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# MESOSCOPIC MODEL FOR TUMOR GROWTH

Elena Izquierdo-Kulich

Departamento de Ingeniería Química. Facultad de Ingeniería Química. Instituto Superior Politécnico, CUJAE, Havana, Cuba

José Manuel Nieto-Villar

Department of Physical Chemistry, Faculty of Chemistry, University of Havana, Havana, Cuba and "H. Poincaré" Complex Systems Division, University of Havana, Havana, Cuba

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Abstract. In this work, we propose a mesoscopic model for tumor growth to improve our understanding of the origin of the heterogeneity of tumor cells. In this sense, this stochastic formalism allows us to not only to reproduce but also explain the experimental results presented by Brú. A significant aspect found by the model is related to the predicted values for $\beta$ growth exponent, which capture a basic characteristic of the critical surface growth dynamics. According to the model, the value for growth exponent is between 0,25 and 0,5, which includes the value proposed by Kadar-Parisi-Zhang universality class (0,33) and the value proposed by Brú (0,375) related to the molecular beam epitaxy (MBE) universality class. This result suggests that the tumor dynamics are too complex to be associated to a particular universality class.

1. **Introduction.** Cancer is a highly complex, nonlinear dynamic system. In early stages, it self-organizes as an invasive and adaptive network in a proliferation-invasion-proliferation sequence [7, 19] in which bifurcations play an important role at a macroscopic level in the origin of its complexity [14].

Transition phenomena, far from being in thermodynamic equilibrium, are related due to bifurcations, to states characterized by correlations that affect the macroscopic behavior of the tumor. Coherence in tumor cells is associated with simultaneous reinforcement of fluctuations. A recent work shows that tumors operate close to an instability threshold [17]. This study demonstrates that tumor cell populations live close to this threshold at a certain level of genetic instability.

An important characteristic of complex dynamic systems is their stability in front of external perturbations. We have recently demonstrated that dynamic systems may or may not be controlled by the effect of periodic external fluctuations, according to the type of dynamic systems' complexity [3]. In other words, the sensitivity of the system to external fluctuations depends on its robustness.

In spite of achievements in molecular biology and genomics, the growth mechanism for tumor cells and the nature of its robustness are still unknown. Tumor cell robustness enables a system to maintain its functionality in the face of various external and internal perturbations [12, 13]. Tumor cells exhibit two aspects of

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robustness: functional redundancy, which is enabled by cellular heterogeneity, and feedback-control systems [12, 13]. Controlling cell robustness by reducing heterogeneity is a potential strategy for the development of drugs and therapies.

Tumor cell heterogeneity is manifested by the irregularity of the tumor boundaries. Fractal geometry proves to be useful for describing the pathological architecture of tumors and for yielding insights into the mechanisms of tumor growth [2].

Mathematical models represent a language for formalizing the knowledge on living systems obtained in theoretical biology. Basic models of tumor growth [10] make possible the description of the principal regularities and are an effective guideline for cancer therapy, drug development, and clinical decision-making [16]. These models can be classified into two general groups: deterministic [11] and stochastic models [1, 8, 15]. The stochastic methods are a natural approach to describe tumor growth, in particular, dynamic behavior, pattern formation, and geometrical characteristics such as a fractal dimension.

The goal of this paper is to give a theoretical framework the mathematical modeling of tumor cell growth, based on a mesoscopic model that allows improving our understanding of the origin of tumor cell heterogeneity and thus its robustness.

## 2. **Mesoscopic model.**

To obtain a mathematical model to predict tumor cell growth, the following considerations were made: the variable to describe the system at a microscopic level is the total number of tumor cells $n$, while at a macroscopic level the variable considered is the tumor radius $r$.

The behavior of the radius is affected only by reproduction and death of tumor cells, near the border, because the mechanism that determines the tumor growth is competition between tumor and host cells for the available space [6]. Thus, a tumor can be divided into an inner compact zone, where the concentration of cells in the surface of the host is constant in space and time, and a bordering zone called contour, where the tumor growth takes place. Both cell reproduction and death in the tumor contour are processes that take place within a certain transition probability per unit of time; the behavior of these processes is established *a priori* so that $r$ is a stochastic variable. The stochastic character of $r$ is manifested in the border roughness and the not uniform distribution of contour cells, which can be characterized by its fractal dimension.

