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Differential equations related to the Williams–Bjerknes tumour model

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Abstract. We investigate an initial value problem which is closely related to the Williams–Bjerknes tumour model for a cancer which spreads through an epithelial basal layer modeled on $I \subset Z^2$. The solution of this problem is a family $p = (p_i(t))$, where each $p_i(t)$ could be considered as an approximation to the probability that the cell situated at i is cancerous at time t. We prove that this problem has a unique solution, it is defined on $[0, +\infty[$, and, for some relevant situations, $\lim_{t\to\infty} p_i(t) = 1$ for all $i \in I$. Moreover, we study the expected number of cancerous cells at time t.

Keywords. Williams–Bjerknes tumour model; expected number of cancerous cells.

1. Introduction

Based on chemical tests and mitotic patterns, Williams and Bjerknes proposed in [8] a model for the cancer spread through an epithelial basal layer. Independently, the Williams–Bjerknes tumour model was formulated within the field of interacting particle systems as the biased voter model (see [7]). Assuming that cells are situated on the lattice Z^2, the set ξ_t^A of sites occupied by cancerous cells at time t, given that the initial state is A, is a Markov process on the state space $\{$finite subsets of $Z^2\}$ thoroughly studied in [1–3,6].

In [5] we studied the spread of cancerous cells through the basal layer of an epithelium modeled on the lattice $I = Z^2$. In that paper we derived differential inequalities for the family $(p_i)_{i\in I}$, where we write $p_i(t)$ for the probability that the cell situated at i is cancerous at time t.

The aim of this paper is to study the following problem:

$$p_i' = -p_i + \frac{\kappa}{\omega_i}\sum_{\|j-i\|_1=1} p_j - (\kappa-1)p_i\frac{1}{\omega_i}\sum_{\|j-i\|_1=1} p_j, \quad \forall i \in I, \tag{1.1}$$

$$p_i(0) = a_i \quad \forall i \in I, \tag{1.2}$$

$$0 \le p_i \le 1 \quad \forall i \in I, \tag{1.3}$$

where I is assumed to be an arbitrary (finite or infinite) nonempty subset of Z^2, for each $i \in I$ the neighbours of the cell located at i are the elements of the set

$$\Omega_i = \{j \in I\colon \|i-j\|_1 = |i_1 - j_1| + |i_2 - j_2| = 1\}$$

whose cardinality is $\omega_i(\le 4)$, and $(a_i)_{i\in I}$ is the initial state of the epithelium. We assume that for $i, j \in I$ there is a sequence of sites $i_0 = i, i_1, \ldots, i_{n-1},\ i_n = j$ with $i_k \in \Omega_{k-1}$ for

$k = 1, \ldots, n$. A computer simulation shows that the solution of the preceding problem provides a good approximation to the Williams–Bjerknes tumour model.

We prove that this problem has a unique solution, it is defined on $[0, +\infty[$, and, for some specially relevant situations, $\lim_{t \to +\infty} p_i(t) = 1 \ \forall i \in I$.

2. The tumour growth model

Cells are assumed to be of two types, normal and cancerous, and are located on a suitable lattice, one at each site. With each cellular division, one daughter remains in the site, while the other displaces a neighbouring cell which is pushed out of the basal layer. Cancerous cells are assumed to divide at a faster rate than normal cells. Splitting times for both normal and cancerous cells are assumed to be independent and have exponential distributions with parameter 1 and $\kappa > 1$, respectively. This makes the probability that a normal cell will split in the time interval $[t, t + \Delta t]$ equals Δt, irrespective of the time since its last division. For the cancerous cells, this event occurs with probability $\kappa \Delta t$.

It is easily seen that the probability of the cell i to be cancerous at time $t + \Delta t$ can be expressed as

$$\begin{aligned} p_i(t + \Delta t) = & p_i(t)\left[1 - \frac{\Delta t}{\omega_i}\sum_{j \in \Omega_i}(1 - u_j(t))\right] + o(\Delta t) \\ & + (1 - p_i(t))\left[\frac{\kappa \Delta t}{\omega_i}\sum_{j \in \Omega_i} v_j(t)\right] + o(\Delta t), \end{aligned}$$

where we write $u_j(t)$ for the conditional probability that the cell located at j is cancerous at time t given that the cell located at i is cancerous and $v_j(t)$ stands for the conditional probability that the cell located at j is cancerous at time t given that the cell located at i is normal. Consequently, we have

$$\frac{p_i(t + \Delta t) - p_i(t)}{\Delta t} = -p_i(t)\frac{1}{\omega_i}\sum_{j \in \Omega_i}(1 - u_j(t)) + (1 - p_i(t))\frac{\kappa}{\omega_i}\sum_{j \in \Omega_i} v_j(t) + \frac{o(\Delta t)}{\Delta t}.$$

Assume that the functions p_i are differentiable on $[0, \tau[$ for some $\tau > 0$ for all $i \in I$ and let Δt approach zero. This yields

$$p_i'(t) = -p_i(t)\frac{1}{\omega_i}\sum_{j \in \Omega_i}(1 - u_j(t)) + (1 - p_i(t))\frac{\kappa}{\omega_i}\sum_{j \in \Omega_i} v_j(t).$$

