A reaction-diffusion model for the growth of avascular tumor

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A nutrient-limited model for avascular cancer growth including cell proliferation, motility and death is presented. The model qualitatively reproduces commonly observed morphologies for primary tumors, and the simulated patterns are characterized by its gyration radius, total number of cancer cells, and number of cells on tumor periphery. These very distinct morphological patterns follow Gompertz growth curves, but exhibit different scaling laws for their surfaces. Also, the simulated tumors incorporate a spatial structure composed of a central necrotic core, an inner rim of quiescent cells and a narrow outer shell of proliferating cells in agreement with biological data. Finally, our results indicate that the competition for nutrients among normal and cancer cells may be a determinant factor in generating papillary tumor morphology.

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I. INTRODUCTION

Cancer is a disease derived, with few exceptions, from mutations on single somatic cells that disregard the normal controls of proliferation, invade adjacent normal tissues and give rise to secondary tumors (metastasis) on sites different from its primary origin. Although cancers are extremely diverse and heterogeneous, a small number of pivotal steps associated to both deregulated cell proliferation and suppressed cell death is required for the development of any and all tumors. Indeed, all neoplasms evolve accordingly to an universal scheme of progression. Neoplastic cells accumulate a series of genetic or epigenetic changes along the tumor progression in response to natural selection and as an integrated defense program against stress situations similar to the response of bacterial colony facing severe and sustained threats. But, unlike of the bacterial growth, tumor progression involves a complex network of interactions among cancer cells and its host microenvironment. It is well known that stressed bacterial colonies can develop diffusion-limited fractal patterns. Recently, normal and tumor cell patterns in vivo and in vitro were characterised by their fractal dimensions and cluster size distribution functions, reinforcing the great current interest in the search for basic principles of growth in living organisms, which are the most complex and challenging self-organized systems. In particular, for cancer growth, one of the most aggressive phenomena in biology, numerous mathematical models have been recently investigated. Examples include studies, based on classical reaction-diffusion equations, of the growth of tumor spheroids, cancer evolution and its interaction with the immune system, and the fundamental problem of tumor angiogenesis.

Recently, we proposed a diffusion-limited model to simulate the growth of carcinoma “in situ” in which cell proliferation, motility and death are locally regulated by the concentration of growth factors produced by each cancer cell. This model was able to generate compact, connected and disconnected morphologies which progress in time according to Gompertz growth curves, and for which the tumor gyration radii scale as in the Eden model for an asymptotically large number of cells. These features were shown to be independent of the detailed functional form of the microscopic growth rules. In contrast, the structure of the tumor border is influenced by the nature of the growth rules as indicated by the different scaling laws for the number of peripheral cancer cells. In particular, for disconnected and connected patterns the surface widths scale with exponents similar to those observed in bacterial colonies. Although the similarities between the simulated and histological tumor patterns were encouraging, the model was unable to generate papillary and ramified morphologies found in many of epithelial cancers and trichoblastomas. In consequence, we were lead to investigate the role of nutrient competition in neoplastic development, a biological feature excluded in our previous model but central in the growth of fractal bacterial colonies. Indeed, cancer cells subvert the evolutionary adaptations to multicellularity and revert to a largely nutrient-limited style of growth.

In this paper we analyze the avascular cancer growth in a model including cell proliferation, motility and death as well as competition for nutrients among normal and cancer cells. The cell actions (division, migration and death) are locally controlled by the nutrient concentration field. In Section 2 we introduce the cancer growth model. In Section 3 the simulational results for the tumor patterns, growth curves and scaling laws are discussed. In Section 4 the diffusion of growth factors secreted by the cancer...
II. THE CANCER GROWTH MODEL

The basic biological principles included in the model are cell proliferation, motility and death and competition for nutrients among normal and cancer cells. Nutrients (oxygen, amino acids, glucose, metal ions, etc.) diffuse from a capillary vessel through the tissue towards the individuals (normal and cancer) cells. Under restricted nutrient supply the growth rate of cancer cells is limited by its ability to compete for nutrients with the normal cells. In our model the division, migration and death of each cancer cell is controlled by the nutrient concentration in its local microenvironment.

