MODELING GROWTH WITH RANDOM SETS

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ABSTRACT

It is often the case that the future growth of an entity depends not only on its current size but on its shape as well. For example, discovery of a spheroidal tumor of volume V in a patient would likely be viewed differently by an oncologist than discovery of two adjacent spheroidal tumors each of volume $V/2$. Much of the literature on growth models ignores the shape aspect. Through stochastic geometric models, their simulation and their fitting to data, it is shown how growth processes can be modeled morphologically.

Keywords: Boolean model, dominoes, foci, hitting function, image analysis, Poisson point process, tumor growth, Williams-Bjerknes tumor growth model
AMS Subject Classification: Primary: 60D05; Secondary: 62F10

1. Introduction

Growth of an entity can be observed and measured in a number of different ways; it is rarely one-dimensional, leading to ambiguity as to how the process can be summarized and analyzed. For example, cellular organization is known to be important in characterizing tumor growth (Rubin, 1982), but most of the mathematical models have used one-dimensional summaries (e.g., volume, number of cells, leading front, mean radius) of the tumor in (sometimes stochastic) differential equations. These contributions (see e.g., Laird, 1964; Burton, 1966; Saidel et al., 1976; Sawyer, 1977; Hanson and Tier, 1982; Bartoszynski et al., 1982; Le Cam, 1982; Miller et al., 1982; Adam, 1986; Swan, 1987) are typically answering different questions than are being asked in this article, and are usually meant for applications where incidence data on many cancer patients are available.

The spatial component of growth models, while less prominent, has not been ignored completely (see e.g., Shymko and Glass, 1976; Green 1980; Goodall, 1985; Tautu, 1986; Adam, 1987). Furthermore, interacting particle models, built at the cellular level (see Section 2.2) allow simulations of and conjectures about the shape of tumors. Theoretical results have appeared that show the tumor to be asymptotically (i.e., as time tends to infinity) circular. Nevertheless, none of these articles is relevant to the inference problems encountered when analyzing data like the sequence of images presented in Section 3.

I am interested in following the growth of *one* tumor in *one* patient at a supracellular level, and modeling its changes in shape and size. Necessarily then, the data have to be good quality images, sequenced at fixed time intervals apart, and photographed under identical conditions. *In vivo* data of this type are unknown (to me), partly because tumors have been surgically removed as soon as possible after discovery, partly because the precision of X-ray pictures has been inadequate for detailing tumor shape, and partly because the importance of taking pictures under *identical* conditions, sequenced at fixed time intervals, has not been clinically appreciated. Apart from simply looking at the sequence of pictures, how can the clinician analyze such data? This article explores some possibilities in this direction. It is hoped that more theoretical research in image analysis, combined with higher resolution sensing, will lead to a better description and understanding of tumor growth. Good quality *in vitro* pictures are analyzed in Section 3 in this article, to demonstrate what can be done at present; the fits are remarkably good.

By now, molecular biologists know quite a lot about the formation of cancer cells and there are a number of theories that explain their clinical observations. It is not my intention here to give a comprehensive review of this literature, nor is it immediately relevant to the spatial scale at which the above-mentioned image data are analyzed. Nevertheless, it seems that several aspects are worth mentioning.

A good review of the mathematical theories of carcinogenesis can be found in the papers by Whittemore (1978), Whittemore and Keller (1978), Forbes and Gibberd (1984), and Murdoch et al. (1987). The process of carcinogenesis is generally considered to follow the degeneration of a normal cell to a malignant state through a finite number of intermediate stages; heritable alterations to the cell are accumulated at each stage. What causes this degeneration? It is generally thought that it starts at the level of DNA, the genetic material of the cell. Normal cells contain DNA segments called protooncogenes that appear to be responsible for regulation of cell growth. A *carcinogen*

alters the DNA by transforming protooncogenes to oncogenes (DNA segments that produce cancer when transferred to normal cells). The effects of exposure to a carcinogen are often not seen for many years after the exposure occurred.

Other factors, such as hormones, dietary components, asbestos, etc. (called *promoters*) then modify cells or body defence mechanisms to allow for more rapid growth once the cellular DNA has been altered. Cell organization is also important, but it seems that this spatial component has not been given the attention it deserves (Rubin, 1982, 1985). The implication is that to understand tumor growth in humans, it is necessary to understand the growth process at the supracellular as well as the cellular level. Section 2 builds a spatial model of growth that can be interpreted at both global and local levels; to illustrate the flexibility of the model, various simulations are presented. Section 3 summarizes a model-based analysis of a sequence of images of a tumor growing. Discussion and conclusions are given in Section 4.