Since $p_j(t) = u_j(t)p_i(t) + v_j(t)(1 - p_i(t))$, we get

$$\sum_{j \in \Omega_i} p_j(t) = \sum_{j \in \Omega_i} u_j(t)p_i(t) + \sum_{j \in \Omega_i} v_j(t)(1 - p_i(t))$$

and therefore

$$p_i'(t) = -p_i(t)\frac{1}{\omega_i}\sum_{j \in \Omega_i}(1 - u_j(t)) + \frac{\kappa}{\omega_i}\left(\sum_{j \in \Omega_i} p_j(t) - \sum_{j \in \Omega_i} u_j(t)p_i(t)\right).$$

To get a closed system of equations one needs to obtain equations for the functions u_j. These equations involve other still higher order correlation functions. Here we replace each u_j by p_j.

3. Existence and uniqueness of solutions

Let $l_\infty(I)$ denote the set of all real families $x = (x_i)_{i\in I}$ for which $\|x\|_\infty = \sup_{i\in I}|x_i| < +\infty$, which becomes a Banach space with pointwise operations and the supremum norm. For every $i \in I$ let E_i denote the continuous linear functional on $l_\infty(I)$ given by $E_i(x) = x_i$. We will denote by P the closed ball

$$\left\{x \in l_\infty(I):\ \sup_{i\in I}|x_i - 1/2| \le 1/2\right\} = \{x \in l_\infty(I):\ 0 \le x_i \le 1\ \forall i \in I\}$$

whose interior is

$$\begin{aligned}\operatorname{int}(P) &= \left\{x \in l_\infty(I):\ \sup_{i\in I}|x_i - 1/2| < 1/2\right\}\\ &= \bigcup_{0<\rho<\frac{1}{2}} \{x \in l_\infty(I):\ \rho \le x_i \le 1-\rho, \forall i \in I\}.\end{aligned}$$

Let f be the function from $l_\infty(I)$ into itself defined by

$$E_i(f(x)) = -x_i + \frac{\kappa}{\omega_i}\sum_{j\in\Omega_i} x_j - (\kappa - 1)x_i \frac{1}{\omega_i}\sum_{j\in\Omega_i} x_j$$

for all $x \in l_\infty(I)$ and $i \in I$. Let $a \in l_\infty(I)$, and consider the initial value problem on $l_\infty(I)$

$$\begin{cases} x' &= f(x)\\ x(0) &= a. \end{cases} \tag{2}$$

It is clear that if a family of functions $(p_i)_{i\in I}$ is a solution of (2) with $a \in P$, then it satisfies (1.1) and (1.2), and it is well-known that the converse is true for a finite I. The problem is that, for an infinite I, a family of differentiable functions $(p_i)_{i\in I}$ on the interval $[0,\tau[$ may be not differentiable as a $l_\infty(I)$-valued function. This difficulty is solved by our next theorem.

Theorem 1. *Let $a \in P$ and let $(p_i)_{i\in I}$ be a family of functions from the interval $[0,\tau[$ into $[0,1]$. Then the following assertions are equivalent:*

(i) *$(p_i)_{i\in I}$ satisfies (1.1) and (1.2).*
(ii) *The function p from $[0,\tau[$ into $l_\infty(I)$ defined by $p(t) = (p_i(t))_{i\in I}$ for all $t \in [0,\tau[$ is a solution of (2) on $[0,\tau[$.*

Proof. If (ii) obtains, then the chain rule shows that the functions $p_i = E_i \circ p$ are differentiable on $[0,\tau[$ with $p_i'(t) = E_i(p'(t)) = E_i(f(p(t)))$ for all $i \in I$. Consequently, $(p_i)_{i\in I}$ satisfies (1.1). (1.2) is obvious.

Assume that (i) holds. Then it is clear that, for all $i \in I$, the function p_i is infinitely differentiable on $[0,\tau[$. Moreover we have

$$\begin{aligned}|p_i'(t)| &\le |p_i(t)| + \frac{\kappa}{\omega_i}\sum_{j\in\Omega_i}|p_j(t)| + (\kappa-1)|p_i(t)|\frac{1}{\omega_i}\sum_{j\in\Omega_i}|p_j(t)|\\ &\le 1 + \kappa + (\kappa - 1) = 2\kappa\end{aligned}$$

and

$$|p_i''(t)| \leq |p_i'(t)| + \frac{\kappa}{\omega_i}\sum_{j\in\Omega_i}|p_j'(t)| + (\kappa-1)|p_i'(t)|\frac{1}{\omega_i}\sum_{j\in\Omega_i}|p_j(t)|$$
$$+ (\kappa-1)|p_i(t)|\frac{1}{\omega_i}\sum_{j\in\Omega_i}|p_j'(t)|$$
$$\leq 2\kappa + \kappa(2\kappa) + (\kappa-1)(2\kappa) + (\kappa-1)(2\kappa) = 6\kappa^2 - 2\kappa$$

for all $t \in [0,\tau[$ and $i \in I$.

