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MORPHOGENESIS OF THE TUMOR PATTERNS

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Abstract. The mathematical modeling of tumor growth allows us to describe the most important regularities of these systems. A stochastic model, based on the most important processes that take place at the level of individual cells, is proposed to predict the dynamical behavior of the expected radius of the tumor and its fractal dimension. It was found that the tumor has a characteristic fractal dimension, which contains the necessary information to predict the tumor growth until it reaches a stationary state. This fractal dimension is distorted by the effects of external fluctuations. The model predicts a phenomenon which indicates stochastic resonance when the multiplicative and the additive noise are correlated.

1. **Introduction.** Cancer is a generic name given to a group of malignant cells which have lost its specialization and control over its normal growth. These groups of malignant cells are nonlinear dynamic systems which self-organize in time and space, far from thermodynamic equilibrium, and exhibit high complexity [9], robustness [12], [13] and adaptability [19].

Mathematical models represent a manner for formalizing the knowledge of living systems obtained through theoretical biology. Mathematical modeling of tumor growth makes possible the description of its most important regularities and is useful in providing effective guidelines for cancer therapy, drug development, and clinical decision-making [18], [21].

On the one hand, most of the mathematical models presented in literature assume by default that they can describe the phenomenological features of the tumor growth using analogue systems. Such models include the Gompertzinan model [6], [7], the logistic model [25], the prey-predator model [14], and so on. On the other hand, such models are focused on some kind of therapy, such as; immunotherapy [20], radiotherapy [18], and combinatory therapy [16] or drug administrations [8].

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In recent studies [4], experimental evidence has shown been found that the main mechanism responsible for tumor growth is the competition for space, and not for nutrients, between the tumor and the host cells, and that the tumor shows a linear growth in time.

In the previous work [11], a mesoscopic model for tumor growth was has been presented, considering only the effect of internal fluctuations, in order to improve our understanding of the origin of tumor cells heterogeneity. In this case, this stochastic formalism allows us not only to reproduce, but also to obtain a better understanding of the experimental results presented by Brú [4]. In fact, the internal fluctuations give an explanation as to the "super-rough" dynamics of tumor growth, where the change of microscopic entities size is taken into account. Another important feature of the mesoscopic model [11] 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 Brú [4] for different tumor cell cultures.

Our hypothesis is that the rugosity of the interface between the tumor and the host is primarily the result of two main effects. One of them is related to the fact that the reproduction and death of cells at the interface occurs with a particular probability, and therefore it is the results of internal fluctuations [11]; the other is associated with the randomness of the environment, in particular the interaction between the tumor and the immune systems and the host, and for that reason it is also associated with the external fluctuations.

Our objective is to extend the study of the morphogenetic basis of two-dimensional tumor patterns. In section 2, formalism is obtained from the master equation (ME) to obtain the mesoscopic model which describes the tumor growth dynamics in absence of external fluctuations, taking into account that the tumor grows in a limited area. The microscopic variable considered to describe the state of the system is the total number of tumor cells, and the macroscopic variables are the expected value of the radius and the fractal dimension, which is a result of internal fluctuations.

In section 3, an extension of the formalism presented in section 2 is developed to obtain the stochastic model to describe the behavior of the expected value of the radius and the fractal dimension, taking into account the external fluctuations.

In section 4, Results and Discussion, the behavior of different types of tumor cell colonies, characterized by Brú [4] is predicted by using the formalism developed in section 2 and 3; and finally, in section 5 the conclusions are presented.

2. **Mesoscopic model.**

To obtain a mathematical model to predict tumor growth, the following considerations were made: the total number of cells n is the microscopic variable that describes the behavior of the system, and macroscopic variables considered were the tumor radius r and the fractal dimension of the interface d_f , related by the expressions:

$$n = \frac{\pi r^2}{\Omega} \tag{1}$$

$$d_f = 2 - \frac{1}{2} G\left(y\right) \tag{2}$$

$$y = \lim_{l \to 1} \frac{\Delta \ln(w)}{\Delta \ln(l)}, \tag{3}$$

where Ω is the area occupied by the cell or cell colony in the contour, w is an adimensional magnitude that expresses the height difference between two points in the contour separated by an adimensional distance l, and $G(y)$ is a linear function of y.

Geometrically, a tumor has the shape shown in Figure 1, in which the distance between the center of the tumor and the point at the interface more distant from the center H, the expected value of the tumor radius R, and the difference between the maximum heights of two points in the contour W are useful variables.