2. Random-set models

A theory of random sets, proposed independently by Matheron (1971, 1975) and Kendall (1974), has been developed to handle data collected by imaging or probing an object. Cressie and Laslett (1987) summarize the theory and identify the *hitting function* as an analogue of the cumulative distribution function for random variables.

Suppose X is a random set in $\mathbb{R}^d$;

$$T_X(K) \equiv Pr(X \cap K \neq \emptyset);\ K \in \mathcal{K}, \tag{2.1}$$

where $\mathcal{K}$ is the space of all compact set in $\mathbb{R}^d$, is defined to be the hitting function of X. Choquet's theorem for random sets (Matheron, 1971) states that X is characterized by its hitting function T_X. In principle then, random-set models can be constructed from specification of the hitting function up to several unknown parameters, and data can be used to make inference on these parameters.

Cressie and Laslett (1987) argue that the real potential of random-set theory is yet to be realized because of a dearth of hitting-function models. One class of models, viz. the Boolean models, have a particularly simple hitting function:

$$T_X(K) = 1 - \exp\{-\lambda E(|\check{Z} \oplus K|)\};\ K \in \mathcal{K}. \tag{2.2}$$

Some explanation of the notation in (2.2) is needed:

$$A \oplus B \equiv \{\underline{a} + \underline{b} : \underline{a} \in A, \underline{b} \in B\};\ A, B \subset \mathbb{R}^d, \tag{2.3}$$

$$\check{A} \equiv \{-\underline{a} : \underline{a} \in A\};\ A \subset \mathbb{R}^d,$$

$$|A| \equiv \int_A d\underline{s};\ A \subset \mathbb{R}^d. \tag{2.4}$$

The random set known as the Boolean model is obtained as follows:

(i) The events $\{\underline{s}_1, \underline{s}_2, \ldots\}$ of a homogeneous Poisson point process D, intensity λ, form the germs (or foci) of the model.

(ii) Independent and identically distributed random sets $Z_1, Z_2, \ldots$, are generated according to the probability law of the random set Z; these form the grains of the model.

(iii) The grains are translated to the germs:

$$Z_1 \oplus \{\underline{s}_1\}, Z_2 \oplus \{\underline{s}_2\}, \ldots$$

(iv) The union of the sets in (iii) define the Boolean model X:

$$X \equiv \cup\{Z_i(\underline{s}_i) : \underline{s}_i \in D\}, \tag{2.5}$$

where D is a homogeneous Poisson point process, and

$$A(\underline{h}) \equiv A \oplus \{\underline{h}\}. \tag{2.6}$$

Cressie and Laslett (1987) summarize various generalizations that are possible; in particular, if (i) is modified to:

(i*) The events $\{\underline{s}_1, \underline{s}_2, \ldots\}$ of an inhomogeneous Poisson point process D, intensity function $\{\lambda(\underline{s}) : \underline{s} \in \mathbb{R}^d\}$, form the germs (or foci) of the model,

then X given by (2.5) has hitting function,

$$T_X(K) = 1 - \exp\{-E(|\check{Z} \oplus K|_\lambda)\};\ K \in \mathcal{K}, \tag{2.7}$$

where

$$|A|_\lambda \equiv \int_A \lambda(\underline{s}) d\underline{s}. \tag{2.8}$$

The idea of tumor growth occurring at (random) germs or *foci*, as in the Boolean model, is clinically verifiable (Chover and King, 1985). The same principle is now applied to the tumor itself as it grows, viz. within the tumor there are foci about which growth occurs. Needless to say, there will be orders of magnitude more foci in malignant tissue than in normal tissue. Let X_1 denote the tumor at time $t = 1$, and $F_1 \subset X_1$ denote the foci, countable in number. Then the tumor at time $t = 2$ is modeled to be:

$$X_2 = \cup\{Z_i(\underline{s}_i) : \underline{s}_i \in F_1\}, \tag{2.9}$$

where $Z_1, Z_2, \ldots$, are independent copies of a random set Z. This model was first proposed by Cressie (1984), where F_1 consisted of Poisson points, homogeneous on X_1; more details are given in Section 2.1. The case where F_1 is a countable number of regularly-spaced nodes of a grid in $\mathbb{R}^d$ is considered in Section 2.2.

