

The plot shows the evolution of the tumour radius, R . The plot also shows the evolution of the interface $r = \rho_N$ between the necrotic core and the viable rim for t larger than the time, t_N , when the necrosis begins to develop.



Spherical vascular tumour

The presence of a **vascular network inside the tumour** can be described by introducing a distributed source of nutrient (Byrne & Chaplain, Math Biosci 1995). The equation for the nutrient concentration (in the non-necrotic case) becomes

$$\frac{\partial \sigma}{\partial t} - \frac{D}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \sigma}{\partial r} \right) = \lambda_b (\sigma_b - \sigma) - \phi(\sigma), \quad 0 < r < R(t),$$

$$\sigma(R(t), t) = \sigma^*,$$

$$\sigma_r(0, t) = 0,$$

where σ_b is the nutrient concentration in blood, taken as a function of space and time, λ_b is the rate coefficient of nutrient transfer from the vascular network to the tumour tissue, and ϕ represents the consumption rate of tumour cells.

Assuming that the cell volume fraction is constant, the mass balance yields

$$\nabla \cdot \mathbf{u} = \chi(\sigma) - \mu(\sigma),$$

where μ represents the death rate of cells, that are assumed to degrade instantly. Thus we get the following equation for $R(t)$:

$$\dot{R}(t) = \frac{1}{R^2(t)} \int_0^{R(t)} r^2 [\chi(\sigma(r, t)) - \mu(\sigma(r, t))] dr.$$