It is also considered that the stochastic process of tumor growth has the Markov property [18]. This property is mathematically expressed as follows:

$$P\left(n_m/n_{m-1}\right) = P\left(n_m/n_{m-1}\ldots n_0\right), \tag{1}$$

where $P\left(n_m/n_{m-1}\right)$ is the probability of having $n_m$ cells in $t_m$ times when there are $n_{m-1}$ cells at time $t_{m-1}$. This supposition implies that the future state depends on the present state and not on the way it was reached. This is only approximately what happens in reality, but one must consider using stochastic modeling techniques based on a master equation (ME) [18].

The magnitude of radius fluctuation scales up with the size of the contour microscopic entities, which can be independent cells or cell aggregates, according to the observation scale.

To obtain the master equation that describes temporal behavior of the probability $P(n;t)$ of having $n$ cells in $t$ time, it is considered *a priori* that the transition probability $T_1$ of contour cell reproduction per unit of time is:

$$T_1 = \frac{\psi}{l}\sqrt[2]{n}, \tag{2}$$

while the transition probability $T_2$ of contour cells death is

$$T_1 = \frac{\eta}{l}\sqrt[2]{n}, \tag{3}$$

where $\psi[L.t^{-1}]$ is a constant that describes the effects of cell reproduction on tumor growth rate, $\eta[L.t^{-1}]$ is a constant related to cell death, and $l$ is the size of the entity in the contour.

After the above-mentioned considerations, the master equation is obtained from equations (2) and (3):

$$\frac{\partial P(n;t)}{\partial t} = \left(E_n^{-1} - 1\right)\frac{\psi}{l}\sqrt[2]{n}P(n;t) + \left(E_n^{+1} - 1\right)\frac{\eta}{l}\sqrt[2]{n}P(n;t). \tag{4}$$

The ME (4) is nonlinear in the sense of its transition probability per unit of time; an exact analytic solution is not possible, and so it is necessary to use approximate methods [9, 18]. In this case the first two terms of Van Kampen's $\Omega$ expansion method will be used [9].

To use this method, the microscopic variable $n$ is expressed as a function of the fluctuations $\xi$ that take place as a result of the probabilistic character of tumor cell reproduction and death, and to the macroscopic variable:

$$\begin{aligned} n &= \Omega\pi R^2 + \Omega^{0.5}, \\ n &= \tfrac{1}{l^2}, \end{aligned} \tag{5}$$

where $R$ is the expected value of the tumor radius. Also, considering that the inverse of probability $P$ is proportional to the average magnitude of fluctuations $\xi$, the following relationship between probability $P(n;t)$, corresponding to the microscopic variable, and probability $\Pi(\xi;t)$, corresponding to its fluctuations, is established:

$$P(n;t) = \Omega^{-0.5}\Pi, \tag{6}$$

$$\frac{\partial P(n;t)}{\partial t} = \Omega^{-0.5}\frac{\partial \Pi}{\partial t} - 2\pi R\frac{dR}{dt}\frac{\partial \Pi}{\partial t}, \tag{7}$$

If we consider that the change $\Delta n$ that takes place when a single cell reproduces or dies is negligible compared to the value of $n$, both $n$ and $r$ can be expressed as continuous variables, and so operator $E$ in ME (4) can be expressed as a differential form so that ME (4) could be written as a function of a series of powers of $\Omega$ where only the first two terms were taken:

$$\Omega^0\frac{1}{2\pi R}\frac{\partial \Pi}{\partial t} - \Omega^{0.5}\frac{dR}{dt}\frac{\partial \Pi}{\partial \xi} = \Omega^{0.5}(-V)\frac{\partial \Pi}{\partial \xi} + \Omega^0(V_t)\frac{\partial^2 \Pi}{\partial \xi^2}, \tag{8}$$