2.1 Poisson foci

For Poisson foci in X_1, the model (2.9) can be written as

$$X_2 = \cup\{Z_i(\underline{s}_i) : \underline{s}_i \in D\}, \tag{2.10}$$

where from (i*), D is an inhomogeneous Poisson process with intensity function,

$$\lambda(\underline{s}) = \begin{cases} \lambda; & \underline{s} \in X_1 \\ 0; & \text{otherwise.} \end{cases} \tag{2.11}$$

Then (2.7) yields the hitting function,

$$T_{X_2}(K) = 1 - \exp\{-\lambda E(|(\check{Z} \oplus K) \cap X_1|)\}, \tag{2.12}$$

which is used extensively in analyzing the tumor-growth data of Section 3.

Simulations of (2.10) yield pictures that evoke images of tumor growth. Figure 1 shows a progression from an initial disk in (a) through to an irregular set in (d). Each set is generated from the previous one via the relations (2.10) and (2.11), with grain Z in each case being a disk centered at the origin, of fixed radius. This spheroidal growth is often seen in experiments (Haji-Karim and Carlsson, 1978; Martinez and Griego, 1980), and has been proved mathematically for certain stochastic models of tumor growth (Richardson, 1973; Schurger, 1979; Bramson and Griffeath, 1980, 1981; Durrett and Liggett, 1981).

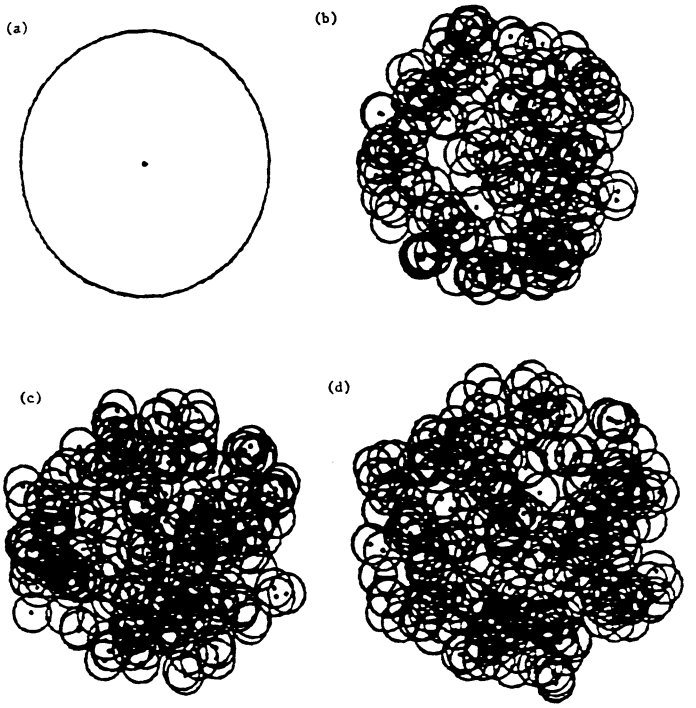

Figure 1: Simulation of the model (2.10), (2.11), where (a) shows the disk (circle and its interior) X_1, and (b) shows X_2. The set X_3 in (c) is obtained from X_2 in the same way X_2 is obtained from X_1; similarly for X_4 in (d). The random grain Z is a disk of fixed radius.

It is not expected that simulations such as Figure 1 are a realistic picture of *in vivo* growth over long time periods. Initially, the growth is uninhibited, but before long lack of blood supply to parts of the tumor, as well as tissue barriers, result in a more complicated growth pattern. It is not my intention to model such patterns here, but I shall mention other researchers who have; without exception they are only able to simulate and not to perform statistical inference (cf. Section 3) with their models. Notable is the work of Duchting (1980) and his co-workers (Duchting and Dehl, 1980;

Duchting and Vogelsaenger, 1981, 1983). See also Ransom (1977), who models and then simulates the displacements that occur when interior tumor cells divide.

It is my hope that the model (2.10), (2.11) provides a good description of a variety of growth processes; this will depend on the spatial scale of observations and the type of questions being asked. An important requirement is to be able to make statistical inferences about λ and the law of Z, from data X_1 and X_2. Section 3 discusses this important inferential aspect.