A. The tissue

The studied system consists of a tissue fed by a single capillary vessel. The tissue is represented by a square lattice of size \((L + 1) \times (L + 1)\) and lattice constant \(\Delta\). The capillary vessel, localized at the top of the lattice at \(x = 0\), is the unique source from which nutrients diffuse through the tissue towards the individuals cells. Although a tumor mass is composed of different cell sub-populations, we shall consider only three types: normal, cancer and tumor necrotic cells. Any site, with coordinates \(\vec{x} = (i\Delta, j\Delta), i, j = 0, 1, 2, \ldots L,\) is occupied by only one of these cell types. In contrast to normal cells, one or more cancer cells can pile up in a given site. In turn, tumor necrotic cells are inert and, for simplicity, will be considered always as a single dead cell. Thus, each lattice site can be thought of as a group of actual cells in which the normal, necrotic and cancer cell populations assume one of the possible values \(\sigma_n(\vec{x}, t) = \sigma_d(\vec{x}, t) = 0, 1\) and \(\sigma_n(\vec{x}, t), \sigma_d(\vec{x}, t) = 0, 1, 2, \ldots\), respectively. As initial “seed” a single cancer cell in the half of the lattice \((x = L\Delta/2)\) and at a distance \(Y\) from the capillary vessel is introduced in the normal tissue, in agreement with the theory of the clonal origin of cancer [17]. Periodic boundary conditions along the horizontal axis are used. The row \(i = 0\) represents a capillary vessel and the sites with \(i = L + 1\) constitute the external border of the tissue.

B. The nutrients

As considered by Scalerandi et al. [18], we assume that dividing cancer cells are especially vulnerable to some critical nutrients such as iron, essential for DNA synthesis and, therefore, for cell division. The many other nutrients necessary for eucariotic cells are supposed to affect mainly the motility and death of the cancer cells. So, the nutrients are divided into two groups: essential and non-essential for cell proliferation, described by the concentration fields \(N(\vec{x}, t)\) and \(M(\vec{x}, t)\), respectively. However, it is assumed that both nutrient types have the same diffusion coefficients and consumption rates by the normal cells. These concentration fields obey the diffusion equations:

\[
\frac{\partial N(\vec{x}, t)}{\partial t} = D\nabla^2 N(\vec{x}, t) - \gamma N(\vec{x}, t)\sigma_n(\vec{x}, t) - \lambda_N\gamma N(\vec{x}, t)\sigma_c(\vec{x}, t) \tag{1}
\]

and

\[
\frac{\partial M(\vec{x}, t)}{\partial t} = D\nabla^2 M(\vec{x}, t) - \gamma M(\vec{x}, t)\sigma_n(\vec{x}, t) - \lambda_M\gamma M(\vec{x}, t)\sigma_c(\vec{x}, t) \tag{2}
\]

in which the nutrient absorption terms are proportional to the cell populations present in each site, and it is assumed differentiated nutrient consumption rates for normal and cancer cells by factors \(\lambda_N\) and \(\lambda_M\). It is important to notice that the present model assumes the simplest form for the nutrient diffusion phenomena, i.e., linear equations with constant coefficients. Also, \(\lambda_N > \lambda_M\) is used, reflecting the larger cancer cells affinity for essential nutrients.

The boundary conditions satisfied by the nutrient concentrations are \(N(x = 0) = M(x = 0) = K_0\), representing the continuous and fixed supply of nutrients provided by the capillary vessel; \(N(y = 0) = N(y = L\Delta)\) and \(M(y = 0) = M(y = L\Delta)\), corresponding to the periodic boundary conditions along the x-axis; at last, Neumann boundary conditions, \(\partial N(x = L\Delta)/\partial y = \partial M(x = L\Delta)/\partial y = 0\), are imposed to the border of the tissue. The hypothesis that a blood vessel provides a fixed nutrient supply to the cells in a tissue is a simplification, which neglects the complex response of the vascular system to metabolic changes of cell behavior [18].

In order to reduce the number of parameters in equations (1) and (2), the new dimensionless variables are defined:

\[
t' = \frac{Dt}{\Delta^2}, \quad \vec{x}' = \frac{\vec{x}}{\Delta}, \quad N' = \frac{N}{K_0}, \quad M' = \frac{M}{K_0}, \quad \alpha = \frac{\Delta}{\sqrt{D}}. \tag{3}
\]

Using these new variables in Eqs. (1) and (2) and omitting the primes we obtain

\[
\frac{\partial N}{\partial t} = \nabla^2 N - \alpha^2 N\sigma_n - \lambda_N\alpha^2 N\sigma_c \tag{4}
\]

and

\[
\frac{\partial M}{\partial t} = \nabla^2 M - \alpha^2 M\sigma_n - \lambda_M\alpha^2 M\sigma_c \tag{5}
\]
for the diffusion equations describing the nutrients concentration fields. In addition, the boundary condition on the capillary vessel becomes $N(x=0) = M(x=0) = 1$ and a value $\Delta = 1$ is defined.