Let $i \in I$, $t \in [0,\tau[$ and $0 \neq h \in R$ such that $t+h \in [0,\tau[$. The mean value theorem provides $\xi,\zeta \in R^+$ such that $|\xi - t| < |h|$, $|\zeta - t| < |\xi - t|$, $p_i(t+h) - p_i(t) = p_i'(\xi)h$, and $p_i'(\xi) - p_i'(t) = p_i''(\zeta)(\zeta - t)$. Hence

$$\left|\frac{p_i(t+h)-p_i(t)}{h} - p_i'(t)\right| = |p_i'(\xi) - p_i'(t)| = |p_i''(\zeta)(\xi - t)|$$
$$\leq (6\kappa^2 - 2\kappa)|\xi - t| \leq (6\kappa^2 - 2\kappa)|h|$$

and therefore

$$\left\|\frac{p(t+h)-p(t)}{h} - (p_i')_{i\in I}\right\|_\infty \leq (6\kappa^2 - 2\kappa)|h|.$$

This shows that p is differentiable on $[0,\tau[$ with $p'(t) = (p_i'(t))_{i\in I}$ for all $t \in [0,\tau[$ and consequently p is a solution of (2). □

In order to apply the classical existence theorem to the problem (2) we first show that the function f is infinitely differentiable.

Lemma 1. *The function f is infinitely differentiable on $l_\infty(I)$ and*

$$\|Df(x)\| \leq 1 + \kappa + 2(\kappa-1)\|x\|_\infty$$

for all $x \in l_\infty(I)$.

Proof. Let $x \in l_\infty(I)$ and T_x be the linear operator from $l_\infty(I)$ into itself defined by

$$E_iT_x(u) = -u_i + \frac{\kappa}{\omega_i}\sum_{j\in\Omega_i}u_j - (\kappa-1)x_i\frac{1}{\omega_i}\sum_{j\in\Omega_i}u_j - (\kappa-1)u_i\frac{1}{\omega_i}\sum_{j\in\Omega_i}x_j$$

for all $u \in l_\infty(I)$ and $i \in I$. We see at once that

$$|E_iT_xu| \leq (1 + \kappa + 2(\kappa-1)\|x\|_\infty)\|u\|_\infty$$

for all $u \in l_\infty(I)$ and $i \in I$, and so

$$\|T_xu\|_\infty \leq (1 + \kappa + 2(\kappa-1)\|x\|_\infty)\|u\|_\infty$$

for all $u \in l_\infty(I)$. Therefore T_x is continuous and

$$\|T_x\| \leq 1 + \kappa + 2(\kappa-1)\|x\|_\infty.$$

Furthermore, for all $i \in I$, we have

$$E_i(f(x+u) - f(x) - T_x(u)) = -(\kappa-1)u_i\frac{1}{\omega_i}\sum_{j\in\Omega_i}u_j$$

and consequently

$$\|f(x+u)-f(x)-T_x(u)\|_\infty \le (\kappa-1)\|u\|_\infty^2$$

for all $u \in l_\infty(I)$. Hence f is differentiable at x with $Df(x)=T_x$.

It is clear that Df is differentiable on $l_\infty(I)$ and $D^2 f$ is easily seen to satisfy

$$E_i(D^2 f(x)(u,v)) = -(\kappa-1)u_i \frac{1}{\omega_i}\sum_{j\in\Omega_i} v_j - (\kappa-1)v_i \frac{1}{\omega_i}\sum_{j\in\Omega_i} u_j$$

for all $x, u, v \in l_\infty(I)$.

Since $D^2 f$ is constant, we conclude that $D^3 f = 0$. □

From the preceding result and ([4]; 10.4.5 and 10.5.2) it may be concluded the following.

Lemma 2. *If* $a \in l_\infty(I)$, *then* (2) *has a unique noncontinuable solution which is defined on an interval* $]-\sigma,\tau[$ *with* $\sigma,\tau > 0$.

From now on, by a solution of (2) we mean a solution of (2) on the interval $[0,\tau[$ which is noncontinuable to the right.

Lemma 3. *If* $a \in \operatorname{int}(P)$, *then the solution* p *of* (2) *is defined on* $[0,+\infty[$ *and there exists* $\rho \in]0,1/2[$ *such that* $\rho e^{-t} \le p_i(t) \le 1-\rho e^{-\kappa t}$ *for all* $t \in [0,+\infty[$ *and* $i \in I$.

Proof. Let $\rho \in]0,1/2[$ such that $\rho \le a_i \le 1-\rho$ for all $i \in I$.

Let $[0,\tau[$ be the interval of existence of p and set

$$\sigma = \sup\{s \in [0,\tau[: p(t) \in \operatorname{int}(P), \forall t \in [0,s[\}.$$

From ([4]; 10.4.5 and 10.5.2) we see that the initial value problem (2) in $\operatorname{int}(P)$ has a unique noncontinuable solution whose restriction to $[0,+\infty[$ is obviously the restriction of p to the interval $[0,\sigma[$.