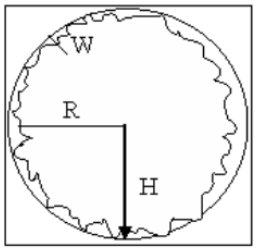

FIGURE 1. Geometric representation of the tumor: H $[L]$ is the distance between the center of the tumor and the point at the interface most distant from the center, R $[L]$ is the expected value of the tumor radius, and W $[L]$ is the difference between the maximum heights of two points on the contour.

As contour rugosity is a property of the tumor, not all the surface of radius H is covered by tumor cells. If it is considered that internal fluctuations scale with the area occupied by the microscopic entities that characterize the tumor (tumor cells or tumor cell colonies), then the percentage of the host area occupied by tumor cells depends on the relation between the size of the entity and the expected value of the area occupied by the tumor, expressed by:

$$\frac{R^2}{H^2} = f\left(\frac{\Omega}{R^2}\right), \tag{4}$$

where f is a function of the relation $\frac{\Omega}{R^2}$ with the following properties:

$$\lim_{\frac{\Omega}{R^2}\to 0} f\left(\frac{\Omega}{R^2}\right) = 1 \Rightarrow W = 0;\ d_f = 1 \tag{5}$$

and

$$\lim_{\frac{\Omega}{R^2}\to\infty} f\left(\frac{\Omega}{R^2}\right) = 0 \Rightarrow W = \infty;\ d_f = 2. \tag{6}$$

The main microscopic processes considered were the interface cells' reproduction, whose transition probability per unit of time T_r $\left[t^{-1}\right]$ is established a priori and is described by

$$T_r = \mu n^{0.5} \tag{7}$$

and by the contour cells' death, whose transition probability per unit of time T_d $\left[t^{-1}\right]$ is described by

$$T_d = k_d n^{0.5}, \tag{8}$$

where

$$\begin{aligned} &k_d = b\left(1 + F_a\right); \\ &b = cte; \end{aligned} \tag{9}$$

$$F_a = \frac{r^2}{D^2} = \frac{n}{N}. \tag{10}$$

In equations (7) and (8) μ $\left[t^{-1}\right]$ is the cell reproduction rate constant, and k_d $\left[t^{-1}\right]$ is the cell death rate constant. The death rate constant k_d includes a correction term F_a, which represents the relation between the tumor radius r and a characteristic length D of the area (see equations (9) and (10)) and takes into account the finite area of the host. The term F_a is equivalent to the relation between the total number of cells and the total sites N which can be occupied.

Considering the transition probabilities (7) and (8), the master equation ME [24], which describes the probability behavior $P(n;t)$ of having n cells in time t, is written as:

$$\begin{aligned} &\frac{\partial P(n;t)}{\partial t} = \left(\mathbf{E}_n^{-1} - 1\right)\mu n^{0.5} P\left(n;t\right) + \left(\mathbf{E}_n^{+1} - 1\right) b\left(1 + \frac{n}{N}\right) n^{0.5} P\left(n;t\right), \\ &P\left(n_0;0\right) = 1, \end{aligned} \tag{11}$$

where $\mathbf{E}_n^a$ is the step operator. There are two different time scales in ME. One is located in the time derivative on the left side and represents the macroscopically measured time. The other is located on the right side of the equation and is related to the duration of the microscopic processes.

Since the reproduction or death of a single cell produces a negligible effect on the system:

$$\frac{\Delta n}{n} \cong 0, \tag{12}$$

then the variable n could be considered continuous. If the step operator is expressed in its differential form,

$$\mathbf{E}_n^{+1} = 1 + \frac{\partial}{\partial n} + \frac{1}{2}\frac{\partial^2}{\partial n^2}, \tag{13}$$

$$\mathbf{E}_n^{-1} = 1 - \frac{\partial}{\partial n} + \frac{1}{2}\frac{\partial^2}{\partial n^2}, \tag{14}$$

the Fokker-Planck equation (FPE) is obtained [24] [10] from the master equation (11):

$$\begin{aligned}\frac{\partial P(n;t)}{\partial t} = &-\frac{\partial}{\partial n}\left[\left(\mu n^{0.5} - b\left(1+\frac{n}{N}\right)n^{0.5}\right)P(n;t)\right] \\ &+\frac{1}{2}\frac{\partial^2}{\partial n^2}\left[\left(\mu n^{0.5} + b\left(1+\frac{n}{N}\right)n^{0.5}\right)P(n;t)\right].\end{aligned} \tag{15}$$