C. Cell dynamics

Each tumor cell can be selected at random, with equal probability, and carry out one of three actions:

(1) **division.** Cancer cells divide by mitosis with probability $P_{\text{div}}$. If the chosen cell is inside the tumor, its daughter will pile up at that site, and $\sigma_c(\vec{x}) \to \sigma_c(\vec{x}) + 1$. Otherwise, if the selected cell is on the tumor border, its daughter will occupy at random one of their nearest neighbor sites $\vec{x}$ containing a normal or a necrotic cell and, therefore, $\sigma_c(\vec{x}) = 1$ and $\sigma_{n,d}(\vec{x}) = 0$. The mitotic probability $P_{\text{div}}$ is determined by the concentration per cancer cell of the essential nutrients $N$ present on the microenvironment of the selected cell:

$$P_{\text{div}}(\vec{x}) = 1 - \exp \left[ -\frac{N}{\sigma_c \theta_{\text{div}}} \right].$$  

(6)

The Gaussian term is included in order to produce a sigmoid curve saturated to the unity, and the model parameter $\theta_{\text{div}}$ controls the shape of this sigmoid.

(2) **migration.** Cancer cells migrate with probability $P_{\text{mov}}$. A selected cell inside the tumor, at a site $\vec{x}_i$, will move to a nearest neighbor site $\vec{x}$ chosen at random. Thus, $\sigma_c(\vec{x'}) \to \sigma_c(\vec{x'}) + 1$ and, clearly, $\sigma_c(\vec{x}) \to \sigma_c(\vec{x}) - 1$. Otherwise, if the selected cell is on the tumor border, the invasion of a normal or necrotic nearest neighbor site will be dependent on the number of cancer cells present in the selected site. If in this site there is a single cancer cell, it migrates by interchanging its position with that of the invaded one. If there are other cancer cells in the same site of the one selected to move, the migrating cell will occupy the position of the normal or necrotic nearest neighbor cell, which, in turn, disappears. In terms of cell populations the migration of a cell on the tumor border corresponds to the following operations: $\sigma_c(\vec{x'}) = 1$, $\sigma_c(\vec{x}) \to \sigma_c(\vec{x}) - 1$, $\sigma_{n,d}(\vec{x'}) = 0$ and $\sigma_{n,d}(\vec{x}) = 1$ if $\sigma_c(\vec{x}) = 1$. The probability of cell migration $P_{\text{mov}}$ has the same functional form of $P_{\text{div}}$, but depends on the concentration of the non-essential nutrients $M$ present on the microenvironment of the selected cell and increases with the local population of cancer cells. So,

$$P_{\text{mov}}(\vec{x}) = 1 - \exp \left[ -\sigma_c \left( \frac{M}{\theta_{\text{mov}}} \right)^2 \right].$$  

(7)

with the model parameter $\theta_{\text{mov}}$ controlling the shape of this sigmoid.

(3) **cell death.** Cancer cells die transforming in a necrotic cell with probability $P_{\text{del}}$. Thus, $\sigma_c(\vec{x}) \to \sigma_c(\vec{x}) - 1$ and $\sigma_{d}(\vec{x}) = 1$ when $\sigma_c$ vanishes. The cell death probability $P_{\text{del}}$ is determined by the concentration per cancer cells of the non-essential nutrients $M$ present on the microenvironment of the selected cell:

$$P_{\text{del}}(\vec{x}) = \exp \left[ -\left( \frac{M}{\sigma_c \theta_{\text{del}}} \right)^2 \right],$$  

(8)

a Gaussian distribution whose variance depends on the model parameter $\theta_{\text{del}}$.

The cell dynamics rules used in our model take into account that, as the cancer growth progress, cell migration increases near the border of the tumor due to the high availability of nutrients and the increase in the number of cancer cells, which release a series of enzymes (collagenases, metalloproteinases, etc.) responsible by the progressive destruction of the extracellular matrix. Also, in the regions where there is a high population density and an ineffective supply of nutrients via diffusion processes, the cell division is inhibited and, at the same time, the probability of cell death increases. But, under these rules cell growth and migration is possible even inside the tumor. Finally, the model parameters $\theta_{\text{div}}, \theta_{\text{mov}}$ and $\theta_{\text{del}}$, which characterize the cancer cells response to nutrient concentrations and embody complex genetic and metabolic processes, should be interpreted in terms of the underlying biochemistry and molecular biology, an still open problem. The other three model parameters $\alpha, \lambda_N$ and $\lambda_M$, associated to the consumption of essential and non-essential nutrients for cell proliferation by the normal and cancer cells, should be more easily determined from biological experiments.