Fix $i \in I$. Since $0 < p_i(t) < 1$ $\forall t \in [0,\sigma[$, we see that

$$\frac{d(\exp(t)p_i(t))}{dt} = \exp(t)(1-p_i(t))\frac{\kappa}{\omega_i}\sum_{j\in\Omega_i} p_j(t) + \exp(t)p_i(t)\frac{1}{\omega_i}\sum_{j\in\Omega_i} p_j(t) \ge 0$$

for all $t \in [0,\sigma[$. Therefore the function $\exp(t)p_i(t)$ is strictly increasing on $[0,\sigma[$. From this we have

$$\rho \le a_i = p_i(0) \le \exp(t)p_i(t),$$

$\forall t \in [0,\sigma[$. On the other hand, we have

$$p_i'(t) = \kappa(1-p_i(t))\frac{1}{\omega_i}\sum_{j\in\Omega_i} p_j(t) - p_i(t)\left[1-\frac{1}{\omega_i}\sum_{j\in\Omega_i} p_j(t)\right] \le \kappa(1-p_i(t))$$

and therefore $p_i'(t)/(1-p_i(t)) \le \kappa$ $\forall t \in [0,\sigma[$. Consequently,

$$\ln\left(\frac{1-p_i(0)}{1-p_i(t)}\right) = \int_0^t \frac{p_i'(s)}{1-p_i(s)}\,ds \le \int_0^t \kappa\, ds = \kappa t,$$

which gives

$$p_i(t) \leq 1 - (1 - a_i)\exp(-\kappa t) \leq 1 - \rho\exp(-\kappa t)$$

for all $t \in [0, \sigma[$. Hence

$$\rho\exp(-\kappa\sigma) \leq \rho\exp(-t) \leq p_i(t) \leq 1 - \rho\exp(-\kappa t) \leq 1 - \rho\exp(-\kappa\sigma)$$

for all $t \in [0, \sigma[$ and $i \in I$.

Thus the closure of the set $p([0, \sigma[)$ in $l_\infty(I)$ is contained in the set

$$\{x \in l_\infty(I) : \rho\exp(-\kappa\sigma) \leq x_i \leq 1 - \rho\exp(-\kappa\sigma) \forall i \in I\} \subset \mathrm{int}(P).$$

Furthermore, it is immediate that $\|f(p(t))\|_\infty \leq 2\kappa$ for all $t \in [0, \sigma[$. According to ([4]; 10.5.5 and 10.5.5.1), we have $\sigma = +\infty$ and, in consequence, $\tau = +\infty$. □

Theorem 2. *If $a \in P$, then (2) has a unique solution p and this solution satisfies the following properties:*

(i) *p is defined on $[0, +\infty[$.*
(ii) *$0 \leq p_i(t) \leq 1$ for all $t \in [0, +\infty[$ and $i \in I$. Accordingly, p is the unique family of differentiable functions on $[0, +\infty[$ satisfying (1.1), (1.2), and (1.3).*
(iii) *If there are $i_0 \in I$ and $t_0 \in]0, +\infty[$ such that $p_{i_0}(t_0) = 0$, then $p_i(t) = 0$ for all $t \in [0, +\infty[$ and $i \in I$. If there are $i_0 \in I$ and $t_0 \in]0, +\infty[$ such that $p_{i_0}(t_0) = 1$, then $p_i(t) = 1$ for all $t \in [0, +\infty[$ and $i \in I$.*

Proof. Let $\{a_n\}$ be a sequence in $\mathrm{int}(P)$ such that $a = \lim a_n$. Let p_n be the unique solution of (2) with $p_n(0) = a_n$.

From Lemma 1 we see that $\|Df(x)\| \leq 3\kappa - 1 \ \forall x \in \mathrm{int}(P)$. On account of the preceding lemma and ([4]; 10.5.1), we have

$$\|p_m(t) - p_n(t)\|_\infty \leq \|a_m - a_n\|_\infty e^{(3\kappa - 1)t}$$

for all $t \in [0, +\infty[$ and $m, n \in N$. It follows that $\{p_n\}$ is uniformly Cauchy on every compact subset of $[0, +\infty[$ and so $\{p_n\}$ converges uniformly on every compact subset of $[0, +\infty[$ to a function q. Since $\{p'_n\} = \{f(p_n)\}$ converges uniformly on every compact subset of $[0, +\infty[$ to $f(q)$, it may be concluded that q is differentiable on $[0, +\infty[$ with $q' = f(q)$. As $q(0) = \lim p_n(0) = \lim a_n = a$ we have $p = q$, which gives (i).

Lemma 3 leads to $p_n(t) \in P$ for all $t \in [0, +\infty[$ and $n \in N$ and therefore $p(t) = \lim p_n(t) \in P$ for all $t \in [0, +\infty[$. Theorem 1 now shows that p is the unique family of differentiable functions on $[0, +\infty[$ satisfying (1.1), (1.2), and (1.3).