where $V = \psi - \eta[L.t^{-1}]$ is the tumor growth rate observed at macroscopic level, and $V = \psi + \eta[L.t^{-1}]$ is the sum of reproduction and death rate constants. In the ME (4), the coefficients associated with the parameter $\Omega^{0.5}$ determine the behavior of the expected value of the tumor radius $R[L]$; consequently:

$$\begin{aligned} -\Omega^{0.5}\frac{dR}{dt}\frac{\partial \Pi}{\partial \xi} &= \Omega^{0.5}(-V)\frac{\partial \Pi}{\partial \xi}, \\ \frac{dR}{dt} &= V, \end{aligned} \tag{9}$$

while the others define the Fokker-Planck equation that describes the temporary behavior of the probability $\Pi(\xi;t)$ as a function of the expected value of the tumor radius:

$$\Omega^0 \tfrac{1}{2\pi R} \tfrac{\partial \Pi}{\partial t} = \Omega^0(V_t) \tfrac{\partial^2 \Pi}{\partial \xi^2}. \tag{10}$$

The solutions of the Fokker-Planck equation (10) for the fluctuations expected values are

$$\tfrac{d\langle \xi \rangle}{dt} = 0, \tag{11}$$

$$\tfrac{d\,\mathbf{var}(\xi)}{dt} = 2\pi V_t R. \tag{12}$$

To obtain the equation that describes the variance $\mathrm{var}(R)$ of the macroscopic variable $r$, the following scaling relation between $\mathrm{var}(r)$ and $\mathrm{var}(\xi)$ is considered:

$$\mathbf{var}(\xi) = \mathbf{\Omega^4} \pi \left(\mathbf{var}\left(\mathbf{r}\right)\right)^{\mathbf{2}}. \tag{13}$$

Then we obtain:

$$\begin{aligned} &\tfrac{d\left(\left(\mathbf{var}(\mathbf{r})\right)^2\right)}{dt} = 2l^8 V_t R, \\ &\left(\left(\mathbf{var}\left(\mathbf{r}\right)\right)^2\right)_{t=t_0} = \left(\left(\mathbf{var}\left(\mathbf{r}\left(\mathbf{t_0}\right)\right)\right)^2\right). \end{aligned} \tag{14}$$

3. **Results and discussion.** The temporary evolution of the tumor is described according to the behavior of the expected value $R$ of the tumor radius and the average magnitude of the radius fluctuations, defined as $\chi = ((var(r)^2))^{0.25}$ (see equations (5), (6), (14)). Both behaviours are obtained from equations (12) and (14), considering an initial value for $R_c$ from which tumor growth is determined, only by cell competition for the available space, or a value for $R_0 \geq R_c$, inside the tumor, for which fluctuations equal zero. It turns out that:

$$R = Vt + R_0, \tag{15}$$

$$\chi = l^2 \left[V_t \left(Vt^2 + 2R_0 t\right)\right]^{0.25}. \tag{16}$$

The contour width $W_i$ in a point $i$ of the border is proportional to the difference between the expected value of the tumor radius, which is in the contours, and the radius of an inner zone of the tumor, where the concentration of cells is constant. This value can be estimated from the average magnitude of internal fluctuations, which is expressed by equation (16), as follows:

$$W_i = \chi. \tag{17}$$

It has been experimentally proven [5, 6] that contour width grows with time according to the following relation:

$$W_i = kt^\beta. \tag{18}$$

As a result, the following equivalence between theoretical and experimental results can be established:

$$l^2 \left[V_t \left(Vt^2 + 2R_0 t\right)\right]^{0.25} = kt^\beta. \tag{19}$$

We can predict from this equation that

$$\begin{aligned} Vt^2 >> R_0 t \Rightarrow \beta = 0.5, \\ Vt^2 << R_0 t \Rightarrow \beta = 0.25. \end{aligned} \tag{20}$$

In this case, it is predicted that the range of possible values (0.25 - 0.5) for the growth exponent $\beta$, which capture a basic characteristic of the critical surface growth dynamics, suggests a Kadar-Parisi-Zhang (KPZ) universality class [4], for which $\beta = 0.33$, and the value suggested by Brú [5], associated to the MBE universality class, is of $\beta = 0.33$.

