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AN UPPER BOUND OF THE MEAN GROWTH IN THE WILLIAMS–BJERKNES TUMOUR MODEL

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Abstract. We consider a cancer started with a single cancerous cell which spreads through an epithelial basal layer according to the Williams–Bjerknes tumour model on the lattice $\mathbb{Z}^2$. We prove that the expected number $\mu(t)$ of cancerous cells at time t satisfies $\lim_{t\to+\infty} \frac{\mu(t)}{t^\rho} = 0$ for all $\rho > 2$.

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 (see also [5]). Independently, the Williams–Bjerknes tumour model was formulated within the field of interacting particle systems as the biased voter model (see [7]).

We consider the spread of cancerous cells started with a single cancerous cell at the origin through the basal layer of an epithelium modeled on

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the lattice $\mathbb{Z}^2$. The set ξ_t^A of sites occupied by cancerous cells at time t, given that the initial state is A, is a Markov proces on the state space $\{\text{finite subsets of } \mathbb{Z}^2\}$ thoroughly studied in [1–3], [6]. Bramson and Griffeath showed that the tumour has a linear rate of radial growth and this suggests that the expected number of cancerous cells has a quadratic rate of growth. In this paper we give a very basic proof, without involve the outstanding results of Bramson and Griffeath, of the following theorem on the asymptotic behaviour of the mean tumour growth.

Theorem. *Let $\mu(t)$ be the expected number of cancerous cells at time t for the Williams–Bjerknes tumour model starting from a single cancerous cell. Then*

$$\lim_{t\to+\infty} \frac{\mu(t)}{t^\rho} = 0$$

for all $\rho > 2$.

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 celular 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 $\kappa\Delta t$.

3. Differential inequalities for the tumour model

Cells are situated on the lattice $\mathbb{Z}^2$. For each $i \in \mathbb{Z}^2$ the neighbours of i are given by

$$\omega_i = \{(i_1-1, i_2), (i_1, i_2-1), (i_1+1, i_2), (i_1, i_2+1)\},$$

$p_i(t)$ stands for the probability that the cell situated at i is cancerous at time t and $\mu(t) = \sum_{i\in\mathbb{Z}^2} p_i(t)$ is the expected number of cancerous cells at time t.

For the cell situated at i to be cancerous at time $t + \Delta t$, either it is cancerous at time t and no normal neighbouring cell displaces it in the time interval $[t, t+\Delta t]$, or else it is normal at time t and a cancerous neighbouring cell splits and displaces it in $[t, t+\Delta t]$. Consequently, for each $i \in \mathbb{Z}^2$, the probability of the cell i to be cancerous at time $t+\Delta t$ can be expressed as

$$p_i(t+\Delta t) = p_i(t)u_i(t) + (1-p_i(t))\left[\frac{\kappa \Delta t}{4}\sum_{j\in\omega_i} v_j(t)\right] + o(\Delta t),$$

where we write $u_i(t)$ for the conditional probability that no normal neighbouring cell displaces the cell located at i in the time interval $[t, t+\Delta t]$ given that the cell i is cancerous and, for $j \in \omega_i$, we write $v_j(t)$ for the conditional probability that the cell located at j is cancerous at time t given that the cell located at i is normal at time t. Since $u_i(t) \leq 1$, we have

$$p_i(t+\Delta t) \leq p_i(t) + (1-p_i(t))\left[\frac{\kappa \Delta t}{4}\sum_{j\in\omega_i} v_j(t)\right] + o(\Delta t).$$

On the other hand, for each $j \in \omega_i$, we have

$$(1-p_i(t))v_j(t) + p_i(t)w_j(t) = p_j(t),$$

where $w_j(t)$ is the conditional probability that the cell located at j is cancerous at time t given that the cell located at i is cancerous at time t. Thus $(1-p_i(t))v_j(t) \leq p_j(t)$. Consequently,

$$\frac{1}{4}\sum_{j\in\omega_i} v_j(t) \leq p_i(t)\frac{1}{4}\sum_{j\in\omega_i} v_j(t) + \frac{1}{4}\sum_{j\in\omega_i} p_j(t).$$