Assume that there exist $i_0 \in I$ and $t_0 \in]0, +\infty[$ such that $p_{i_0}(t_0) = 0$. We claim that $p_i(t) = 0$ for all $t \in [0, +\infty[$ and $i \in I$. By the uniqueness of solutions it suffices to prove that $p_i(t_0) = 0$ for all $i \in I$. If there existed $i_1 \in I$ such that $p_{i_1}(t_0) > 0$, there would be $p_i(t_0) = 0$ and $\sum_{j \in \Omega_i} p_j(t_0) > 0$ for a suitable $i \in I$. Consequently,

$$p'_i(t_0) = \frac{\kappa}{\omega_i} \sum_{j \in \Omega_i} p_j(t_0) > 0.$$

This implies that p_i is strictly increasing on $]t_0 - \delta, t_0 + \delta[$ for a suitable $\delta > 0$, which leads to $p_i(t) < p_i(t_0) = 0$ for some $t \in]0, t_0[$, a contradiction. Likewise, $p_i(t) = 1$ for all $t \in [0, +\infty[$ and $i \in I$ if $p_{i_0}(t_0) = 1$. □

4. Asymptotic behaviour of the tumour model

Theorem 3. *If* $a \in P$ *and* $\inf_{i\in I} a_i > 0$, *then the solution* p *of* (2) *satisfies*

$$\lim_{t\to\infty} \sup_{i\in I} [1 - p_i(t)] = 0.$$

Accordingly, $\lim_{t\to+\infty} p_i(t) = 1$ *for all* $i \in I$.

Proof. Set $\rho = \inf_{i\in I} a_i > 0$. We claim that $p_i(t) \geq \rho$ for all $t \in [0, +\infty[$ and $i \in I$. We only need to show that $q_i(t) \geq \rho \sum_{m=0}^{n} \kappa^m t^m/m!$, for all $t \in [0, +\infty[$, $i \in I$, and $n \in N \cup \{0\}$, where $q_i(t) = \exp(\kappa t) p_i(t)$ $\forall t \in [0, +\infty[$.

From Theorem 2(ii) we deduce that

$$\begin{aligned} p_i'(t) &\geq -p_i(t) + \frac{\kappa}{\omega_i} \sum_{j\in\Omega_i} p_j(t) - (\kappa - 1) p_i(t) \\ &= \frac{\kappa}{\omega_i} \sum_{j\in\Omega_i} p_j(t) - \kappa p_i(t) \end{aligned}$$

and therefore

$$\begin{aligned} q_i'(t) &= \kappa \exp(\kappa t) p_i(t) + \exp(\kappa t) p_i'(t) \\ &\geq \kappa \exp(\kappa t) p_i(t) + \exp(\kappa t) \left(\frac{\kappa}{\omega_i} \sum_{j\in\Omega_i} p_j(t) - \kappa p_i(t) \right) \\ &= \frac{\kappa}{\omega_i} \sum_{j\in\Omega_i} q_j(t) \end{aligned}$$

for all $t \in [0, +\infty[$ and $i \in I$. In particular, $q_i'(t) \geq 0$ and therefore $q_i(t) \geq q_i(0) \geq \rho$ for all $t \in [0, +\infty[$ and $i \in I$. Assume the inequality holds for n; we will prove it for $n + 1$. Since $q_i(t) \geq \rho \sum_{m=0}^{n} \kappa^m t^m/m!$, we have

$$q_i'(t) \geq \frac{\kappa}{\omega_i} \sum_{j\in\Omega_i} q_j(t) \geq \frac{\kappa}{\omega_i} \sum_{j\in\Omega_i} \rho \sum_{m=0}^{n} \frac{\kappa^m t^m}{m!} = \rho \sum_{m=0}^{n} \frac{\kappa^{m+1} t^m}{m!}.$$

Thus

$$q_i(t) \geq q_i(0) + \rho \sum_{m=0}^{n} \frac{\kappa^{m+1} t^{m+1}}{(m+1)!} \geq \rho \sum_{m=0}^{n+1} \frac{\kappa^m t^m}{m!}$$

for all $t \in [0, +\infty[$ and $i \in I$, which proves our claim.

For every $n \in N$, let

$$\nu_n = \frac{\kappa^n \rho \prod_{m=1}^{n} (1 - (m+1)^{-2})}{1 + (\kappa^n - 1) \rho \prod_{m=1}^{n} (1 - (m+1)^{-2})}.$$

We next prove that for every $n \in N$ there is $t_n \in]0, +\infty[$ such that $t_n < t_{n+1}$ and $p_i(t) \geq \nu_n$ for all $i \in I$ and $t \in [t_n, +\infty[$. From what has already been proved, it follows that

$$\begin{aligned} p_i'(t) &= -p_i(t) + (\kappa - 1)(1 - p_i(t)) \frac{1}{\omega_i} \sum_{j\in\Omega_i} p_j(t) + \frac{1}{\omega_i} \sum_{j\in\Omega_i} p_j(t) \\ &\geq -p_i(t) + (\kappa - 1)(1 - p_i(t))\rho + \rho \\ &= \kappa\rho - (1 + (\kappa - 1)\rho) p_i(t) \end{aligned}$$

for all $i \in I$ and $t \in [0, +\infty[$. For every $i \in I$ the function

$$u_i(t) = \exp((1 + (\kappa - 1)\rho)t)p_i(t)$$

satisfies

$$\begin{aligned} u_i'(t) &= (1 + (\kappa - 1)\rho)\mathrm{e}^{(1+(\kappa-1)\rho)t}p_i(t) + \mathrm{e}^{(1+(\kappa-1)\rho)t}p_i'(t) \\ &\geq (1+(\kappa - 1)\rho)\mathrm{e}^{(1+(\kappa-1)\rho)t}p_i(t) + \mathrm{e}^{(1+(\kappa-1)\rho)t}[\kappa\rho - (1 + (\kappa - 1)\rho)p_i(t)] \\ &\geq \kappa\rho\mathrm{e}^{(1+(\kappa-1)\rho)t}, \end{aligned}$$

