Models of Growth Heterogeneous Cancer Cells with Chains Markoviens and Estimation of Their Fractal Dimension

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Abstract

Although little work in biometrics uses fractal geometry, we will discuss here biometrics cancer tissue examined under a microscope or simulated. The main purpose of our work is the simulation of the heterogeneous growth of cancerous tumors and the analysis of the appearance of their textures. The problem is to quantify the irregularity of their edges, which help enormously oncologists to give diagnoses to evaluate the treatment issued to their patients.
We propose new algorithms, which generates growth models with the ability to produce a border irregularity similar to that of cancerous tumors and value their fractal dimension.
The established models have two types of parameters: Algorithms describing the structure, and Scalar to quantify aspects modeled

Keywords: Simulation, cancerous tumour growth, Markov fields, fractal dimension**.**

1. Introduction

Several methods have been proposed to simulate tumour growth as the approach used by cellular automata (Alarcon, T., H.M. Byrne, and P.K 2003) [2]. The models that we developed are based on the assumption that the tumour began as a single mother cell, which will gradually develop to form a cluster of girls cells .

Each daughter cell of the tumour could be linked to the mother by a connexity walk. Stochastic growth mechanisms have been carried out by Markov fields. To simulate a tumour epithelial monolayer, we used a grid plane. To characterize the form of compact cell clusters, we propose new algorithms, which generates growth models with the ability to produce a border irregularity Similar to that of cancerous tumours and value their fractal dimension [1].

The model we developed is done with help of a formal language to specify process of formation and evolution of structures random using carcinogenic among other Markov chains. The established models have two types of parameters: Algorithms describing the structure, and Scalar to quantify aspects modelled

Various attempts have been made to construct a mathematical model that describes tumour growth [6, 3], but the cases are too limited. Growth process dominated by surface diffusion and deposition were described in some deposits models (4-6)

2. Formulation of models

2.1 First model

The epithelial monolayer could be represented by a planar square grid A($m \times n$) whose elements Aij correspond to cells Cij. Each cell is connected by “adherent junctions” with 4 neighbours, and has a proper activity process which defines its different states, the eventual transformation from one type to another and the interaction with its neighbours. A given state of a cell at instant t+1 may change depending on its state and the states of the neighbours at instant t. A cell Cij may be ‘ill ’, in which case we set Aij = 1, or ‘healthy’, and Aij = 0.

Initially, all elements of A are set equal to 0 except one which is set equal to 1 at any position. This first element of

ill cell IC corresponds to the mother cell engaged in a cancerous process.
From an ill cell IC, we generate a process which consists of visiting healthy cells in the four directions: left, right, up, down (Fig. 1). As shown in Fig. 2, we scan lines and columns in the order (1), (2), (3), (4) and stop scanning whenever an IC is encountered.
Three cases can occur: the actual visited healthy cell HC is surrounded by 1,2 or 3 ill cells in these directions. Hence, we introduce the following given probabilities α, β, γ: α (resp. β) (resp. γ) is the probability that HC falls ill when it is surrounded by one (resp. two) (resp. three) ill cell(s). HC cannot be surrounded by four ill cells.

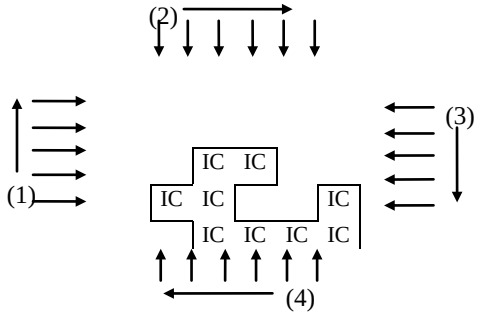


Fig. 1: visiting healthy cells.

The basic idea behind this model is that we do not visit the cell which has not orthogonal projection on the sides.
As in the initial state of the process there was only one cell sick, so there will be four sites to visit: Either A (i, j) = 1 the 1st cell disease.
So the four cells to visit are: A (i + 1, j), A (i – 1 , j), A (i , j + 1), A (i , j - 1)

NOTE:

whenever a rotation is established (i.e. go 1, 2, 3 and 4) see Fig1: we increase by two pixels each side, to visit the brink of a spot following the rotation
At each visit of a site that is naturally a healthy cell three scenarios are obtained. This implies the introduction of three probabilities:

Pr (C is sick / surrounded by 3 C patients) = γ
Pr (C is sick / surrounded by 2 C patients) = β
Pr (C is sick / surrounded by a sick C) = α

Then we draw a random variable Y = RND (1), and three cases this may present:

1st Case :
If γ [0, Y] then A (i, j) = 1 "is to say that the C is sick"
If not A (i, j) = 0.