If we take into account the following relations between the probability related to the microscopic $P(n,t)$ and the one related to the macroscopic variables $P(r,t)$ [10],

$$\partial P(n;t)\,\partial n = \partial P(r;t)\,\partial r; \tag{16}$$

$$\frac{\partial P(n;t)}{\partial t} = \frac{\partial r}{\partial n}P(r;t), \tag{17}$$

then the FPE related to the behavior of the macroscopic variable is

$$\begin{aligned}\frac{\partial P(r;t)}{\partial t} = &-\frac{\partial}{\partial r}\left[\left(\psi - \eta\left(1+\frac{r^2}{D^2}\right) - \frac{\Omega}{2r^2}\left(\psi+\eta\left(1+\frac{r^2}{D^2}\right)\right)\right)P(r;t)\right] \\ &+\frac{1}{2}\frac{\partial^2}{\partial r^2}\left[\frac{\Omega}{2r}\left(\psi+\eta\left(1+\frac{r^2}{D^2}\right)\right)P(r;t)\right],\end{aligned} \tag{18}$$

in which the relations among macroscopic and microscopic rate constants are

$$\psi = \left(\frac{\Omega}{4}\right)^{0.5}\mu, \tag{19}$$

$$\eta = \left(\frac{\Omega}{4}\right)^{0.5} b. \tag{20}$$

In FPE (18), the first term on the right hand side is a convective term related to the expected or deterministic value, while the second one is a diffusive term related to the fluctuation's value. If it is considered that

$$\psi - \eta\left(1+\frac{r^2}{D^2}\right) >> \frac{\Omega}{2r^2}\left(\psi+\eta\left(1+\frac{r^2}{D^2}\right)\right) \tag{21}$$

then the equation (18) can be written as:

$$\begin{aligned}\frac{\partial P(r;t)}{\partial t} = &-\frac{\partial}{\partial r}\left[\left(\psi - \eta\left(1+\frac{r^2}{D^2}\right)\right)P(r;t)\right] \\ &+\frac{1}{2}\frac{\partial^2}{\partial r^2}\left[\frac{\Omega}{2r}\left(\psi+\eta\left(1+\frac{r^2}{D^2}\right)\right)P(r;t)\right], \\ P(r_0;t_0) = 1.&\end{aligned} \tag{22}$$

From the FPE (22) the expected radius of the tumor R is obtained [24]:

$$\begin{aligned}&\frac{dR}{dt} = \psi - \eta\left(1+\frac{R^2}{D^2}\right); \\ &\frac{dR}{dt} = V - \eta\frac{R^2}{D^2}, \\ &R_0 > 0\end{aligned} \tag{23}$$

and for variance σ:

$$\begin{array}{l} \frac{d\sigma}{dt} = -2\frac{\eta R}{D^2}\sigma + \frac{\Omega}{2R}\left(\psi + \eta\left(1 + \frac{R^2}{D^2}\right)\right), \\ \sigma_0 = 0 \end{array} \tag{24}$$

where $V\left[L.t^{-1}\right]$ is the tumor growth rate macroscopically observed during the linear growth stage [4]. The system of ordinary differential equation given by (23) and (24) represents the mesoscopic model which describes the tumor dynamics in absence of external fluctuations considering the finite host area. The stability analysis [1] shows that the radius grows to a stable stationary state, also called the dormant tumor stage [15].

The analytic solution of the differential equation (23) gives the behavior of the expected value of the radius

$$\begin{array}{l} R = R_{ss}\frac{(R_0+R_{ss})\exp\left(2\frac{V}{R_{ss}}t\right)+(R_0-R_{ss})}{(R_0+R_{ss})\exp\left(2\frac{V}{R_{ss}}t\right)-(R_0-R_{ss})}; \\ R_{ss} = \left(\frac{\psi}{\eta} - 1\right)^{0.5} D, \end{array} \tag{25}$$

where R_{ss} is the expected value of the tumor radius in the stationary state or dormant tumor stage. As the tumor can not physically exceed the size of the area in which it grows, the relation between reproduction and endogenous death rates is limited by the possible values; so,

$$1 < \frac{\psi}{\eta} < 2. \tag{26}$$

If the initial radius of the tumor, when only interface cells can reproduce and die, is negligible with respect to the size of the system, $R_0 << R_{ss}$, then equation (25) can be written as:

$$R = R_{ss}\frac{\exp\left(2\frac{V}{R^s}t\right)-1}{\exp\left(2\frac{V}{R^s}t\right)+1}. \tag{27}$$

Additionally, if in the initial stages of the tumor development, we take into account that $1 >> \frac{R^2}{D^2}$, the equation (23) is reduced to a differential equation of order zero with respect to tumor radius and its solution is

$$\begin{array}{l} R = Vt + R_0, \\ R = (\psi - \eta)\, t + R_0, \end{array} \tag{28}$$

which reproduces the experimental behavior observed by Brú [4].