It is worthwhile to notice that from the point of view of the so-called kinetic cellular theory, which provides a general framework for the statistical description of the population dynamics of interacting cells [12], the local probabilities $P_{\text{div}}, P_{\text{mov}}$ and $P_{\text{del}}$ can be thought as an effective kinetic cellular model.

D. Computer implementation

The growth model simulations were implemented using the following procedure. At each time step, the diffusion Eqs. (4) and (5) are numerically solved in the stationary state through relaxation methods, providing the nutrient concentration at any lattice site. Then, $N_C(t)$ cancer cells are sequentially selected at random with equal probability. For each one of them, a tentative action (division, death or movement) is chosen at random with equal probability and the time is incremented by $\Delta t = 1/N_C(t)$. The selected cell action will be implemented or not according to the correspondent local probabilities determined by Eqs. (6), (7) or (8). If the selected cell divides or die, therefore changing the number of cancer cells which consume nutrients, we solve the diffusion equations in a small neighborhood of linear size.
patterns than compact ones, suggesting that the optimal growth morphology under strong nutrient limitation is fractal. Finally, the higher cell migration is, more homogeneous are the patterns, faster is the tumor growth, and smaller is the fraction of necrotic cells.

The tumor patterns generated by the present model were characterized by its gyration radius $R_g$, total number of cancer cells $N_C$, and number of cells on tumor periphery $S$ (including the surface of holes, if any). The gyration radius $R_g$ is defined as

$$
R_g = \left( \frac{1}{n} \sum_{i=1}^{n} r_i^2 \right)^{2}
$$

where $n$ is the number of sites occupied by the pattern (cancer or necrotic cells) and $r_i$ is the distance of the occupied site $i$ from the tumor mass center. These quantities could be related to clinically important criteria such as progress curves, rate of growth (volumetric doubling time) at given radii, proliferative and necrotic fractions of the tumor. In medicine, these data are used to determine tumor’s malignancy and its prognosis. The obtained results are summarized in Table 1.

Despite of the detailed microscopic mechanisms of growth, for all the simulated patterns the progress in time of cancer cell populations follows a Gompertz curve

$$
N_C(t) = A \exp\left[-\exp(-k(t-t_c))\right]
$$

as one can see in Figure 3. Moreover, the tumor gyration radius $R_g$ as well as the number of peripheral cells $S$ also exhibit a Gompertz growth, contrary to the linear regimes observed for $R_g$ and even $S$ in our previous non-nutrient-limited model [16]. So, the present model reveals that the Gompertz law of growth for the cancer cell populations and tumor size is a robust emergent feature of cancer dynamics under nutrient competition. It is important to notice that linear or power law fittings for the growth in time of $R_g$ and $S$ can also be very satisfactory for several simulated patterns, therefore explaining our previous findings [16] and the recent experimental observations of brain tumors grown in vitro [21]. However, only the Gompertz law can provide good fittings for all the three quantities $N_C$, $R_g$ and $S$.

On the other hand, as a function of the total number of cancer cells both $R_g$ and $S$ obey power law scaling given by $R_g \sim N_C^{g}$ and $S \sim N_C^{g}$, respectively. For solid patterns these exponents are $\nu \sim 0.5$ and $\sigma \sim 0.5$, corresponding to effective circular and non fractal patterns. As the nutrient consumption increases the patterns tend to papillary-like shapes for which the exponent $\sigma$ increases towards the value 1 and the exponent $\nu$ varies in the range $[0.50, 0.60]$, indicating a fractal morphology for the tumor. It is important to mention that increasing cell motility contributes to round and homogenize these patterns, progressively destroying their fractal features.

III. SIMULATIONAL RESULTS

In Figure 1 the most commonly observed morphologies in tumor growth such as papillary, compact and disconnected are shown. Disconnected patterns, typical of round cells neoplasies such as lymphoma, mastocytoma, and plasmacytoma, correspond to transient simulated patterns in which cancer cells have high motility but a low mitotic rate. In turn, if the cell migration is very small and the high mitotic rate demands large amounts of essential nutrients, then the simulated patterns exhibit finger-like shapes similar to the papillary morphologies found in epithelial tumors, such as basal and skin cells carcinomas, and hepatomas. If nutrient availability in the tissue is further reduced by an increasing cell consumption, the papillary-like patterns become progressively thin and similar to the chords or filaments of cells which constitute one of the hallmarks of the cholangioblastoma morphology. Finally, under high nutrient supply, which means low cell consumption of both nutrient types, the simulated patterns are compact such as those observed for solid tumors.