2nd Case :
If β ε [0, Y] then A (i, j) = 1
If not A (i, j) = 0.

3 rd Case :
If α ε [0, Y] then A (i, j) = 1
If not A (i, j) = 0.

NOTE:

Aij is set at 1, but when the model is type (homogeneous) and Aij takes the values 1, 2, 3 or more when sick cell model is defined (Heterogeneous). According to the simulation model 1, α = 0.50 β = 0.55, γ = 0.75
Step 1 simulation based on probabilities
Step 2 Textures of the tumour
Step 3 Recovery of the border by the small number of squares (a minimum)

Fig. 2: cancer cells

2.2 Second model

The second model is to generate a process whose aim is to visit all the sites of the healthy state that are just boundary with the edge of the stain. With this model we got very few irregular spots , so far from approaching real cancerous tumor.

2.3 Third model

This model is identical to the 1st unless we introduce the following condition:
Each site can be visited only a single time, if it remains tests after the state healthy, it would no longer be visited another time. So we introduced an artifice to scoring, instead of leaving the site A (i, j) = 0 on the door at 2 in order to avoid the test a second time.

At the end of the simulation all sites at Level 2 will bring the state out.

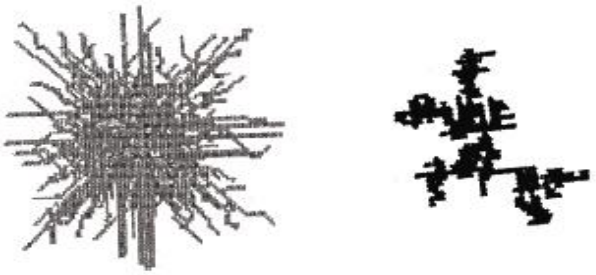


Fig. 3 : Simulation results (model 3)
$\alpha = 0.40, \gamma = 0.60, \beta = 0.80$

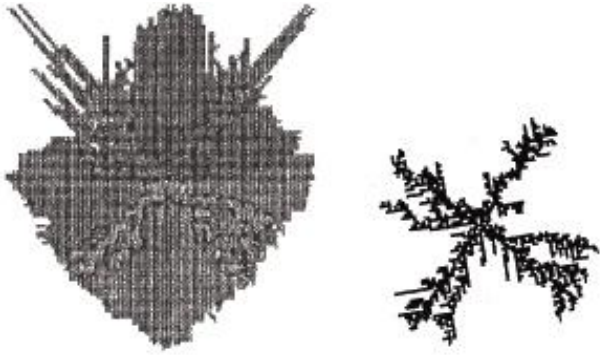


Fig. 4 : Simulation results (model 3)
$\alpha = 0.70, \gamma = 0.50, \beta = 0.60$

3. Simulation of heterogeneous cancer tumors

In this paragraph it is assumed we have three types of cancer cells different C/c1; C/c2 and C/c3. This heterogeneity better reflects the reality of cancer in hospital environments. For this the process of the evolution of the tumour remains the same up to the stage or the test result is that the probabilistic test cell becomes sick. Then three possibilities may arise.

The test cell is surrounded by one, two or three sick cells. Next each case the cell test takes the nature of the cell number upper it, (Supi C / ci), i Є [1.3]. Which leads 19 scenarios to study for each test. The simulation steps of heterogeneous cancer tumors are presented by the organigram N°1.

4. Simulation with markoviens fields

Consider a region "S" shared flat (n * m) small squares called "pixels, which are located by couples (i, j) where i=1.. n and j=1..m.

4.1 Methodology

Let X be a field of Markov, with a value in a series of statements E, defined at all locations. In our case, E = { 0 , 1 } and S = { 1 , 2 ,..., n * m }

$$\text{Let} \quad X = \begin{pmatrix} X_{11} \ldots\ldots\ldots\ldots X_{1n} \\ X_{21} \ldots\ldots\ldots\ldots X_{2n} \\ \\ X_{m1} \ldots\ldots\ldots\ldots X_{nm} \end{pmatrix}$$

J = Xij (state pixel A (i, j)). Hence $\Omega = \{ 0 , 1 \}^{n*m}$ the total configurations The transition from one configuration X to another X * is performed on a field Markov dependence on local density P (x) which represents a priori distribution of X *.