hence

$$u_i(t) \geq p_i(0) + \frac{\kappa\rho}{1 + (\kappa - 1)\rho}(\mathrm{e}^{(1+(\kappa-1)\rho)t} - 1)$$

and therefore

$$\begin{aligned} p_i(t) &\geq p_i(0)\mathrm{e}^{-(1+(\kappa-1)\rho)t} + \frac{\kappa\rho}{1 + (\kappa - 1)\rho}(1 - \mathrm{e}^{-(1+(\kappa-1)\rho)t}) \\ &\geq \rho\mathrm{e}^{-(1+(\kappa-1)\rho)t} + \frac{\kappa\rho}{1 + (\kappa - 1)\rho}(1 - \mathrm{e}^{-(1+(\kappa-1)\rho)t}) \end{aligned}$$

for all $t \in [0, +\infty[$. Since

$$\lim_{t\to+\infty}\left[\rho\mathrm{e}^{-(1+(\kappa-1)\rho)t} + \frac{\kappa\rho}{1 + (\kappa - 1)\rho}(1 - \mathrm{e}^{-(1+(\kappa-1)\rho)t})\right] = \frac{\kappa\rho}{1 + (\kappa - 1)\rho}$$

and $\kappa\rho/(1 + (\kappa - 1)\rho) > \nu_1$, there exists $t_1 \in]0, +\infty[$ such that

$$\rho\mathrm{e}^{-(1+(\kappa-1)\rho)t} + \frac{\kappa\rho}{1 + (\kappa - 1)\rho}(1 - \mathrm{e}^{-(1+(\kappa-1)\rho)t}) \geq \nu_1$$

for all $t \in [t_1, +\infty[$. Consequently, $p_i(t) \geq \nu_1$ for all $i \in I$ and $t \in [t_1, +\infty[$. Assume that $t_n \in [0, +\infty[$ has been chosen satisfying our requirements. Then we have

$$\begin{aligned} p_i'(t) &= -p_i(t) + (\kappa - 1)(1 - p_i(t))\frac{1}{\omega_i}\sum_{j\in\Omega_i}p_j(t) + \frac{1}{\omega_i}\sum_{j\in\Omega_i}p_j(t) \\ &\geq -p_i(t) + (\kappa - 1)(1 - p_i(t))\nu_n + \nu_n \\ &= \kappa\nu_n - (1 + (\kappa - 1)\nu_n)p_i(t) \end{aligned}$$

for all $t \in [t_n, +\infty[$. Arguing as before we see that

$$p_i(t) \geq \nu_n\mathrm{e}^{-(1+(\kappa-1)\nu_n)(t-t_n)} + \frac{\kappa\nu_n}{1 + (\kappa - 1)\nu_n}(1 - \mathrm{e}^{-(1+(\kappa-1)\nu_n)(t-t_n)})$$

for all $i \in I$ and $t \in [t_n, +\infty[$. Since

$$\begin{aligned} &\lim_{t\to+\infty}\left[\nu_n\mathrm{e}^{-(1+(\kappa-1)\nu_n)(t-t_n)} + \frac{\kappa\nu_n}{1 + (\kappa - 1)\nu_n}(1 - \mathrm{e}^{-(1+(\kappa-1)\nu_n)(t-t_n)})\right] \\ &\quad = \frac{\kappa\nu_n}{1 + (\kappa - 1)\nu_n} \end{aligned}$$

and

$$\frac{\kappa\nu_n}{1 + (\kappa - 1)\nu_n} = \frac{\kappa^{n+1}\rho\prod_{m=1}^{n}(1 - (m + 1)^{-2})}{1 + (\kappa^{n+1} - 1)\rho\prod_{m=1}^{n}(1 - (m + 1)^{-2})} > \nu_{n+1},$$

there exists $t_{n+1} \in]t_n, +\infty[$ such that

$$\nu_n e^{-(1+(\kappa-1)\nu_n)(t-t_n)} + \frac{\kappa\nu_n}{1+(\kappa-1)\nu_n}(1 - e^{-(1+(\kappa-1)\nu_n)(t-t_n)}) \geq \nu_{n+1}$$

for all $t \in [t_{n+1}, +\infty[$. Consequently, $p_i(t) \geq \nu_{n+1}$ for all $i \in I$ and $t \in [t_{n+1}, +\infty[$.

Since $\sup_{i\in I}[1 - p_i(t)] \leq 1 - \nu_n \ \forall t \in [t_n, +\infty[\ \forall n \in N$ and $\lim \nu_n = 1$, it may be concluded that $\lim_{t\to+\infty} \sup_{i\in I}[1 - p_i(t)] = 0$. □

COROLLARY 1

Assume that I is finite. If $a \in P$ and $a \neq 0$, then the solution p of (2) satisfies

$$\lim_{t\to+\infty} p_i(t) = 1$$

for all $i \in I$.