Typical patterns generated by the present model are shown in Figure 2. As one can see, nonspherical morphologies growing towards the capillary vessel are observed, according to the rigorous results for moving boundary problems of cancer growth [22]. The nutrient consumption by normal and cancer cells, controlled by the model parameters $\alpha$, $\lambda_N$ and $\lambda_M$, plays a central role in morphology determination. For small values of these parameters, corresponding to growth conditions in which individual cells demand small nutrients supplies, the patterns tend to be compact and circular. However, if the mitotic rate of cancer cells is small due to the large amount of nutrients demanded for cell division, generating a significant nutrient competition, these compact patterns progressively assume papillary-like morphologies. At high nutrient consumption rates these papillary patterns become the rule and, for low cancer cell division, continuously transform in thin tips, filaments or chords of cells. Also, the smaller the $\alpha$ and $\lambda_N$ values are, the larger is the fraction of necrotic cancer cells for a fixed cellular response leading to cell death (controlled by $\theta_{det}$). In particular, this fraction is smaller for papillary

order to take into account these local perturbations and to speed up the computer algorithm, since the number of numerical iterations need to solve the diffusion equation is proportional to $L^2$. At the end of this sequence of $N_C(t)$ tentative, a new time step begins and the entire procedure (solution of the diffusion equations and application of the cell dynamics) is iterated. The simulations stop if any tumor cell reaches the capillary vessel. In all the simulations, the exact solutions for the stationary diffusion equations in the absence of tumor cells were used for the nutrient concentration fields at $t = 0$. 

$l = 20$ centered in the altered site. This is done in order to take into account these local perturbations and to speed up the computer algorithm, since the number of numerical iterations need to solve the diffusion equation is proportional to $L^2$. At the end of this sequence of $N_C(t)$ tentative, a new time step begins and the entire procedure (solution of the diffusion equations and application of the cell dynamics) is iterated. The simulations stop if any tumor cell reaches the capillary vessel. In all the simulations, the exact solutions for the stationary diffusion equations in the absence of tumor cells were used for the nutrient concentration fields at $t = 0$. 

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Also, the tumor growth is faster for higher cancer cell migration.

An interesting result, shown in Figure 4, is the existence of a necrotic core in the center of the simulated tumors for high nutrient consumption or cell division rates. As observed in real tumors and in vitro multicell spheroids [12], a simulated pattern consists of three distinct regions: a central necrotic core, an inner rim of quiescent cancer cells and a narrow outer shell of proliferating cells. These different regions are evident in Figure 5 where the cancer cell density and average cell division rate are plotted for a longitudinal cut across the growth pattern. As one can see, both the cancer cell density and mitotic rates have neat sharp maxima at the tumor borders in front and opposed to the capillary vessel. Notice that the peaks for division rates are significantly more narrow than those for cancer cells density, demonstrating that the proliferative fraction of the tumor comprises just a small part of the cancer cells localized at the tumor border.

However, in the present nutrient-limited model the disconnected patterns common in cancers of round cells (Fig. 1e) correspond to transient behaviors of the model for low mitotic rates and high cell migration of cancer cells. Also, the ramified morphology of a trichoblastoma seem in Fig. 6d could not be qualitatively reproduced by the model. A worthwhile feature of this pattern is the presence of “leaves”, the growth of each one clearly influencing the others. The simple introduction of cell motility sensitive to the nutrients gradients failed to generate stationary disconnected or ramified patterns. Therefore, in addition to the nutrient field, it appears that a chemotactic interaction among cancer cells guiding their migration must be in action. The nature of this biological interaction and the results of its simulation will be focused in the next section.

IV. GROWTH FACTORS

From the biological point of view the chemotactic response to growth factors released by cancer cells seems to be, in addition to nutrient supply, another central feature in cancer development. The reciprocal influence among cancer cells mediated by autocrine and paracrine growth factors, motility factors, etc., influence the microenvironment of each cancer cell and hence its division and migration. Thus, both diffusive fields (nutrients and growth factors) determine the local probabilities for cancer cells divide, migrate and die.