2.2 Nonrandom foci

Suppose F_1 in (2.9) is an at most countable collection of foci, where the foci locations $\{\underline{s}_1, \underline{s}_2, \ldots\}$ are fixed. Define

$$T_Z(K) \equiv Pr(Z \cap K \neq \emptyset);\ K \in \mathcal{K}, \tag{2.13}$$

the hitting function of the grain Z. Then from (2.9), (2.13),

$$T_{X_2}(K) = 1 - \prod_{i=1}^{\infty} \{1 - T_Z(K(-\underline{s}_i))\};\ K \in \mathcal{K}. \tag{2.14}$$

A special case is when F_1 is the set of nodes of a regular grid; in $\mathbb{R}^2$,

$$F_1 = \{(i\Delta_1, j\Delta_2) : i, j \in \mathbb{Z}\} \cap X_1. \tag{2.15}$$

It is easy to simulate

$$X_2 = \cup\{Z_i(\underline{s}_i) : \underline{s}_i \in F_1\}, \tag{2.16}$$

where F_1 is given by (2.15). Figure 2 shows the analogous simulation to Figure 1, where now foci are nonrandom and belong to a square grid in X_1; the grains are once again disks of fixed radius.

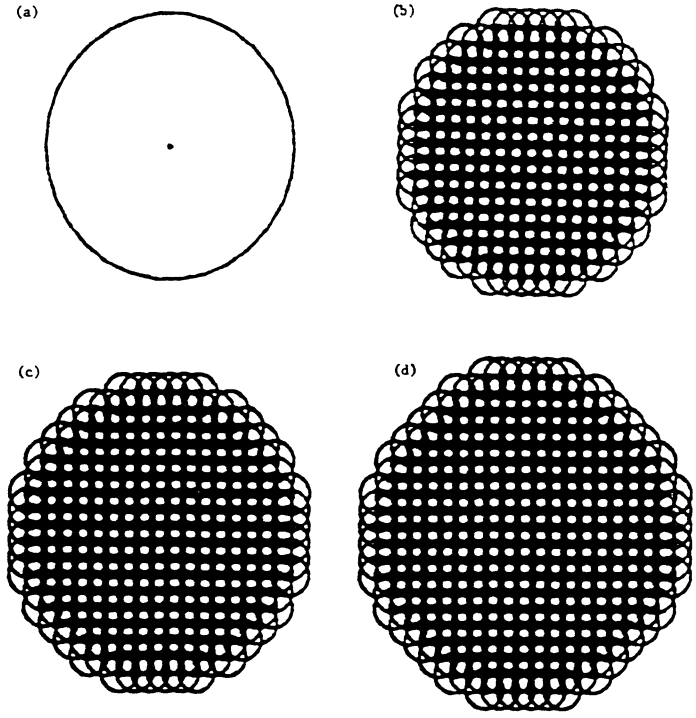

Figure 2: Same as in Figure 1, except now the model (2.16) is used to simulate growth.

Grains need not be disks, and if one is modeling tumor growth at the cellular level, it makes more sense to choose them as rectangular blocks (dominoes) of dimension $2\Delta \times \Delta$, where Δ is the square-grid spacing. A growth process can then be generated by (2.16), where Z is a north-pointing domino with probability (wp) p_1, a south-pointing domino wp p_2, an east-pointing domino wp p_3, a west-pointing domino wp p_4, and a $\Delta \times \Delta$ square wp $1 - p_1 - p_2 - p_3 - p_4$. Figure 3 shows an analogous simulation to Figure 2 (i.e., regular foci) with these dominoes and the square as realizations of the random grain.