Fig. 1 shows the comparison between the experimental results [6] and the range of values predicted by the model. The space and time invariance of $\beta$ for one specific type of tumor implies that the $R_0$ value is not arbitrary, but the $R_0$ value must take into account this invariance. This shows a correlation between $R$ and $R_0$, which implies that fluctuation autocorrelation time is different from zero. In this regard, when we considered the Markov property to model the system with methods based on the master equation, the autocorrelation time was not taken into account, but this can be corrected with the condition of invariance in scale.

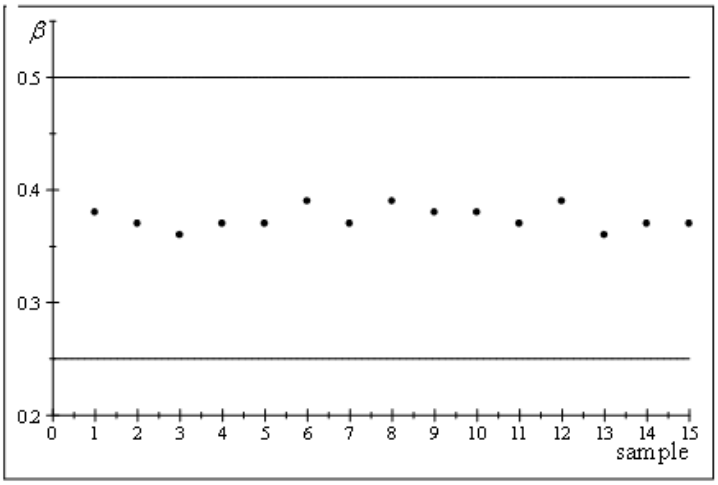



FIGURE 1. Comparison of the value of $\beta$ determined for different cultures [6] (dots) with the range of values predicted by the model (lines).

It has been experimentally demonstrated that at certain times fluctuations reach a critical value in such a way that the contour width in the $i$ zone of the border is different from the total width, because of spatial fluctuations in the expected value of $R$ [5]. This phenomenon is known as super-roughness, and it occurs at a specific time, designated saturation time $t_s$. As experiment results show, in situations like these the total width of the contour scale up with the perimeter $L$ according to the relation

$$W \equiv L^{\alpha_{glo}}, \tag{21}$$

where $\alpha_{glo}$ is the global roughness exponent.

To describe this phenomenon, we will consider that two other processes could take place, apart from cell reproduction and death, when fluctuations in the contour reach certain critical value. One of these processes is the migration of cells to a zone with a higher concentration of cells to form an aggregate in the border. In the other process, a cell receives other cells to form an aggregate that will increase its size exponentially until the aggregated cells start competing for the available space. Both phenomena change the size of the contour microscopic entities and break the correlation between $R$ y $R_0$ in such a way that the contour width in a point $i$ will be expressed as

$$W_i = l^2 \left[\frac{V_t}{V} R_i^2\right]^{0.25} = l^2 \left[\frac{V_t}{V}\right]^{0.25} R_i^{0.5}, \tag{22}$$

while space fluctuations in $R$, as a result of the above mentioned processes, which determine the total width of the contour will be expressed by

$$\chi_R = \omega^2 \left[\frac{V_t}{V}\right]^{0.25} R^{0.5}, \tag{23}$$

where $\omega$ represents the characteristic length of the small aggregates formed by cell migrations and of the conglomerate that can be formed by the reproduction of one cell in the contour. Because the available space for these phenomena to take place is proportional to the local width of the contour in a point $i$,

$$\omega = W_i. \tag{24}$$

Consequently the total width of the contour is expressed as

$$W = l^4 \left[\frac{V_t}{V}\right]^{0.75} R^{1.5}. \tag{25}$$

If we express the expected value of radius $R$ as a function of the perimeter $L$, it turns out that

$$W = \frac{l^4}{(2\pi)^{1.5}} \left[\frac{V_t}{V}\right]^{0.75} L^{1.5}, \tag{26}$$

and an equivalence between the experimental and the theoretical results can be established as

$$W = \frac{l^4}{(2\pi)^{1.5}} \left[\frac{V_t}{V}\right]^{0.75} L^{1.5} \equiv L^{\alpha_{glo}}. \tag{27}$$

As a result, the global-roughness exponent $\alpha_{glo} = 1.5$ is obtained. Fig. 2 shows the comparison between experimental [6] and theoretical results.

