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Basic ingredients for mathematical modeling of tumor growth *in vitro*: Cooperative effects and search for space

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AUTHOR-HIGHLIGHTS

- We show that a basic requirement to simulate successfully the tumor growing *in vitro* is to adopt a sigmoidal growth rate.
- We use a different kind of dynamical Monte Carlo method, building the waiting times along the simulation.
- We have obtained non-Poissonian distributions for these waiting times.

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ABSTRACT

Based on the literature data from HT-29 cell monolayers, we develop a model for its growth, analogous to an epidemic model, mixing *local* and *global* interactions. First, we propose and solve a deterministic equation for the progress of these colonies. Thus, we add a stochastic (local) interaction and simulate the evolution of an Eden-like aggregate by using dynamical Monte Carlo methods. The growth curves of both deterministic and stochastic models are in excellent agreement with the experimental observations. The waiting times distributions, generated via our stochastic model, allowed us to analyze the role of mesoscopic events. We obtain log-normal distributions in the initial stages of the growth and Gaussians at long times. We interpret these outcomes in the light of cellular division events: in the early stages, the phenomena are dependent each other in a multiplicative geometric-based process, and they are independent at long times. We conclude that the main ingredients for a good minimalist model of tumor growth, at mesoscopic level, are intrinsic cooperative mechanisms and competitive search for space.

1. Introduction

Mathematical modeling of biological systems, such as tumor growth, has an important role on *in vitro* (or *in vivo*) experiments concerning to formulate hypotheses about mechanisms and in sugesting new assays (Byrne, 2010). In fact, there is a growing interest in cancer modeling, since the scientific community begins to see it as a complex systems disease (Hornberg et al., 2006; Laubenbacher et al., 2009), which involves from genetic alterations (Hanahan and Weinberg, 2000) up to tissue aspects (Titz and Jeraj, 2008; Rejniak and McCawley, 2010). Regarding to clinical applications, one believes that the integration of imaging, treatment-response relationships, molecular basis, and predictive trials might speed up the development of more specific and more effective therapies (Byrne, 2010; Laubenbacher et al., 2009; Stewart and Li, 2007; Titz and Jeraj, 2008; Barazzuol et al., 2010; Kazmi et al., 2012; Román-Romaán and Torrez-Ruiz, 2012). Thus, we emphasize the importance of both mathematical and biological modeling and their uses in a complementary way (Byrne, 2010).

Tumor evolution is a complex process involving several phenomena at different scales (Preziosi, 2003). An approach for the growth may be done looking at mesoscopic events; e.g., cell–cell and cell–environment interactions, time interval between duplications, competition for space, formation or break of bonds that maintain the aggregate structure, and the temporal dynamics of the colonies size. To simulate such tumor progress, we may construct simple models just representing cells by its physical properties, despite their biological complexity (Drasdo et al., 2007). An important contribution of such systematizations (Block et al., 2007; Huergo et al., 2012), even if in two dimensions, is the classification of tumor growth patterns (Guiot et al., 2003),

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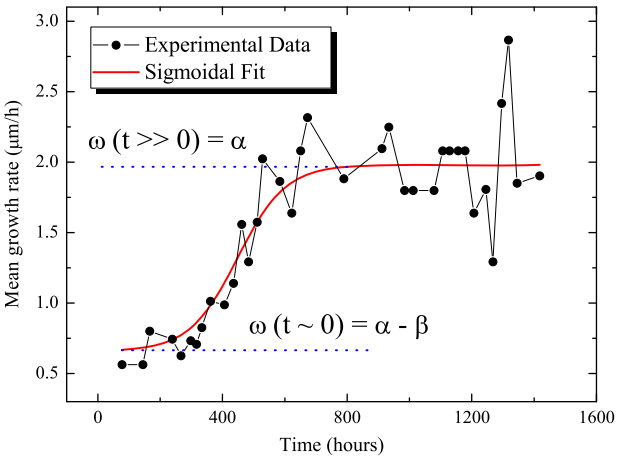

Fig. 1. The growth rate of the mean radius of aggregates of HT-29 cells (Brú et al., 2003). The blue dotted lines show the initial rate and its saturation. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

by generic mechanisms at individual cell level (migration, division, etc.), including molecular inter and intracellular regulation effects (Jiang et al., 2005), pressure effects (Brú and Casero, 2006) and evolution of cooperation (Alexrod et al., 2006). Also, one could use these models to identify cellular activities, which modified, would result in a maximal inhibition of multicellular evolution, and thus, point out potential therapeutic targets (Block et al., 2007; Katira et al., 2012). Brú and colleagues (Brú et al., 1998, 2003), in their investigation of pattern formation from several cell lines, highlighted the importance of the geometric structure and competition for space on the aggregate boundary. In recent work (Radszuweit et al., 2009), the authors search for simple and common mechanisms for tumor growth; through analysis of 2D and 3D models they suggested that single cell-based models in two-dimensions may describe well the general dynamics of its population.