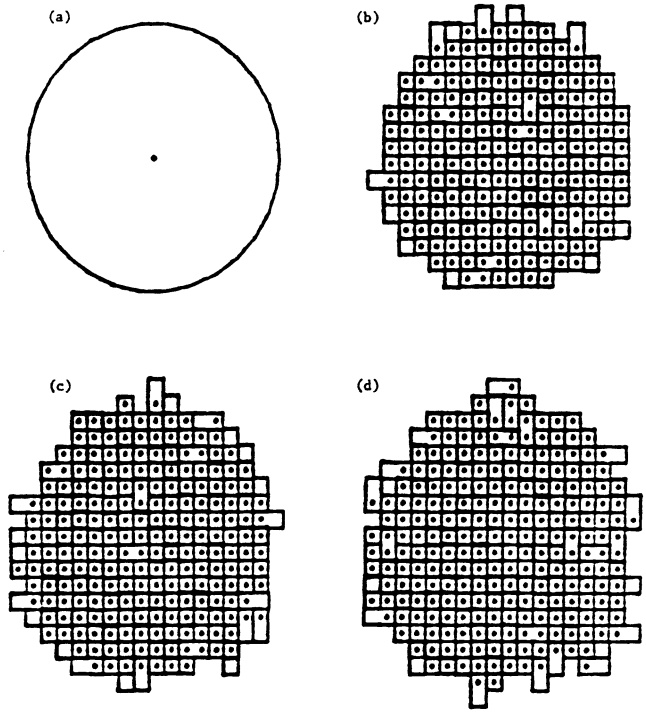

Figure 3: Same as in Figure 2, except now the random grain Z is a square wp 1/5, or dominoes in each of the four directions, each wp 1/5.

A natural question to ask is whether models of the type presented in Figure 3 have anything in common with interacting particle systems (see e.g., Liggett, 1985; Durrett, 1988). Although the latter are typically continuous time models, they can be discretized in time by considering small time intervals. That is, they are Markov processes whose state ξ_t at time t is a subset of $\mathbb{Z}^2$ (more generally $\mathbb{Z}^d$), and for u small:

(i) tumor cells die at rate δ; i.e.,

$$Pr(\underline{s} \notin \xi_{t+u} | \underline{s} \in \xi_t) \sim \delta.u; \tag{2.17}$$

(ii) tumor cells are born at rate $b_{\underline{s}}(\xi_t)$; i.e.,

$$Pr(\underline{s} \in \xi_{t+u} | \underline{s} \notin \xi_t) \sim b_{\underline{s}}(\xi_t).u. \tag{2.18}$$

Contact processes occur when $b_{\underline{s}}(\xi_t) = 0$ if $\underline{s}$ is not a nearest neighbor of any point in ξ_t (Harris, 1974).

Suppose ξ_1 is given and ξ_{1+u} is the random set obtained from the Markov process (2.17) and (2.18); u small. Let $F_1 = \xi_1$ in (2.16). Does there exist a random grain Z in (2.16) that yields the random set X_2, identical in distribution to ξ_{1+u}? Consider the contact process, $b_{\underline{s}}(\xi)$ = number of points in $(\xi \cap N_{\underline{s}})$, where $N_{\underline{s}} = \{\underline{r} : ||\underline{r} - \underline{s}|| = 1\}$; then clearly such a random grain does exist (Figure 3 gives an example where $\delta = 0$; when $\delta > 0$, $Z = \emptyset$ with a positive probability). But the contact process just described is simply the Williams-Bjerknes (1972) tumor growth model (which was built in two dimensions since they were restricting attention to the basal layer of an epithelium). Eden's (1961) model is the special case $\delta = 0$. Thus, the process defined by repeated application of (2.9) is flexible enough to include various contact processes as special cases.

Much research has been devoted to these models, usually with the aim of obtaining asymptotic ($t \to \infty$) properties such as an asymptotically circular shape (Richardson, 1973; Schurger, 1979; Bramson and Griffeath, 1980, 1981; Durrett and Liggett, 1981), a critical value of δ above which the tumor eventually dies out (Harris, 1974; Griffeath, 1981; Andjel, 1988), and rates of convergence (Griffeath, 1981).

To test out the asymptotically circular shape mentioned above, I used the same parameters as in Figure 3, but now with a rectangular initial set X_1. Shown in (a) through (d) of Figure 4 are generations of the tumor at respectively, $t = 1$, $t = 6$, $t = 11$, and $t = 16$.