Since $\frac{1}{4}\sum_{j\in\omega_i} v_j(t) \leq 1$, we have

$$\frac{1}{4}\sum_{j\in\omega_i} v_j(t) \leq p_i(t) + \frac{1}{4}\sum_{j\in\omega_i} p_j(t)$$

and so

$$\frac{p_i(t+\Delta t) - p_i(t)}{\Delta t} \leq (1-p_i(t))\kappa\left[p_i(t) + \frac{1}{4}\sum_{j\in\omega_i} p_j(t)\right] + \frac{o(\Delta t)}{\Delta t}.$$

Assume that the functions p_i are differentiable for all $i \in \mathbb{Z}^2$ and let Δt approach zero. This yields the following family of differential inequalities

$$p_i'(t) \leq \kappa(1-p_i(t))\left[p_i(t) + \frac{1}{4}\sum_{j\in\omega_i} p_j(t)\right], \forall t \in [0, +\infty[, \forall i \in \mathbb{Z}^2.$$

The initial state of the epithelium is given by $p_0(0) = 1$ and $p_i(0) = 0$ for all $i \in \mathbb{Z}^2 \setminus \{0\}$.

Lemma. *$p_i(t) \leq 1 - \exp(-2^n\kappa^n t^n/n!)$ for all $t \in [0, +\infty[$, $i \in \mathbb{Z}^2 \setminus \Omega_{n-1}$, and $n \in \mathbb{N}$, where we write Ω_n for the set $\{j \in \mathbb{Z}^2 \colon |j_1| + |j_2| \leq n\}$.*

Proof. For all $t \in [0, +\infty[$ and $i \in \mathbb{Z}^2$, we have $\frac{1}{4}\sum_{j\in\omega_i} p_j(t) \leq 1$, and hence

$$p_i'(t) \leq 2\kappa(1 - p_i(t)).$$

From this we deduce that

$$p_i(t) \leq 2\kappa t - 2\kappa \int_0^t p_i(s)ds,$$

and Gronwall lemma [4, 10.5.1.3] gives $p_i(t) \leq 1 - e^{-2\kappa t}$ for all $t \in [0, +\infty[$ and $i \in \mathbb{Z}^2 \setminus \Omega_0$.

Assume that $p_i(t) \leq 1 - e^{-2^n\kappa^n t^n/n!}$ for all $t \in [0, +\infty[$ and $i \in \mathbb{Z}^2 \setminus \Omega_{n-1}$. Let $i \in \mathbb{Z}^2 \setminus \Omega_n$. Then $\omega_i \subset \mathbb{Z}^2 \setminus \Omega_{n-1}$ and hence

$$\begin{aligned} p_i'(t) &\leq \kappa(1 - p_i(t)) \left[p_i(t) + \frac{1}{4}\sum_{j\in\omega_i} p_j(t) \right] \\ &\leq \kappa(1 - p_i(t)) \left[\left(1 - e^{-2^n\kappa^n t^n/n!}\right) + \frac{1}{4}\sum_{j\in\omega_i} \left(1 - e^{-2^n\kappa^n t^n/n!}\right) \right] \\ &= 2\kappa(1 - p_i(t)) \left(1 - e^{-2^n\kappa^n t^n/n!}\right) \leq 2\kappa(1 - p_i(t)) \frac{2^n\kappa^n t^n}{n!} \end{aligned}$$

which gives

$$p_i(t) \leq \frac{2^{n+1}\kappa^{n+1}t^{n+1}}{(n+1)!} - \int_0^t \frac{2^{n+1}\kappa^{n+1}s^n}{n!} p_i(s)ds$$

for all $t \in [0, +\infty[$. Finally, Gronwall lemma [4, 10.5.1.3] yields $p_i(t) \leq 1 - e^{-2^{n+1}\kappa^{n+1}t^{n+1}/(n+1)!}$ for all $t \in [0, +\infty[$, which proves the result. □

Proof of the Theorem. Since, for every $n \in \mathbb{N}$, the cardinality of the set $\Omega_n \setminus \Omega_{n-1}$ is $4n$, the preceding lemma shows that

$$\mu(t) \leq 1 + \sum_{n=1}^{\infty} 4n \left(1 - e^{-\tau^n t^n/n!}\right) \tag{1}$$

for all $t \in [0, +\infty[$, where we write $\tau = 2\kappa$.