Proof. Let $t_0 \in]0, +\infty[$. Theorem 2(iii) now shows that $p_i(t_0) > 0 \ \forall i \in I$. The family $(q_i(t))_{i\in I} = (p_i(t + t_0))_{i\in I}$ is a solution of (2) with $a = (p_i(t_0))_{i\in I}$ which satisfies the requirement in the preceding theorem. Consequently, $\lim_{t\to\infty} q_i(t) = 1 \ \forall i \in I$, which proves the theorem. □

5. Mean tumour growth

In the remainder of this paper we assume that $a \in P$ and p is the solution of (2). For every $t \in [0, +\infty[$,

$$\mu(t) = \sum_{i\in I} p_i(t) \in [0, +\infty]$$

is the expected number of cancerous cells at the time t.

To study the function μ we introduce the set $l_1(I)$ set of all real families $x = (x_i)_{i\in I}$ such that $\|x\|_1 = \sum_{i\in I} |x_i| < +\infty$. $l_1(I)$ with pointwise operations and the norm $\|\cdot\|_1$ is a Banach space. It should be noted that $l_1(I) \subset l_\infty(I)$ and $\|x\|_\infty \leq \|x\|_1 \ \forall x \in l_1(I)$.

It is a simple matter to show that the restriction of f to $l_1(I)$ maps into $l_1(I)$. We write g for this restriction. If $a \in l_1(I)$ then we can consider the following initial value problem on $l_1(I)$

$$\begin{cases} x' &= g(x) \\ x(0) &= a. \end{cases} \tag{3}$$

Lemma 4. *The function g is infinitely differentiable on $l_1(I)$ and*

$$\|Dg(x)\| \leq 1 + 4\kappa + 5(\kappa - 1)\|x\|_\infty$$

for all $x \in l_1(I)$.

Proof. Let $x \in l_1(I)$ and S_x be the linear operator from $l_1(I)$ into itself defined by

$$E_i S_x(u) = -u_i + \frac{\kappa}{\omega_i}\sum_{j\in\Omega_i} u_j - (\kappa - 1)x_i \frac{1}{\omega_i}\sum_{j\in\Omega_i} u_j - (\kappa - 1)u_i \frac{1}{\omega_i}\sum_{j\in\Omega_i} x_j$$

for all $u \in l_1(I)$ and $i \in I$. We have

$$|E_i S_x u| \leq |u_i| + \frac{\kappa}{\omega_i} \sum_{j \in \Omega_i} |u_j| + (\kappa - 1)\|x\|_\infty \frac{1}{\omega_i} \sum_{j \in \Omega_i} |u_j| + (\kappa - 1)|u_i| \|x\|_\infty$$

$$\leq |u_i| + \kappa \sum_{j \in \Omega_i} |u_j| + (\kappa - 1)\|x\|_\infty \sum_{j \in \Omega_i} |u_j| + (\kappa - 1)|u_i| \|x\|_\infty$$

for all $u \in l_1(I)$ and $i \in I$, and so

$$\|S_x u\|_1 \leq \|u\|_1 + 4\kappa \|u\|_1 + 4(\kappa - 1)\|x\|_\infty \|u\|_1 + (\kappa - 1)\|u\|_1 \|x\|_\infty$$

for all $u \in l_1(I)$, since obviously $\sum_{i \in I} \sum_{j \in \Omega_i} |u_j| \leq 4 \sum_{i \in I} |u_i|$. Consequently, S_x is continuous and $\|S_x\| \leq 1 + 4\kappa + 5(\kappa - 1)\|x\|_\infty$. If $i \in I$ then

$$E_i(g(x + u) - g(x) - S_x(u)) = -(\kappa - 1) u_i \frac{1}{\omega_i} \sum_{j \in \Omega_i} u_j$$

and therefore $\|g(x + u) - g(x) - S_x(u)\|_1 \leq 4(\kappa - 1)\|u\|_1^2$ for all $u \in l_1(I)$. Thus g is differentiable at x with $Dg(x) = S_x$. From this g is easily checked to be 2 times differentiable on $l_1(I)$ with

$$E_i(D^2 g(x)(u, v)) = -(\kappa - 1) u_i \frac{1}{\omega_i} \sum_{j \in \Omega_i} v_j - (\kappa - 1) v_i \frac{1}{\omega_i} \sum_{j \in \Omega_i} u_j$$

for all $x, u, v \in l_1(I)$. Since $D^2 g$ is constant, we conclude that $D^3 g = 0$. □

Theorem 4. *If* $\mu(0) < +\infty$ *then* $\mu(t) \leq \mu(0) e^{(5\kappa - 4)t} < +\infty$ *for all* $t \in [0, +\infty[$.

Proof. As $\mu(0) < +\infty$ we have $a \in P \cap l_1(I)$. From the preceding lemma and ([4]; 10.4.5 and 10.5.2) it follows that (3) has a unique noncontinuable solution q which is defined on an interval $]-\sigma, \tau[$ with $\sigma, \tau > 0$.

Since $\|\cdot\|_\infty \leq \|\cdot\|_1$, it follows immediately that q is differentiable on $]-\sigma, \tau[$ as a $l_\infty(I)$-valued function and obviously satisfies (2). Consequently, $q(t) = p(t)$ for all $t \in [0, \tau[$.