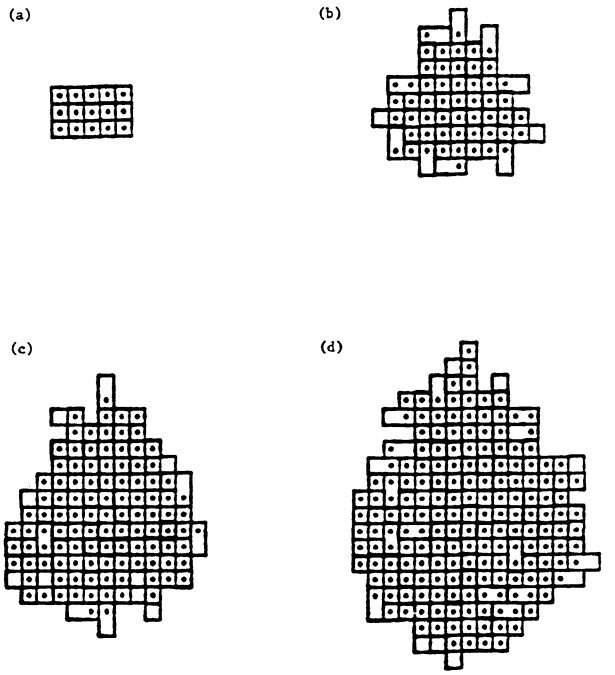

Figure 4: Same as in Figure 3, except now X_1 is a rectangle and not a disk, and (b) is X_6, (c) is X_{11}, (d) is X_{16}.

2.3 Discussion

One could now return to the Poisson-foci case of Section 2.1 and ask the same questions on asymptotics as in Section 2.2. Most notably, is there an asymptotically circular shape? I conjecture that there is; see Figure 1.

One could also combine the approaches of Sections 2.1 and 2.2 and build a random-set model based on *random regular* foci. Suppose F_1 is defined by (2.15); define F_1^* as follows. For each $\underline{s}_i \in F_1$, $\underline{s}_i \in F_1^*$ wp p_i, independently of whether $\underline{s}_j \in F_1^*$, for any $j \neq i$. Finally, define

$$X_2 = \cup\{Z_i(\underline{s}_i) : \underline{s}_i \in F_1^*\}, \tag{2.19}$$

where $Z_1, Z_2, \ldots$ are independent copies of the random set Z (with hitting function T_Z). The hitting function of X_2 is,

$$T_{X_2}(K) = 1 - \prod_{i=1}^{\infty}[1 - p_i + p_i\{1 - T_Z(K(-\underline{s}_i))\}]; \quad K \in \mathcal{K}. \tag{2.20}$$

If $p_i \sim \lambda.d\underline{s}_i$, where $d\underline{s}_i$ is an infinitesimal area element about $\underline{s}_i$, then

$$\begin{aligned} T_{X_2}(K) &\sim 1 - \exp\{-\lambda \int_{X_1} T_Z(K(-\underline{s})d\underline{s}\} \\ &= 1 - \exp\{-\lambda E(|(\check{Z} \oplus K) \cap X_1|)\}. \end{aligned}$$

Thus $\lim_{\Delta \to 0} T_{X_2}(K)$ is precisely (2.12), the hitting function of the random-set model based on Poisson foci (as it should be).

3. Analyzing tumor growth data

Figure 5 depicts a sequence of 3 digitized images obtained from *in vitro* growth of a human breast cancer cell line; shown are the boundaries of the same cell island pictured 72 hours apart. These data were supplied by Dr. G.C. Buehring (School of Public Health, University of California, Berkeley) and come from experiments like those described in Buehring and Williams (1976). The data are truly two-dimensional since the tumor was grown on a flat dish covered with a nutrient medium.

The model I shall fit to these data is described in Section 2.1. My reason for using this model, which admittedly requires certain unverified (but not implausible) assumptions, goes as follows. Since Poisson foci are seen in normal tissue, I assume that the same occurs in malignant tissue, only at very, very much higher intensities. Since at the cellular level *asymptotic* growth is spheroidal, I assume that at the supracellular level (after 72 hours of growth), the grains are disks with random radius R.

After transformation to spaces where the model is likely to hold, data of Figure 5 are analyzed by matching theoretical hitting functions given by (2.12), with empirical hitting functions calculated from the images. This yields estimates and standard deviations of parameters λ, $E(R)$ and $\mathrm{var}(R)$. Full details can be found in Cressie and Hulting (1989). I shall present a summary of their results below.

Table 1 shows estimates (along with biases and standard deviations) of model parameters for time-1-to-time-2 growth and for time-2-to-time-3 growth. There is clearly a significant difference in λ (foci intensities) and $E(R)$ (grain sizes) over the two growth periods.