4.2 Definition

A field is markovien local dependence if the state is taking the pixel A (i, j), depends only on the condition of neigh boring pixels *A* (i, j). That is to say:

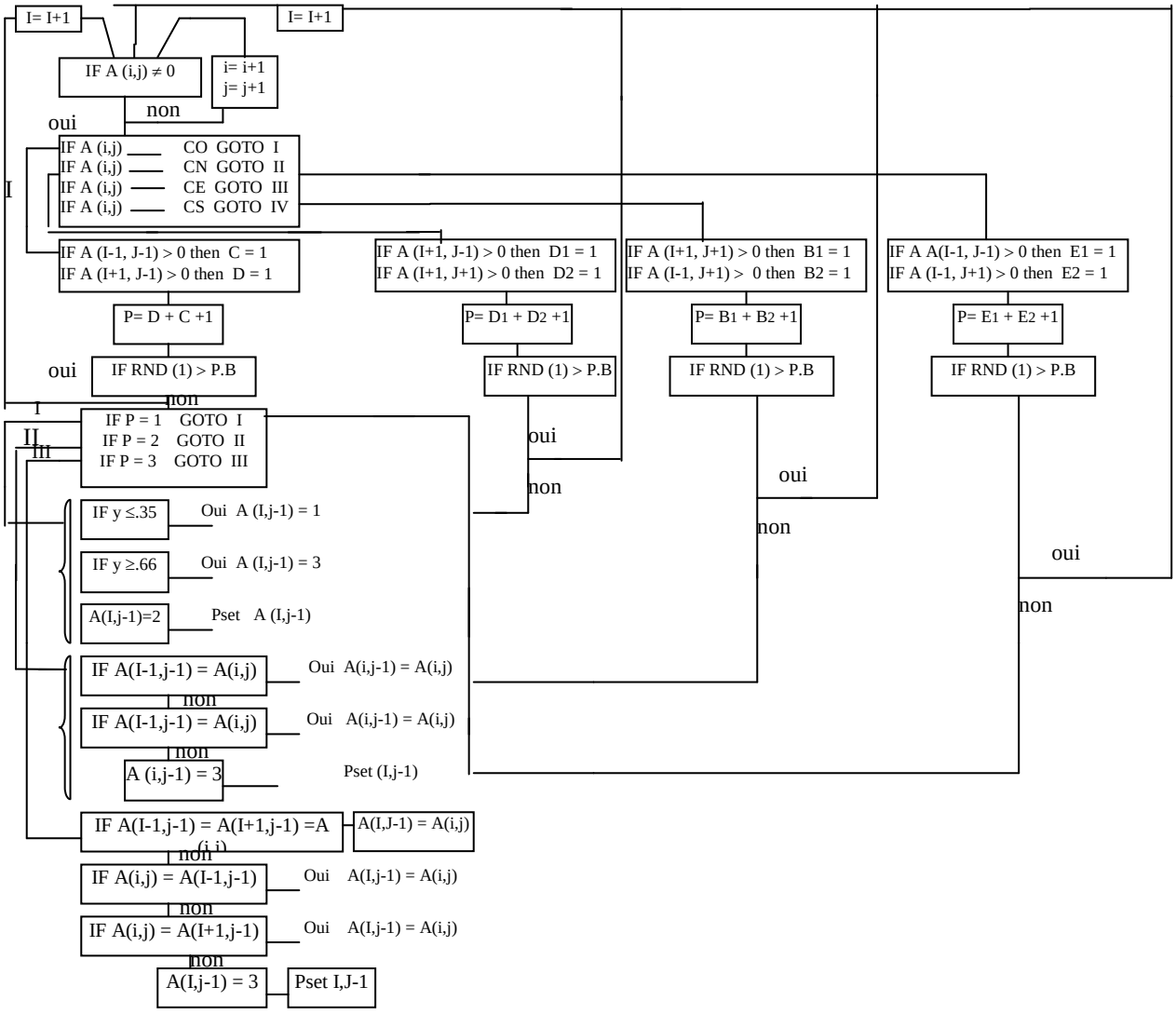
$$P\,(x\,(i,j) / x_m\,(i,j)\,) = P\,(x(i,j) / x_d\,(i,j))$$

Where x_m (i, j) represents the state of all the pixels other than A (i, j) and x_j (i, j) is all neighbours local A (i, j).

4.3 Markovien field of 1st order

Is submitted by: J (i, j) = closest neighbours from A (i, j). If we consider two outcomes which differ only in the A pixel (i, j), we find that the conditional probability that the state appears K (i, j) (the rest being given), (ie holy and ill) only $\{0, 1\}$ Given that two states arise in our case, this means that we are facing a situation where states are disordered therefore a simple model is obtained by asking :

$$P\left(A_{ij} = {}^{k}/_{A_{\partial(i,j)}}\right) = \exp\left(B_k U_{ij}(k)\right) / \sum_{k} \exp\left(B_k U_{ij}(k)\right)$$



Organigram N°1 : The steps of simulation

ALGORITHM

1. Attribution of initial configuration of X.
2. Random visit all sites S.
3. Calculation on each site visited in the number of neighbours same state, and different state of the site.
4. Calculation probability of each state "K" in order to appear in (i, j) using (1)
5. Obtain a random variable Y and establish a test for each state "K":
   If $Y \leq P(x)$ the pixel takes the state K otherwise it is the second state to be selected.
6. Return.