The tumor fractal dimension is considered as the fractal dimension of its perimeter which, is equivalent to the fractal dimension of the irregular distribution of cells in a local area ai of the contour. The dimension of this local area is determined by the relation:

$$a_i = \theta \left(R + \frac{W_i}{2}\right)^2 - \theta R^2 = \theta W_i \left(R + \frac{W_i}{4}\right). \tag{28}$$

If the equation is reformulated as a function of $W_i$ for $t << t_s$:

$$a_i = \theta^2 \left[\frac{V_t}{V}\right]^{0.25} (R - R_0)^{\beta} \left(R + \frac{l^2}{4} \left[\frac{V_t}{V}\right]^{0.25} (R - R_0)^{\beta}\right), \tag{29}$$

and for $t >> t_s$ :

$$a_i = \theta^2 \left[\frac{V_t}{V}\right]^{0.25} R^{0.5} \left(R + \frac{l^2}{4} \left[\frac{V_t}{V}\right]^{0.25} R^{0.5}\right), \tag{30}$$

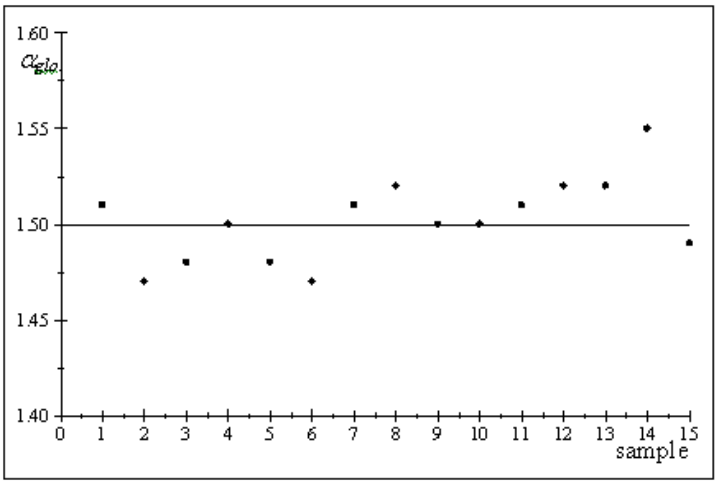



FIGURE 2. Comparison of the values of $\alpha_{glo}$ determined for different cultures [6] with the value predicted by the model (continuous line).

where $\theta$ is the angle of the contour section analyzed and $t_s$ is the time when the phenomenon of super-roughness appears [5]. Taking into account that the contour area is equivalent to the total amount of cells, the following relation to predict the fractal dimension $d_f$ is obtained: for $t << t_s$:

$$kR^{d_f} = \theta^2 \left[\frac{V_t}{V}\right]^{0.25} (R - R_0)^{\beta} \left(R + \frac{l^2}{4} \left[\frac{V_t}{V}\right]^{0.25} (R - R_0)^{\beta}\right), \tag{31}$$

for $t >> t_s$:

$$kR^{d_f} = \theta^2 \left[\frac{V_t}{V}\right]^{0.25} R^{0.5} \left(R + \frac{l^2}{4} \left[\frac{V_t}{V}\right]^{0.25} R^{0.5}\right). \tag{32}$$

From this, a fractal dimension from 1 and 1.5 is predicted, according to the value of the following relation:

$$\frac{l^2}{4} \left[\frac{V_t}{V}\right]^{0.25} = \Phi, \tag{33}$$

and the value of $\beta$, according to the specific case. On the one hand, the fact that the fractal dimension is constant for a time shorter than the saturation time could be explained by the correlation between the expected value of the contour radius and the expected value of the culture inner radius, and this is related to the way information in the inner radius of the culture is transmitted to the culture contour. On the other hand, the fact that the fractal dimension is constant in a time longer than the saturation time when the super-roughness property appears could be the result of a change in the size of cell aggregates in the contour. Fig. 3 shows a comparison between the range of fractal dimension values predicted by the model and the experimental values obtained [6]:

As demonstrated in this paper, the mesoscopic model of the tumor growth explains the fact that contour roughness is a manifestation of the internal fluctuations system as a result of the probabilistic character of the processes that take place in individual cells.