According to our hypothesis, the tumor fractal dimension depends on the physiological condition of active cells at the interface, and it must include the reproduction and death rate constants. To determine the characteristic fractal dimension of the tumor, the right side of equation (24) is equaled to zero, so that

$$\begin{array}{l} \frac{d\sigma}{dt} = 0; \\ D = H, \end{array} \tag{29}$$

and the variance is expressed as

$$\sigma = \frac{H^2}{4}\frac{\Omega}{R^2}\left(\frac{\psi}{\eta} + 1 + \frac{R^2}{H^2}\right). \tag{30}$$

Because the height difference between two points at the interface is equivalent to the magnitude of internal fluctuations (expressed by the square root of the variance) [3], the following adimensional expression is obtained from equation (30):

$$w^2 = \frac{l^2}{4}\left(\frac{\psi}{\eta} + 1 + L^2\right), \tag{31}$$

where:

$$w = \frac{\sigma^{0.5}}{H}, \tag{32}$$

$$l = \left(\frac{\Omega}{R^2}\right)^{0.5}, \tag{33}$$

$$L = \frac{R}{H}, \tag{34}$$

$$L^2 = f\left(l^2\right). \tag{35}$$

In equation (35), $f(l^2)$ is, according to the preestablished considerations (see equation (4)), a scale down function which takes into account the fact that that internal fluctuations will depend on the size of the microscopic entities and the size of the system.

Also, because there is a linear relation between the expected value of the radius and the perimeter, the adimensional variable l is equivalent to the distance between two interface points. Consequently, the following scaling relation can be assumed:

$$\begin{aligned} L^2 &= f\left(l^2\right) \\ L^2 &= 1 - l^2, \end{aligned} \tag{36}$$

so, equation (31) is expressed as

$$w^2 = \frac{l^2}{4}\left(\frac{\psi}{\eta} + 2 - l^2\right). \tag{37}$$

Substituting equation (37) in (3) gives:

$$\begin{aligned} y &= \lim_{l\to 1} \frac{\Delta \ln\left(\left(\frac{l^2}{4}\left(\frac{\psi}{\eta}+2-l^2\right)\right)^{0.5}\right)}{\Delta \ln(l)} \\ y &= \lim_{l\to 1} \left(\frac{d \ln\left(\left(\frac{l^2}{4}\left(\frac{\psi}{\eta}+2-l^2\right)\right)^{0.5}\right)}{dl}\right)\left(\frac{d \ln(l)}{dl}\right)^{-1} \\ y &= \left(\frac{\psi}{\psi+\eta}\right) \\ y &= \left(\frac{\mu}{\mu+b}\right), \end{aligned} \tag{38}$$

and finally, (38) in equation (2) gives:

$$d_f = 2 - \frac{1}{2}\left[C_1\left(\frac{\mu}{\mu+b}\right) + C_2\right], \tag{39}$$

where constants C_1 and C_2 are evaluated, taking into account the interval of values physically possible that can be obtained by the relation between the reproduction

and endogenous death rate constants expressed by equation (26) and its correspondent fractal dimension value. Then two extreme cases appear:

$$\frac{\psi}{\eta} = 1 \Rightarrow d_f = 2, \tag{40}$$

because when $\frac{\psi}{\eta} = 1$, the tumor does not grow and so the fractal dimension is equal to the surface dimension; and

$$\frac{\psi}{\eta} = 2 \Rightarrow d_f = 1, \tag{41}$$

because when $\frac{\psi}{\eta} = 2$, the contour rugosity is zero and the fractal dimension is equal to the topological dimension of the contour of a circle of radius H. Taking into account both extreme conditions given by equations (40) and (41), the following expression is proposed to determine the characteristic fractal dimension of the tumor:

$$d_f = \frac{5 - \frac{\psi}{\eta}}{\frac{\psi}{\eta} + 1}. \tag{42}$$

3. **Stochastic model.** External fluctuations have been taken into account in order to understand the effects that the host and immune system produce in the tumor. The differential equation to determine the expected value of the tumor radius is taken as a starting point, and the random nature of the environment (action of the host and immune system) is considered to be reflected by the stochastic nature of the reproduction and death rate constants; so, equation (23) can be expressed as

$$\frac{dR}{dt} = \hat{\psi} - \hat{\eta}\left(1 + \frac{R^2}{D^2}\right); \tag{43}$$

$$\hat{\psi} = \psi + \xi; \tag{44}$$

$$\hat{\eta} = \eta + \zeta; \tag{45}$$

$$R_0 > 0, \tag{46}$$

where ψ and η are the expected values, while ξ and ζ are the fluctuations related to these parameters, respectively. According to the mathematical structure of the model, ξ is an additive noise to the system, while ζ is a multiplicative noise. These noises, by simplification, are considered to have the following properties:

$$\langle \xi \rangle = 0, \tag{47}$$

$$\langle \zeta \rangle = 0, \tag{48}$$

$$\left\langle \xi^2 \right\rangle = 2\left(\sigma_\psi\right), \tag{49}$$

$$\left\langle \zeta^2 \right\rangle = 2\left(\sigma_\eta\right), \tag{50}$$

$$\left\langle \xi\zeta \right\rangle = 2\lambda\left(\sigma_\psi\sigma_\eta\right)^{0.5}, \tag{51}$$

where λ is the coefficient of correlation between the additive and the multiplicative noises, σ_ψ is the variance of the additive noise, and σ_η is the variance of the multiplicative noise. From equation (43) to equation (51), the stochastic differential equation (SDE) is obtained:

$$\begin{aligned} dR = &\left(\psi - \eta\left(\frac{R^2}{D^2}+1\right)\right)dt \\ &+ \left(2\sigma_\psi + 2\sigma_\eta - 2\lambda\left(\sigma_\psi\sigma_\eta\right)^{0.5}\right)^{0.5} d\varpi \\ &+ \left(2\frac{R^2}{D^2}\sigma_\eta + \frac{R^4}{D^4}\sigma_\eta - 2\frac{R^2}{D^2}\lambda\left(\sigma_\psi\sigma_\eta\right)^{0.5}\right)^{0.5} d\varpi, \end{aligned} \tag{52}$$

where ϖ is a stochastic variable whose probability function is a Wiener process [10]. The FPE corresponding to the SDE (52) is:

$$\begin{aligned} \frac{\partial P(r;t)}{\partial t} = &-\frac{\partial}{\partial r}\left[\left(\psi - \eta\left(1+\frac{r^2}{D^2}\right)\right)P\left(r;t\right)\right] \\ &+ \frac{1}{2}\frac{\partial^2}{\partial r^2}\left[\left(2\sigma_\psi + 2\sigma_\eta - 2\lambda\left(\sigma_\psi\sigma_\eta\right)^{0.5}\right)P\left(r;t\right)\right] \\ &+ \frac{1}{2}\frac{\partial^2}{\partial r^2}\left[\left(2\frac{R^2}{D^2}\sigma_\eta + \frac{R^4}{D^4}\sigma_\eta - 2\frac{R^2}{D^2}\lambda\left(\sigma_\psi\sigma_\eta\right)^{0.5}\right)P\left(r;t\right)\right], \\ P\left(r_0;t_0\right) = 1. \end{aligned} \tag{53}$$

Because we want to know the effect of external fluctuations over the macroscopic features of the tumor, that is, over the fractal dimension which is related to rugosity and the scope of the fluctuations in the radius as a result of environment randomness, only the expected value and the variance obtained from the equation (53) are needed. So, for the expected value

$$\frac{dR}{dt} = \left(\psi - \eta\left(\frac{R^2}{D^2}+1\right)\right), \tag{54}$$

and for variance σ_e related to the external fluctuations

$$\begin{aligned} \frac{d\sigma_e}{dt} = &-\frac{4\eta R}{D^2}\sigma_e + 2\left(I_\psi\right)^2\psi^2 + 2\left(I_\eta\right)^2\eta^2 - 2\lambda I_\psi I_\eta\psi\eta \\ &+ 2\frac{R^2}{D^2}\left(I_\eta\right)^2\eta^2 + 2\frac{R^4}{D^4}\left(I_\eta\right)^2\eta^2 - 2\frac{R^2}{D^2}\lambda I_\psi I_\eta\psi\eta, \end{aligned} \tag{55}$$