The algorithm described above was done without the worry of the model that seeks to create (Task cancerous), but we realized that it does not accurately reflect the image of a task cancerous. That's why he has changed the mode of visiting the sites, which has prompted us to develop four modes of visits:

1st mode: The visit is made at random.
2nd mode: Visit column by column.
3rd mode: The visit is entering spiral.
4th mode: The visit takes place in orthogonal projection on the image while outgoing doing a spiral, we will explain later

Fig. 5: Markovien model.

5. Evolution of the fractal dimension in the probabilities space

The size variation depends only on three parameters P1, P2, P3, it is estimated that it would be desirable to have an idea about the evolution of the dimension in the space formed by the probabilities P1, P2, P3. So we are given values to P1, P2, P3 so as to have a better spread over the whole space. Let P be in step with probability: p = 0.05 This gives us a distribution of space and generally fairly homogeneous, and that schematized as follows:

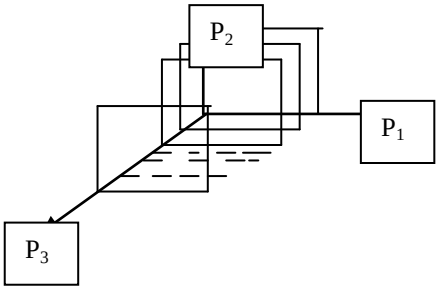


Fig. 6: Distribution of space.

We scans in the plane formed by P1, P2, P3, P1 induced space while respecting the assumption P1 <P2 <P3. Then for each triplet (P1, P2, P3) we do a 200 simulations (Randomization), which calculates the mean and standard deviation. as we are working on 80 points of space, which gives us 80 * 200 = 16000 simulations.

5.1 Data processing

The data acquired are two important points:

1. whenever P2, or P3 increases by a pitch (p = 0.05), the size decreases 0.02.
2. by cons p1 increases each time the same pitch p, the dimension increases 0.03.

The probability is constant, then one can conclude that the dimension is linearly dependent on the triple (P1, P2, P3) and is written:

$$D=a+ b.P1+c.P2+f.P3$$

Now it remains to find the four parameters a, b, c, f.
so we make a multilinear regression. The 80 data we have:
let $D(i) = a + b*P1(i) + c\,P2(i) + f\,P3(i)$

$$\begin{cases} a\sum_{i=1}^{80} P_1(i)+b\sum_{i=1}^{80} P_1^2(i)+c\sum_{i=1}^{80} P_1(i)P_1(i)+f\sum_{i=1}^{80} P_3(i)P_1(i)=\sum_{i=1}^{80} d_iP_1(i) \\ a\sum_{i=1}^{80} P_2(i)+b\sum_{i=1}^{80} P_2(i)P_1(i)+c\sum_{i=1}^{80} P_2^2(i)+f\sum_{i=1}^{80} P_3(i)P_2(i)=\sum_{i=1}^{80} d_iP_2(i) \\ a\sum_{i=1}^{80} P_3(i)+b\sum_{i=1}^{80} P_3(i)P_1(i)+c\sum_{i=1}^{80} P_2(i)P_3(i)+f\sum_{i=1}^{80} P_3^2(i)=\sum_{i=1}^{80} d_iP_3(i) \\ a\sum_{i=1}^{80} i+b\sum_{i=1}^{80} P_1(i)+c\sum_{i=1}^{80} P_2(i)+f\sum_{i=1}^{80} P_3(i)=\sum_{i=1}^{80} d_i \end{cases}$$

The Calculation of coefficient multilinear regression. with Statpal Regression software

5.2 Results (of 16000 simulations)

Dependent variable: Fractal Dimension.
Independent variable Model: P1, P2, P3.

Variable	Coefficients	Errors Std	Total score
Intersept	1.7488	0.0113	154.9098
P1	0.5060	0.0183	27.6554
P2	-0.6334	0.0170	-37.1914
P3	-0.4160	0.0163	-25.5748

So any tumors generates from P1, P2, P3 thier fractal dimension is estimated by:

$$D_F=1.7488+0,5060P1 – 0,6334P2 -0,4160P3$$

6. Conclusion

Once again the proposed method confirms its effectiveness for the following reasons:

- If P1 increases (even at (0.05)) the increases of the irregularity of the tumor cause an increase of the fractal dimension (detected by the method developed).

- if P2 and P3 increase, the irregularity decreases (even small) which causes the decrease in the fractal dimension, that is detectable by the method developed.

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