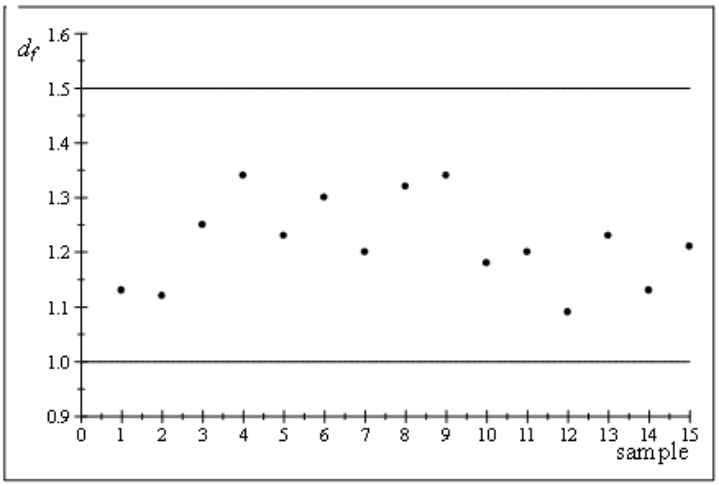



FIGURE 3. Comparison of the values of $d_f$ determined for different cultures [6] (dots) with the range of values predicted by the model (lines).

With this model, it is possible to simulate the stochastic growth of the culture; that is, its morphology. The morphology of tumor contours determines the dynamic behavior of growth by means of the scale invariance of their complex structures. In this regard, if the total cell growth rate is defined as the difference between the reproduction rate and the death rate, then as the difference between the total growth rate and the reproduction rate decreases, contour roughness increases.

As demonstrated, the fractal dimension is related to the average magnitude of the culture radius fluctuation equations (31) and (32); therefore, it can be used to establish the relation between $V$ and $V_t$, and consequently characterize the culture behavior at a microscopic level.

To obtain the culture morphology from the solution of the mesoscopic model and geometrical relation, the fractal dimension of the culture perimeter could be determined by

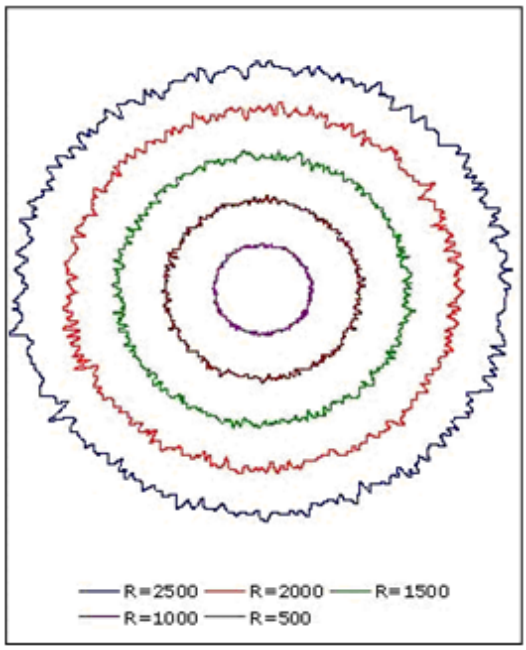
$$2R^{d_f} = 4R^{1.5}\Phi. \tag{34}$$

Equation (34) is equivalent to equation (31) and (32) if the contour fluctuations are taken into account as the cause of the perimeter-fractal dimension greater than its topological dimension. If we consider Brú's experimental findings [6] that the fractal dimension remains constant with the radius, the following relation is established to determine the value of the scaled-up parameter $\Phi$ for a radius of 1000 (arbitrary units):