where I_ψ and I_η are the intensity of the additive and multiplicative noises respectively, which are defined as

$$I_\psi = \frac{\left(\sigma_\psi\right)^{0.5}}{\psi} \tag{56}$$

and

$$I_\eta = \frac{\left(\sigma_\eta\right)^{0.5}}{\eta}. \tag{57}$$

The ODE (54) is structurally equivalent to the relation obtained from the mesoscopic model (see equation (23)). In this case, the formalism ignores the effect of external fluctuations on the expected value of the radius. Also, the variance σ_e

expresses the magnitude of fluctuations of the tumor radius due to the random nature of the environment (host-immune system). If in a particular case, the noise intensity is considered constant, the system can be "frozen" in time:

$$\begin{array}{l} \frac{d\sigma_e}{dt} = 0; \\ D = H, \end{array} \tag{58}$$

and the following adimensional relation is obtained:

$$(w_e)^2 = l\frac{\left((I_\psi)^2\mu^2+(I_\eta)^2b^2-\lambda I_\psi I_\eta \mu b+(I_\eta)^2b^2L^2+(I_\eta)^2b^2L^4-\lambda I_\psi I_\eta \mu b L^2\right)}{8\left(\frac{\Omega}{4}\right)^{0.5}b}. \tag{59}$$

In this case, although external fluctuations are not considered to affect the expected value of the radius, these fluctuations are manifested at a macroscopic level in the distortion of the tumor fractal dimension with respect to its characteristic fractal dimension.

To find the relation among the fractal dimension in front of external fluctuations d_f^e, the characteristic fractal dimension d_f, and the intensity of noises I_ψ and I_η, the following is considered. First, the relation between the reproduction and death rate constants is related to the fractal dimension through and expression obtained from equation (42):

$$\frac{\psi}{\eta} = \frac{\mu}{b} = \frac{(5-d_f)}{d_f+1}. \tag{60}$$

Second, the scaling relation given by equation (36) will be considered, and third, the total height difference between two interface points separated by a perimeter distance l will be considered as the sum of the height difference due to external fluctuations w_e and a height difference due to internal fluctuations w, so the fractal dimension d_f^e will be calculated as:

$$d_f^e = 2 - \tfrac{1}{2}y_e + C_3, \tag{61}$$

where:

$$y_e = \lim_{l\to 1}\frac{\Delta \ln(w_e+w)}{\Delta \ln(l)} \tag{62}$$

and C_3 is a constant evaluated taking into account that when there is no external noise, the fractal dimension d_f^e has the same value as the characteristic fractal dimension of the tumor d_f . Then,

$$\begin{array}{l} d_f^e = 0.833\,33 d_f + 0.833\,33 - \dfrac{(5-d_f)}{6\left(\sqrt{0.333\,34\left(\frac{\eta}{\Omega}\right)A_1}+1\right)} \\ \qquad + \dfrac{0.408\,24\left(\frac{\eta}{\Omega}\right)^{0.5}\left(\left(I_\eta^2-\left(\frac{(5-d_f)}{(d_f+1)}\right)^2 I_\psi^2-\lambda\left(\frac{(5-d_f)}{(d_f+1)}\right)I_\psi I_\eta\right)\right)(d_f+1)^{0.5}}{A_2\sqrt{\left(I_\eta^2+\left(\frac{(5-d_f)}{(d_f+1)}\right)^2 I_\psi^2-\lambda\left(\frac{(5-d_f)}{(d_f+1)}\right)I_\psi I_\eta\right)}} \\ A_1 = \left((d_f+1)\,I_\eta^2 + \frac{(5-d_f)^2}{(d_f+1)}I_\psi^2 - \lambda\,(5-d_f)\,I_\psi I_\eta\right) \\ A_2 = \left(\sqrt{0.333\,34\,\left(\frac{\eta}{\Omega}\right)A_1}+1\right). \end{array} \tag{63}$$

4. **Results and discussion.** To analyze the validity of the developed formalism (section 2, equation (25)), a parameterization of the model is carried out to compare the temporal behavior of the radius of the tumor with that experimentally observed by Brú [4] for a HT-29 (colon adenocarcinoma) cell colony growing in a Petri dish 5 cm in diameter at a rate of 1.93 $\mu m.h^{-1}$ and a fractal dimension of 1.13. The macroscopic parameters, reproduction constants and death rate constants are determined from equations (28) and (60), to obtain

$$\psi = 4.29\ \mu m.h^{-1}$$

and

$$\eta = 2.36\ \mu m.h^{-1}.$$

Given that the Petri dish has a radius of 2.5 cm, as an initial condition we select the one given by Brú [4] for a colony of HT-29 (colon adenocarcinoma) cells ($R_0 = 250\ \mu m, t_0 = 400\ h$). The graph shown in Figure 2 is obtained from equation (25).