A. The model

In order to investigate the role of growth factors in a nutrient-limited growth, we simplify our model by considering a single nutrient field described by the diffusion equation:

\[ \frac{\partial N}{\partial t} = D_N \nabla^2 N - \gamma N \sigma_n - \lambda \gamma N \sigma_c, \]

in which \( \gamma \) and \( \lambda \gamma \) are the nutrients consumption rates of normal and cancer cells, respectively. The boundary conditions are the same described in Section 2. In turn, the growth factors (GFs) concentration obeys the diffusion equation:

\[ \frac{\partial G}{\partial t} = D_G \nabla^2 G - k^2 G + \Gamma \sigma_c N (G_M - G), \]

which includes the natural degradation of GFs, also imposing a characteristic length \( \sim 1/k \) for GFs diffusion, and a production term increasing linearly with the local nutrient concentration up to a saturation value \( G_M \). Therefore, we are assuming that the release of GFs involves complex metabolic processes supported by nutrient consumption. The boundary conditions satisfied by the GFs concentration field is \( G(\bar{x}, t) = 0 \) at a large distance \( (d > 2/k) \) of the tumour border.

Again, the number of parameters in equations (9) and (10) can be reduced by using the new dimensionless variables

\[ t' = \frac{D_N t}{\Delta^2}, \quad \bar{x}' = \frac{\bar{x}}{\Delta}, \quad \alpha' = \frac{\alpha}{\Delta^2}, \quad g' = \frac{G}{G_M}, \]

\[ \alpha = \sqrt{\frac{\gamma \Delta^2}{D_N}}, \quad k' = k \sqrt{\frac{\Delta^2}{D_N}}, \quad \Gamma' = \frac{\Gamma \Delta^2}{D_N}, \quad D = \frac{D_N}{D_G}, \]

Using these new variables in Eqs. (9) and (10) and omitting the primes we obtain

\[ \frac{\partial N}{\partial t} = \nabla^2 N - \alpha^2 N \sigma_n - \lambda \alpha^2 N \sigma_c \]

and

\[ \frac{\partial G}{\partial t} = D \nabla^2 G - k^2 G + \Gamma \sigma_c N (1 - G) \]

for the diffusion equations. The boundary condition for the nutrients on the capillary vessel becomes \( N(x = 0) = 1 \) and a value \( \Delta = 1 \) is defined. In addition, at the stationary state the parameter \( D \) in Eq. (13) can be put equal to the unity by rescaling the parameters \( k \) and \( \Gamma \). So, the diffusion equations for the nutrients and GFs involve four parameters.

On the other hand, the cell dynamics has essentially the same rules used in Section 2, but with different cell action probabilities. The single change introduced is that after cell division the daughter cell stands at the same site occupied by its mother. Since nutrients are essential to the large protein and DNA synthesis necessary to cell mitosis and GFs act as mitotic inducers, the proposed form to \( P_{\text{div}} \) is:
The parameter $N^*$ determines the nutrient-poor level below which the cancer cells reproduction is inhibited. Cell migration involves large citoskeleton reorganizations which consume energy and is facilitated by GFs which destroy the extracellular matrix and the adhesivity structures between normal cells. Thus, $P_{\text{mov}}$ is written as:

$$P_{\text{mov}}(\vec{x}, \vec{x'}) = 1 - \exp \left( - \frac{N}{\sigma_c} \frac{G^2(\vec{x} - \vec{x'})}{\theta_{\text{mov}}} \right),$$  \hspace{1cm} (17)

implying that a cell migrates in a gradient-sensitive way towards sites where the GFs concentration is lower than that in its starting point.

Finally, cell death is produced by the lack of nutrients:

$$P_{\text{del}}(\vec{x}) = \exp \left[ - \left( \frac{N}{\sigma_c \theta_{\text{del}}} \right)^2 \right].$$  \hspace{1cm} (18)

B. Results

In Figure 6 typical compact, ramified and disconnected simulated patterns are shown. The ramified structure shown in Fig. 6b should be compared with the pattern of a trichoblastoma exhibited in Fig. 6d. In contrast to the compact fingers of the papillary patterns of the previous section, in these ramified morphologies the tumor has fjords and tips similar to those observed in DLA patterns. We emphasize that without chemotactic signaling among cancer cells the nutrient-limited model can not generate stationary disconnected patterns. The reason is that in average GFs driven cell migration outwards, promoting the tumor expansion and, in consequence, generating disconnected patterns for high cell motility. Again, the patterns were characterized by its gyration radius $R_g$, total number of cancer cells $N_C$, and number of cells on tumor periphery $S$. Essentially the same results were obtained for cancer progress in time, scaling relations and spatial structures exhibiting a central necrotic core, an inner rim of quiescent cells and a narrow outer shell of proliferating cells.