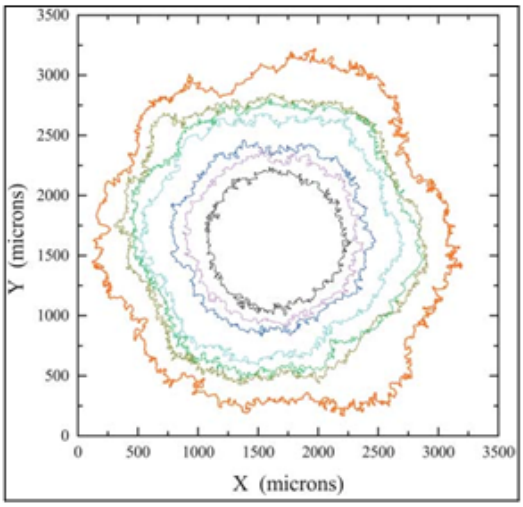
$$\Phi_{esc} = 2(1000)^{d_f - \alpha_{glob}}, \tag{35}$$

where the value for the parameter , which determines the different morphologies simulated for the culture, will be of

$$\Phi = \tfrac{\Phi_{esc}}{2\pi}(1000)^{0.5}. \tag{36}$$




(a)




(b)

FIGURE 4. (a) Evolution of the tumor morphology obtained using the model for different tumor sizes, $d_f = 1.20$; (b) Cell colony contours of a C6 cell line at different culture times, $d_f = 1.20$ [6]

The culture morphology is simulated considering the culture radius with a stochastic variable which has a normal distribution function whose expected value and standard deviation are

$$R = 1000$$

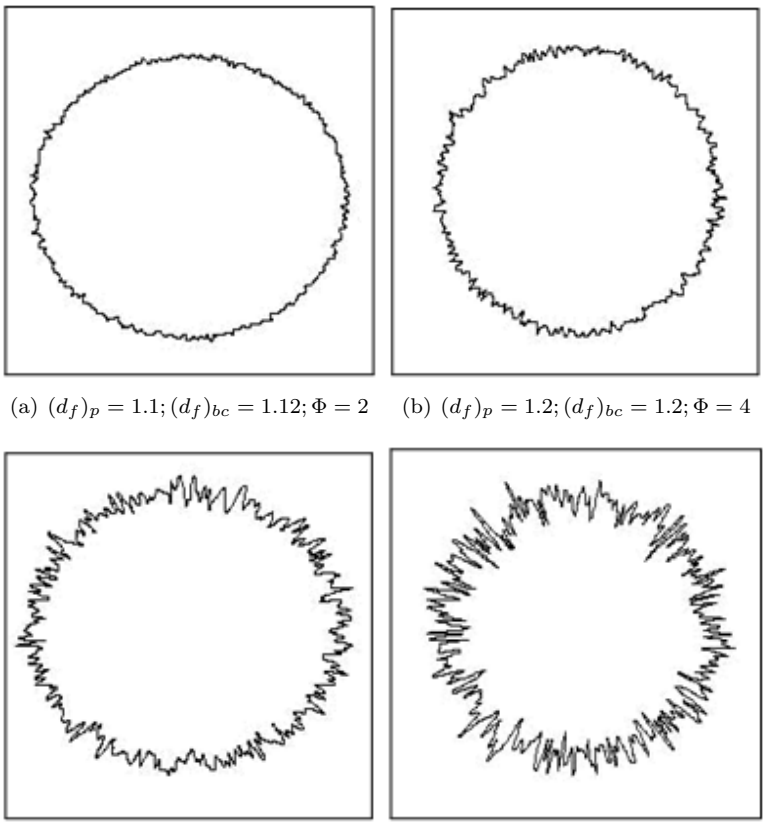
$$\chi = \Phi_{esc} R^{0.5}$$

To simulate the culture morphology with an expected value for the radius different from 1000, the standard deviation of the normal probability function is determined from the following scaling relation:

$$\Phi_{esc}(1000)^{-0.5} = \tfrac{\chi}{R}. \tag{37}$$

Fig. 4(a) shows the morphology of a hypothetical culture, simulated using the mesoscopic model for different values of the culture radius, the fractal dimension, $d_f = 1.20$, obtained using the box counting method. A similarity with the morphology (Fig. 4(b)) of a real cultures observed [6], C6 cell line, with fractal dimension, $d_f = 1.20$.