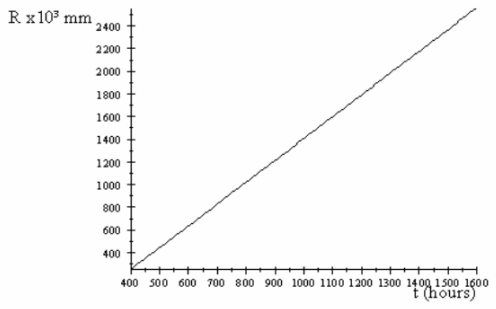

FIGURE 2. Predicted behavior of R for a colony of HT-29 colon adenocarcinoma cells. The initial condition was selected according to the results shows by Brú [14] ($R_0 \sim 250\ \mu m, t_0 \sim 400\ hour$).

As observed, the macroscopic model (equation (23)) which is derived from stochastic formalism reproduces the experimental results found by Brú [4]. To generalize the model, five tumor cell lines shown in Figure 3, were selected. The features of theses cells are reported by Brú [4]. Table 1 shows the linear growth rates V $\mu m.h^{-1}$, their fractal dimension d_f [4], as well as the reproduction ψ and death η $\left[\mu m.h^{-1}\right]$ rate constants of these cells, predicted by the model.

As can be seen, in the absence of external fluctuations, the stochastic formalism allows formulating a macroscopic model that on the one hand describes the linear

TABLE 1. Macroscopic characteristics reported by Brú observed in different types of in vitro cell lines were formed in 5-cm-diameter petri dishes. a: macroscopic characteristics reported by Bru; b: Reproduction and death rate constants calculated by the proposed model from the observed macroscopic characteristics.

Number	Cell line Type	d_f^a	V^a	ψ^b	η^b
1	HT-29 Colon adenocarcinoma	1.13	1.93	4.29	2.36
2	C-33 cervix carcinoma	1.25	6.40	16.00	9.00
3	Saos-2 osteosarcoma	1.34	0.94	2.60	1.66
4	AT5 primary human foreskin fibroblasts	1.23	8.72	21.34	12.62
5	3T3 mouse fibroblasts	1.20	1.10	2.61	1.51

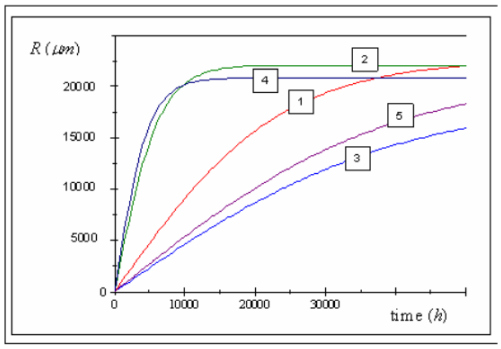

FIGURE 3. Predicted dynamical behavior of expected radius: (1) HT-29 Colon adenocarcinoma; (2) C-33 cervix carcinoma; (3) Saos-2 osteosarcoma; (4) AT5 primary human foreskin fibroblasts; (5) 3T3 mouse fibroblasts.

growth of the tumor radius in time and on the other hand its evolution until reaching a stable stationary state, which seems to be associated with tumor dormant state.

On one hand, it has been experimentally demonstrated that once the tumor appears, which is considered as a self-organising systems, spatial and temporarilly far from thermodynamic equilibrium, it shows a linear growth in the host [4] until reaching a critical size; then, for reasons not yet clarified, it stops growing for a period known as the dormant state [22]. After this, the tumor metastasizes, invading other organs, and this is main cause of death for cancer patients.

On the other hand, the host responds to the tumor growth. Where the active tumor cells try to escape from the host's action, they concentrate within a rough border, which shows the robustness of the tumor [5], which can be measured through the tumor fractal dimension. After this, the immune system cannot to eliminate it [23].

Three extreme cases are considered to analyze the effect of the external noise on the tumor in the dormant state; that is, the random action of the immune systems and the host over the tumor systems: 1. the effect of additive noise in absence of multiplicative noise, 2. the effect of the multiplicative noise in absence of additive noise, and 3. the effect of the additive and multiplicative noises when both are present with or without correlation. To evaluate these effects, the fractal dimension is calculated by equation (63) for the five tumor cell lines used before (see Table 1) [4]. The results obtained are shown in Figure 4.