For every $t \in [0, \tau[$, the mean value theorem ([4]; 8.5.4) gives

$$\|g(q(t))\|_1 = \|g(q(t)) - g(0)\|_1 \leq \|q(t)\|_1 \sup_{0 \leq \xi \leq 1} \|Dg(\xi q(t))\|$$

and lemma 4 now shows that

$$\|g(q(t))\|_1 \leq \|q(t)\|_1 \sup_{0 \leq \xi \leq 1} [1 + 4\kappa + 5(\kappa - 1)\|\xi q(t)\|_\infty]$$

$$\leq \|q(t)\|_1 [1 + 4\kappa + 5(\kappa - 1)].$$

Since $q(t) = q(0) + \int_0^t g(q(s)) \mathrm{d}s$, we see that

$$\|q(t)\|_1 \leq \|q(0)\|_1 + \int_0^t \|g(q(s))\|_1 \mathrm{d}s$$

$$\leq \|q(0)\|_1 + \int_0^t (5\kappa - 4)\|q(s)\|_1 \mathrm{d}s$$

for all $t \in [0, \tau[$ and Gronwall lemma ([4]; 10.5.1.3) now yields

$$\|q(t)\|_1 \leq \|q(0)\|_1 e^{(5\kappa - 4)t}$$

for all $t \in [0, \tau[$. Therefore

$$\|q(t)\|_1 \leq \|q(0)\|_1 e^{(5\kappa - 4)\tau}$$

for all $t \in [0, \tau[$. On account of ([4]; 10.5.5 and 10.5.5.1), we have $\tau = +\infty$. Since $q(t) = p(t) \in [0, 1]$ $\forall t \in [0, +\infty[$, we conclude that $\mu(t) = \|q(t)\|_1 < +\infty$ for all $t \in [0, +\infty[$. □

Theorem 5. *If* $\mu(0) < +\infty$ *then the function* μ *is increasing and infinitely differentiable on* $[0, +\infty[$ *with* $\mu^{(n)}(t) = \sum_{i \in I} p_i^{(n)}(t)$ *for all* $t \in [0, +\infty[$ *and* $n \in N$.

Proof. In the proof of the preceding theorem we proved that p is the solution of (3), and consequently $p : [0, +\infty[\to l_1(I)$ is infinitely differentiable on $[0, +\infty[$. On the other hand, let φ be the continuous linear functional on $l_1(I)$ defined by $\varphi(x) = \sum_{i \in I} x_i$ $\forall x \in l_1(I)$. φ is infinitely differentiable on $l_1(I)$. Hence $\mu = \varphi \circ p$ is infinitely differentiable on $[0, +\infty[$ and an easy computation shows that $\mu^{(n)}(t) = \sum_{i \in I} p_i^{(n)}(t)$ for all $t \in [0, +\infty[$ and $n \in N$.

For every $t \in [0, +\infty[$, we have

$$\begin{aligned}
\mu'(t) &= \sum_{i \in I} p_i'(t) \\
&= -\sum_{i \in I} p_i(t) + \kappa \sum_{i \in I} \frac{1}{\omega_i} \left(\sum_{j \in \Omega_i} p_i(t) \right) - (\kappa - 1) \sum_{i \in I} \left(p_i(t) \frac{1}{\omega_i} \sum_{j \in \Omega_i} p_j(t) \right) \\
&= -\mu(t) + \kappa \mu(t) - (\kappa - 1) \sum_{i \in I} \left(p_i(t) \frac{1}{\omega_i} \sum_{j \in \Omega_i} p_j(t) \right) \\
&\geq -\mu(t) + \kappa \mu(t) - (\kappa - 1) \sum_{i \in I} p_i(t) = 0
\end{aligned}$$

which shows that μ is increasing on $[0, +\infty[$. □

From Corollary 1 and the preceding theorem we deduce the following.

COROLLARY 2

If I *is finite then* μ *is an infinitely differentiable increasing function on* $[0, +\infty[$. *If* $a \neq 0$, *then* $\lim_{t \to +\infty} \mu(t)$ *equals the cardinality of* I.

References

[1] Bramson M and Griffeath D, The asymptotic behavior of a probabilistic model for tumor growth, in: *Biological growth and spread.* Lecture Notes in Biomath. (Berlin: Springer-Verlag) (1979) vol. 38, pp. 165–172.

[2] Bramson M and Griffeath D, On the Williams–Bjerknes tumour growth model: II. *Math. Proc. Cambridge Philos. Soc.* **88** (1980) 339–357.

[3] Bramson M and Griffeath D, On the Williams–Bjerknes tumour growth model I. *Ann. Probab.* **9** (1981) 173–185.

[4] Dieudonne J, *Foundations of modern analysis*. (New York: Academic Press) (1960)
[5] Martinez F and Villena A R, An upper bound of the mean growth in the Williams–Bjerknes tumour model. *J. Appl. Anal.* **5** (1999) 277–282
[6] Richardson D, Random growth in a tessellation. *Math. Proc. Cambridge Philos. Soc.* **74** (1973) 515–528
[7] Schwartz D, Applications of duality to a class of Markov processes, *Ann. Probab.* **5** (1977) 522–532
[8] Williams T and Bjerknes R, Stochastic model for abnormal clone spread through epithelial basal layer. *Nature* **236** (1972) 19–21