V. CONCLUSIONS

A nutrient-limited model for the growth of avascular tumors was investigated by numerical simulations. In its original version, cell proliferation, motility and death were locally regulated by the concentration of nutrients supplied by a distant capillary vessel. These nutrients were divided into two groups, the first one associated to the usual metabolic cell needs, and the second essential to the synthesis of proteins and nucleic acids involved in cell division. The nutrients concentration fields were determined by solving the diffusion equation on the square lattice modeling the primary tissue. Our simulation results show that the progress in time of the total number of cancer cells, tumor gyration radius and number of cells on the tumor border is described by Gompertz curves. The generated compact and papillary or finger-like morphologies obey different scaling laws for the number of peripheral cancer cells. For compact patterns $S \sim N_C^{1/2}$ as in the Eden model, whereas for papillary patterns the exponent in the power-law increases towards unity as the nutrient consumption increases, indicating a fractal morphology for the tumor. Since in this model version the cell migration is not driven by chemotactic signals secreted by the cancer cells, cell motility contributes to round and homogenize the growth patterns. Also, the simulated tumors incorporate a spatial structure composed of a central necrotic core, an inner rim of quiescent cells and a narrow outer shell of proliferating cells in agreement with biological data.

In order to simulate disconnected and ramified tumor patterns, typical of round cells tumors and trichoblastoma, a chemotactic interaction among cancer cells mediated by growth factors was added to the competition for nutrients. Again, similar results were obtained for cancer progress in time and scaling relations. Thus, the Gompertz law emerges as a robust feature of the nutrient-limited model of cancer growth.

Despite the encouraging results for the progress curves, scaling laws and growth patterns morphology, including nonspherical symmetries, the major feature of the present work is an attempt in connecting the macroscopic diffusion equations for nutrients and/or growth factors to cell response and interactions at the microscopic scale through an effective kinetic cellular model. Indeed, the local probabilities $P_{\text{div}}, P_{\text{mov}}$ and $P_{\text{del}}$ describe in a stochastic way the dynamical processes occurring in cell populations as a response to the nutrient and growth factors diffusive fields. Finally, further studies on angiogenesis, therapy and tumor-host interactions using variants of the present model are under progress.

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D. Hanahan and R. A. Weinberg, Cell 100, 57 (2000).
W. H. Clark, J. Cancer 64, 631 (1991).
G. I. Evan and K. H. Vousden, Nature 411, 342 (2001).
L. Israel, J. Theor. Biol. 178, 375 (1996).
L. A. Liotta and E. C. Kohn, Nature 411, 375 (2001).
I. Golding, Y. Kozlovsky, I. Cohen, and E. Ben-Jacob, Physica A 260, 510 (1998).
Y. Kozlovsky, I. Cohen, I. Golding, and E. Ben-Jacob, Phys. Rev. E 59, 7025 (1999).
S. S. Cross, J. Pathol. 182, 1 (1997).
T. Sato, M. Matsuoka, and H. Takayasu, Fractals 4, 463 (1996).
R. L. Mendes, A. A. Santos, M. L. Martins, and M. J. Vilela, Physica A 298, 471 (2001).
G. J. Pettet, C. P. Please, M. J. Tindall, and D. L. S. McElwain, Bull. Math. Biol. 63, 231 (2001).
N. Bellomo and L. Preziosi, Mathl. Comp. Modelling 32, 413 (2000).
H. A. Levine, S. Pamuk, B. D. Sleeman, and M. Nilsen-Hamilton, Bull. Math. Biol. 63, 801 (2001).
E. De Angelis and L. Preziosi, Math. Models Meth. in Appl. Sci. 10, 379 (2000).
S. C. Ferreira Junior, M. L. Martins, and M. J. Vilela, Physica A 261, 569 (1998).
S. C. Ferreira Junior, M. L. Martins, and M. J. Vilela, Physica A 272, 245 (1999).
P. C. Nowell, Science 194, 23 (1976).
M. Scalerandi, A. Romano, G. P. Pescarmona, P. P. Delsanto, and C. A. Condat, Phys. Rev. E 59, 2206 (1999).
M. Scalerandi, G. P. Pescarmona, P. P. Delsanto, and B. Capogrosso Sansone, Phys. Rev. E 63, 011901 (2000).
A. Friedman and F. Reitich, Math. Models Meth. in Appl. Sci. 11, 601 (2001).
A. Brú, J. M. Pastor, I. Fernaud, I. Brú, S. Melle, and C. Berenguer, Phys. Rev. Lett. 81, 4008 (1998).
TABLE I: Morphology, progress curves and scaling laws for the patterns generated by the nutrient-limited model