In this case, two extreme behaviors are observed. Additive noise (Figure 4.A) implies a slight decrease of the tumor fractal dimension, while the multiplicative noise (Figure 4.B) and the action of both in absence of correlation causes an increase of the tumor fractal dimension. On the other hand, a correlation of both noises leads to a stochastic resonance [1], which means that at low noise intensity values, the fractal dimension first decreases and then increases. A similar result was reported by Zhong et al. [26].

This stochastic resonance phenomenon could explain as to why tumors remain in the dormant state for some time and then metastasize.

If we considered, as stated at the beginning of this work, that the external noise is associated with the random host-immune system action, in an early stage (Fig. 4 D) the appearance of an atypical behavior of the stochastic resonance is observed. That is, the fractal dimension decreases with low noise intensity, which could mean that the action of both systems reduces the malignancy of the tumor. This has been observed in the anticancer therapy processes [17] where the tumor fractal dimension decreases after therapy.

In addition, as the host and immune system effects have a random nature, the fractal dimension increases with noise intensity which produces an increasing malignity of the tumor, as experimentally observed that the increase in the malignancy of the tumor produces an increase of the tumor's fractal dimension [2]. This seems to be related to the increase in the number of active cells at the interface. Finally, it is important to highlight that although it is possible to predict when a tumor will reach the dormant state it is nearly impossible to predict when the tumor will reach the metastatic stage due to the highly random nature of the host and immune system actions, which involves not only the noise intensity but also the correlation among them. This aspect is something that which must be considered in cancer treatments.

5. **Conclusions and remarks.**

In summary, in this work, a stochastic formalism that allows a better understanding of the morphogenesis of the tumor pattern formation dynamics has been developed. The stochastic formalism developed not only reproduces the experimental results observed by Brú [4] but clarifies the physics of the complexity observed of the tumor patterns.

From the mesoscopic model, an ordinary differential equation which describes the tumor radius change, including both the linear growth and the dormant stages, was obtained. The parameterization of this model allows us to reproduce the experimental results observed by Brú [4]. Another important characteristic of the formalism is that the resulting equation allows us to relate the fractal dimension of the tumor with the tumor reproduction and death rate constants.

According to the hypothesis presented, when the external fluctuations are relevant (that is to say, the magnitude of the fluctuations related to the effect of the

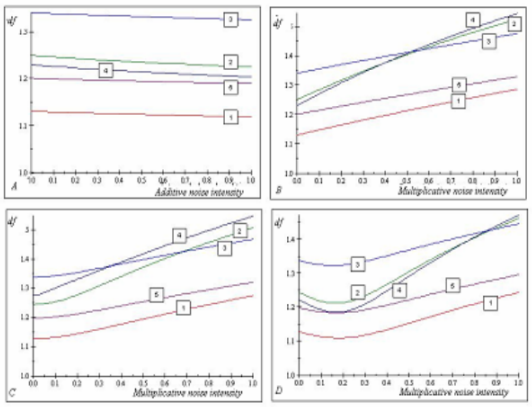

FIGURE 4. Effect of the external noise on the fractal dimension dfe for different tumor cell lines [14]. (1) HT-29 Colon adenocarcinoma; (2) C-33 cervix carcinoma; (3) Saos-2 osteosarcoma; (4) AT5 primary human foreskin fibroblasts; (5) 3T3 mouse fibroblasts. A. Effect of additive noise in absence of multiplicative noise; B. Effect of multiplicative noise in absence of additive noise; C. Effect of additive and multiplicative noise in absence of correlation; D. Effect of additive and multiplicative noise in presence of correlation.

immune systems and the host on the tumor is significant), the fractal dimension of the tumor is distorted with respect to the tumor's characteristic fractal value, which influences the amount of active cells found at the interface of the tumor in the dormant state.

When a correlation between both noises exists, a typical phenomenon of the stochastic resonance appears. This could be an acceptable explanation for why a tumor in a dormant phase, stationary state stable, can reach a critical state and then metastasize in spite of the host and immune actions.

It is important to clarify the fact that although in first approximation it is possible to predict when tumors reach the dormant state, it is practically impossible to forecast when a tumor will metastasize, given the highly random character of the action of immune system and the host.

The present theoretical framework for mathematical modeling of tumor growth will, we hope, improve cancer therapy.

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