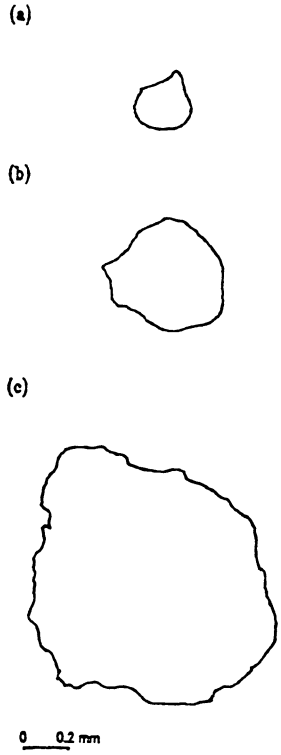

Figure 5: Digitized boundary of cancer cells grown *in vitro*; (a), (b), and (c) represent the same cell island photographed 72 hours apart.

To see how much of this difference is simply due to the disparity of size of the initial cell island in the two growth periods, each of the estimates was standardized so that the initial cell island had a "size" of 1. This was achieved by computing the mean caliper width (average of the largest inscribed circle and smallest circumscribed circle) for X_1 ("size" of X_1) and rescaling the analysis of the first growth period by this size. The same was done with X_2 for the second growth period. Since the estimators from which Table 1 is calculated, are equivariant under scale change, it is a simple matter to compute *standardized* model-parameter estimates; these are presented in Table 2.

Table 2 refers to *shape* information in the data. The shape of X_2 is significantly different from that of X_3, as evidenced by a significantly larger Poisson foci intensity and a significantly smaller grain radius, during the earlier period of growth. From simulations, I have determined that a growth process given by (2.10) with larger radius and smaller intensity is more dangerous in the sense that the area of the future cell island tends to be larger. As has been mentioned before, this accelerated growth in the latter period will likely not continue *in vivo* due to lack of blood supply and to tissue barriers.

4. Conclusions

The sequential growth models given by (2.10), (2.16), and (2.19), are a very flexible class, whose hitting functions can be computed (see (2.2), (2.14), and (2.20) respectively). In fact, the Williams-Bjerknes (1972) tumor growth process is seen to be a

TABLE 1

Estimates of growth parameters, their standard deviations, and their biases.

time 1 to time 2

parameter	estimate	$(\widehat{sd})$	[bîas]
λ	438.495 mm^{-2}	(24.733)	[0.0]
$E(r)$	0.11492 mm	(0.00225)	[0.00012]
var (R)	0.000357 mm^2	(0.00009)	[−0.00001]

time 2 to time 3

parameter	estimate	$(\widehat{sd})$	[bîas]
λ	59.685 mm^{-2}	(4.7035)	[0.0]
$E(R)$	0.2975 mm	(0.00737)	[0.00057]
var (R)	0.00133 mm^2	(0.00077)	[−0.00001]

special case of (2.16). But, from a statistician's viewpoint, flexibility and simulated pictures are not enough to solve the inverse problem, viz. given data, what are the "most likely" parameters to have generated those data? Inference on image data is addressed in Section 3.

Cressie and Hulting (1989) provide evidence that the tumor growth model of Section 2.1, with appropriately estimated parameters, provides an excellent fit to the data in Figure 5. Although the actual growth process clearly does not occur according to the time scale of 72 hours, the Poisson-foci model fitted may provide a conjecture about how the tumor is growing. Why and how do these foci of growth develop? Moreover, growth where the foci intensity is high but the growth radii are small may yield identical cell island *area* at time 2, to the situation where foci intensity is low but the growth radii are large. However the cell island appears to take on a different character in these two situations. How can the estimable parameters, viz. foci intensity and moments of growth radius, be used to explain this "character"? Simulation indicates that the latter is more dangerous since it represents greater growth potential.

Acknowledgements

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TABLE 2

Estimates of growth parameters, their standard deviations, and their biases, after standardization by size (size = mean caliper width)

time 1 to time 2 (size of $X_1 = 0.1097$ mm)

parameter	estimate	$(\widehat{sd})$	[bîas]
λ	5.26194	(0.29682)	[0.0]
$E(R)$	1.04758	(0.02050)	[0.00113]
var (R)	0.02978	(0.00764)	[−0.00071]

time 2 to time 3 (size of $X_2 = 0.2604$ mm)

parameter	estimate	$(\widehat{sd})$	[bîas]
λ	4.04668	(0.31894)	[0.0]
$E(R)$	1.14240	(0.02826)	[0.00221]
var (R)	0.01967	(0.01142)	[−0.00146]

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