Let $\rho > 2$ and fix $\rho > \eta > 2$. For every $n \in \mathbb{N}$ with $n > \eta$ let φ_n and ϑ_n be the functions from $]0, +\infty[$ into $\mathbb{R}$ defined by

$$\begin{aligned}\varphi_n(t) =& \frac{1 - e^{-\tau^n t^n/n!}}{t^\eta} \\ \vartheta_n(t) =& \frac{\tau^n t^n}{(n-1)!} e^{-\tau^n t^n/n!} + \eta e^{-\tau^n t^n/n!} - \eta\end{aligned}$$

and let

$$t_n = \tau^{-1}[(n-\eta)(n-1)!]^{1/n}.$$

It is a simple matter to show that ϑ_n is strictly increasing on $]0, t_n]$ and therefore

$$0 = \lim_{t \to 0} \vartheta_n(t) < \vartheta_n(t)$$

for all $t \in]0, t_n]$. ϑ_n is easily checked to be strictly decreasing on $[t_n, +\infty[$ and obviously $\lim_{t\to+\infty} \vartheta_n(t) = -\eta$. Hence $\vartheta_n(s_n) = 0$ for some $s_n \in]t_n, +\infty[$. Since $\varphi_n'(t) = t^{-\eta-1}\vartheta_n(t)$ $\forall t \in]0, +\infty[$, it may be concluded that φ_n is strictly increasing on $]0, s_n]$ and it is strictly decreasing on $[s_n, +\infty[$. Consequently, we have

$$0 = \lim_{t \to 0} \varphi_n(t) < \varphi_n(t) \leq \varphi_n(s_n) \qquad \forall t \in]0, s_n],$$

$$0 = \lim_{t \to +\infty} \varphi_n(t) < \varphi_n(t) \leq \varphi_n(s_n) \quad \forall t \in [s_n, +\infty[$$

and therefore

$$0 < \varphi_n(t) \leq \frac{1 - e^{-\tau^n s_n^n/n!}}{s_n^\eta} \leq \frac{1}{s_n^\eta} < \frac{1}{t_n^\eta} = \frac{\tau^\eta}{[(n-\eta)(n-1)!]^{\eta/n}}$$

for all $t \in]0, +\infty[$ and $n > \eta$. On the other hand, $\sum_{n=1}^\infty n^{1-\eta} < +\infty$ and by the Stirling formula

$$\lim_{n \to +\infty} \frac{\tau^\eta n^\eta}{[(n-\eta)(n-1)!]^{\eta/n}} = (\tau e)^\eta.$$

Consequently,

$$M = \sum_{n=1}^\infty 4n \frac{\tau^\eta}{[(n-\eta)(n-1)!]^{\eta/n}} = \sum_{n=1}^\infty 4n^{1-\eta} \frac{\tau^\eta n^\eta}{[(n-\eta)(n-1)!]^{\eta/n}} < +\infty.$$

Set $m \in \mathbb{N}$ with $m > \eta$. From (1) it may be concluded that

$$\begin{aligned}\frac{\mu(t)}{t^\rho} \quad &\leq \frac{1 + 4(1 + \cdots + m)}{t^\rho} + \frac{1}{t^{\rho-\eta}} \sum_{n=m+1}^\infty 4n\varphi_n(t) \\ &\leq \frac{1 + 4(1 + \cdots + m)}{t^\rho} + \frac{M}{t^{\rho-\eta}}\end{aligned}$$

for all $t \in]0, +\infty[$ and therefore $\lim_{t \to +\infty} \dfrac{\mu(t)}{t^\rho} = 0.$ □

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