Fig. 5 shows the morphology of cultures with different fractal dimensions and an expected value for the radius of 1000.



(a) $(d_f)_p = 1.1; (d_f)_{bc} = 1.12; \Phi = 2$ (b) $(d_f)_p = 1.2; (d_f)_{bc} = 1.2; \Phi = 4$

(c) $(d_f)_p = 1.3; (d_f)_{bc} = 1.31; \Phi = 8$ (d) $(d_f)_p = 1.4; (d_f)_{bc} = 1.41; \Phi = 16$

FIGURE 5. Morphology of cultures with different fractal dimension and radius expected value of 1000.

In this case, the value of parameter $\Phi$, established to simulate the morphology, the fractal-dimension value predicted by the model $(d_f)_p$ and the fractal dimension value calculated by the box counting method $(d_f)_{bc}$, are shown.

Having a culture morphology calculated for different values of $\Phi$, the fractal dimension is calculated by the box-counting method. Fig. 6 shows the comparison between the fractal dimension values predicted by the model and those calculated by the box-counting method.

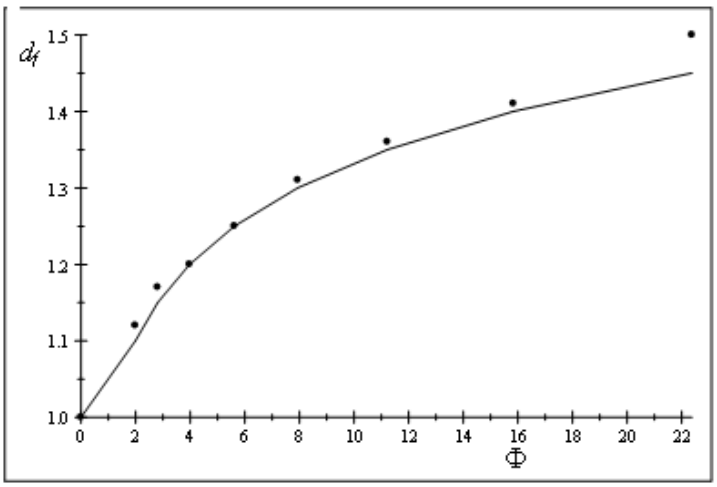



FIGURE 6. Comparison of the fractal dimension value predicted for different value of parameter $\Phi$ (line) with the fractal dimension calculated by the box-counting method (dots).

4. **Conclusions and remarks.** In summary, in this work a mesoscopic model for tumor growth has been presented, considering only the effect of internal fluctuations, to improve our understanding of the origin of tumor cells' heterogeneity. In this sense, this stochastic formalism permits us not only to reproduce but also to better understand the experimental results presented by Brú [6]. The presented formalism is conceptually related to Kitano's theoretical considerations [12, 13] on cancer robustness, regarding the role of internal fluctuations in tumor cells' heterogeneity. In fact, the internal fluctuations give an explanation to the super-rough dynamics on tumor growth [5], where the change of microscopic entities size is taken into account. Another important feature of the mesoscopic model is that it allows us to predict a range of values for the critical exponents and the fractal dimensions corresponding to the experimental findings presented by Br [6] for different tumor cell cultures. A significant aspect of the model's findings relates to the predicted values for $\beta$ growth exponent (0.25-0.5), which capture a basic characteristic of the critical surface growth dynamics, suggesting a Kadar-Parisi-Zhang (KPZ) universality class [4], for which $\beta = 0.33$, and those proposed by Brú [5] associated with the MBE universality class, for which $\beta = 0.375$. This result suggests that the tumor dynamics are too complex to be associated with a particular class.

Finally, the mesoscopic model allows simulating the morphology of tumor cells. In this sense, the fractal dimension calculated using the box-counting method applied to the morphology simulated by the model coincides with the fractal dimension values used to build this morphology. We hope the present theoretical framework in mathematical modeling for tumor growth will lead to improved cancer therapy.

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*E-mail address*: elenaik@fq.uh.cu
*E-mail address*: nieto@fq.uh.cu