| Morphology   | Characteristic features                                      | Growth in time | Exponents |   |
|--------------|-------------------------------------------------------------|----------------|-----------|---|
| Compact      | low nutrient consumption; low cell motility                 | Gompertz       | Gompertz  | Gompertz | 0.50 | 0.50 |
| Papillary    | high nutrient consumption; low cell motility                | Gompertz       | Gompertz  | Gompertz | 0.50-0.60 | 0.60-1 |
| Disconnected | low mitotic rate; high cell motility; transient behavior    | Gompertz       | Gompertz  | Gompertz | 0.50 | 1    |
FIG. 1: Common morphologies observed in cancer growth. (a) Papillary pattern of a squamous papyloma, (c) a compact solid basocellular carcinoma, (e) a disconnected pattern of a plasmacytoma, and (g) characteristic cell filaments of a trichoblastoma. All these histological patterns were obtained from dogs. The corresponding simulated patterns are shown in (b), (d), (f) and (h), respectively.
FIG. 2: Simulational results of the nutrient-limited cancer growth model. The patterns are organized as function of nutrient consumption rate $\alpha$ for normal cells and the multiplicative factor $\lambda_N$ to the consumption rate of mitotic essential nutrients by the cancer cells. The remaining four parameters of the model were fixed in $\lambda_M = 10$, $\theta_{\text{div}} = 0.3$, $\theta_{\text{mov}} = \infty$ (absence of cell migration) and $\theta_{\text{del}} = 0.01$. The patterns are drawn in a gray scale where the darker regions represent higher cancer cell populations. The tissue size is $500 \times 500$, with the initial “cancer seed” distant 300 sites from the capillary. The total number of cancer cells depends on tumor morphology and attains up to $2 \times 10^5$ for compact patterns. The simulated patterns are compact for low $\lambda_N$ values and become papillary or finger-like for high $\lambda_N$. For the same $\lambda_N$ the patterns are more papillary for higher $\alpha$. Since the capillary vessel provides a fixed nutrients supply, the dimensionless consumption rate of the normal tissue $\alpha$ set up the levels of available resources for which cancer cells compete. So, high $\alpha$ and/or $\lambda_N$ values correspond to the limit of strong nutrient competition.
FIG. 3: Gompertz growth of cancer cell population. The model parameters were fixed in $\alpha = 2/L$, $\lambda_M = 10$, $\lambda_N = 200$, $\theta_{\text{div}} = 0.3$, $\theta_{\text{mov}} = 2$ and $\theta_{\text{del}} = 0.03$. The solid line correspond to a nonlinear fitting with $r^2 = 0.9995$.

FIG. 4: Simulated growth patterns exhibiting a necrotic core (in black). The model parameters are $\alpha = 2/L$, $\lambda_M = 25$, $\theta_{\text{div}} = 0.3$, $\theta_{\text{mov}} = \infty$ (without cell migration) and $\theta_{\text{del}} = 0.03$. The fraction of necrotic cells is smaller for papillary patterns than compact ones, suggesting that the optimal growth morphology under strong nutrients limitation is fractal.
FIG. 5: (a) Density of cancer cells $\sigma_c$ and (b) division rates $w_{\text{div}}$ as a function of the distance from the capillary vessel along a tumor longitudinal cut. The model parameters were fixed in $\alpha = 2/L$, $\lambda_M = 25$, $\lambda_N = 50$, $\theta_{\text{div}} = 0.3$, $\theta_{\text{mov}} = \infty$ (without cell migration) and $\theta_{\text{del}} = 0.03$. Sharp maxima at the tumor borders near and opposed to the capillary vessel at $x = 0$ are evident. Therefore, the proliferative fraction of cancer cells is distributed in a thin shell on the tumor border.

FIG. 6: Simulated patterns of the nutrient-limited cancer growth model including the influence among cancer cells mediated by growth factors. (a) compact ($k = 0.1$ and $\theta_{\text{mov}} = 1$), (b) disconnected ($k = 0.025$ and $\theta_{\text{mov}} = 0.1$), and (c) ramified ($k = 0.025$ and $\theta_{\text{mov}} = 1$) morphologies. The remaining parameters of the model were fixed in $\alpha = 3/L$, $\theta_{\text{div}} = 0.5$, $N^* = \theta_{\text{del}} = 0.01$, $\lambda = 5$ and $\Gamma = 10$. The tissue size is 500 $\times$ 500, with the initial “cancer seed” distant 300 sites from the capillary and the total number of cancer cells is $5 \times 10^4$. For comparison, a real ramified pattern observed in trichoblastoma is shown in (d).