In the search of mechanisms for tumor growth, by using simple models, we raised the following question: what ingredients are necessary to capture important features of tumor kinetics in the mesoscopic scale? Our belief is that cooperative effects and competitive search for space is the answer. In the next section we present the numerical method and the model used to simulate tumor growth; results and discussion appear within the third section, and in the last one we show the conclusions and point out our perspectives for future works.

2. Model and methods

We start our modeling approach, in the continuous limit, by fitting the experimental data (see Fig. 1) by using the following sigmoidal equation:

$$\omega(t) = \alpha - \frac{\beta}{1+\exp[\gamma(t-t_c)]}, \tag{1}$$

with $\omega(t) \equiv dr(t)/dt$ being the mean radius rate.[1] At early times the growth rate is lower, constant, and given by $\omega_0 = \alpha - \beta$. After a critical time t_c, the curve changes its behavior by going to another constant value (α). The parameter γ determines how fast the rate changes from $\alpha-\beta$ to α ($\alpha > \beta$). Thus, given the condition $r(0) = r_0$, we can find the equation to the mean radius:

$$r(t) = r_0 + \frac{\beta}{\gamma}\ln\left\{\frac{\exp[-\gamma(t-t_c)]+1}{\exp(\gamma t_c)+1}\right\} + \alpha t. \tag{2}$$

Now, we introduce a discrete (minimalist) model using a lattice with $M = L \times L$ sites, in which each site can only be in a tumor *status T* or in an empty *status V*. We assume that the occupancy probability (p_0) of an empty site next to a tumor site carries the local and global information of the system at each instant; our global/local interaction is different from the one in the literature for epidemic models (Aièllo et al., 2000; Aiello and da Silva, 2003; Cardy and Grassberguer, 1985). There, they put the effects explicitly, while here, we bring them together. In this context, we assume that p_0 comes directly from Eq. (1) by doing $p_0 = p_0(t) \equiv \omega(t)/\alpha$; consequently, we can write the transition rate for each empty site in the form $g_q(t) \propto [1-(1-p_0)^{\eta_q}]$ (Cardy and Grassberguer, 1985), where η_q is the number of neighbors with status T of an empty site labeled with index q. Finally, we can write the transition probability per unit of time as

$$g_q(t) = b\left\{1-\left[\left(\frac{\beta}{\alpha}\right)\frac{1}{1+\exp[\gamma(t-t_c)]}\right]^{\eta_q}\right\}, \tag{3}$$

where b is the frequency of new tumor sites in a colony. Here we consider the first and second nearest neighbors, i.e., $0 \le \eta_q \le 8$. Also we consider that just one event occurs at each time interval Δt, i.e., $|\Delta n_T| = |\Delta n_V| = 1$. Thus, we can write the stochastic equation (Aiello and da Silva, 2003)

$$\frac{d}{dt}n_T(t) = \sum_j \langle g(t)\rangle_j P_j(t) n_0^{(j)}, \tag{4}$$

where $\sum_j(\cdots)$ is the sum of over all possible system configurations available at time t; $\langle g(t)\rangle_j = \sum_q g_q^{(j)}(t)/n_0^{(j)}$ represents the mesoscopic rate of the growth (an average over each configuration j); $P_j(t)$ is the probability of finding the system in the state j at time t; and n_0 (from now on we will omit the configurational index j for all variables) is the total number of empty sites in the colony–medium interface; some of these sites may be inside the colony. The total number of lattice sites is $M = n_T + n_V$, being $n_V = n_0 + \tilde{n}_V$ the total number of empty sites, i.e., those (n_0) which contribute to the increase of n_T (with $\eta_q > 0$), plus those ($\tilde{n}_V$) that do not contribute (with $\eta_q = 0$). We neglect (explicitly) the cell death, migration and other process that could reduce the aggregate area, i.e., the transition $T \to V$.

We solve Eq. (4) using the dynamical Monte Carlo method (DMC) approach (Aiello and da Silva, 2003). In the simulations, we estimate the average waiting time between two events with the expression

$$\Delta t^{(n_T)} = \frac{1}{\sum_q g_q(t)}. \tag{5}$$

The superscript (n_T) denotes the average waiting time between the ($n_T - \Delta n_T$)-th and the (n_T)-th *cell*[2] growth event. Finally, we use the following dynamical hierarchy (Aièllo et al., 2000):

$$H_q = \frac{g_q(t)}{\max[g_q(t)]} = \frac{1-(1-p_0)^{\eta_q}}{1-(1-p_0)^{\eta_{\max}}}, \tag{6}$$

where $\max[g_q(t)]$ denotes the maximum value of $g_q(t)$.

Operationally, one does the DMC procedure by choosing a site of the set $\{n_0\}$ with equal probability, and then compares H_q with a random number ξ, uniformly distributed in the interval $[0,1)$. If $H_q > \xi$, one accepts the new configuration and updates the

[1] The derivative is obtained from the average slopes of adjacent points for each experimental data point.

[2] The word *cell* (in italic) does not represent biological cells, but just the T sites; we believe that a reescale factor can make the direct correspondence between n_T and the actual number of cells (Jiang et al., 2005).