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How the growth rate of host cells affects cancer risk in a deterministic way

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It is well known that cancers are significantly more often encountered in some tissues than in other ones. In this paper, by using a deterministic model describing the interactions between host, effector immune and tumor cells at the tissue level, we show that this can be explained by the dependency of tumor growth on parameter values characterizing the type as well as the state of the tissue considered due to the "way of life" (environmental factors, food consumption, drinking or smoking habits, etc.). Our approach is purely deterministic and, consequently, the strong correlation ($r = 0.99$) between the number of detectable growing tumors and the growth rate of cells from the nesting tissue can be explained without evoking random mutation arising during DNA replications in nonmalignant cells or "bad luck". Strategies to limit the mortality induced by cancer could therefore be well based on improving the way of life, that is, by better preserving the tissue where mutant cells randomly arise. *Published by AIP Publishing.* [http://dx.doi.org/10.1063/1.5000713]

Cancer is clearly a disease triggered by initial mutations arising randomly during cell divisions, but these initial mutated cells become a tumor (a colony) only when the environment (the body to the largest extent) is no longer able to provide sufficiently strong barriers against that proliferation. If there is no doubt that the faster organ's stem cells replicate, the larger the risk of cancer in that organ, it is not yet clear whether these cancers are only due to random mutations in a fully genetically oriented approach (therefore to "bad luck") or if they result from deterministic processes whose mechanisms involve the way of life (food consumption, drinking, smoking, lack of exercise…) and external factors such as air pollutants, for instance. Using a cancer model taking into account the interactions between the tumor cells and the healthy cells of the tumor micro-environment, we investigate whether cancer randomness is only apparent or could be explained by the causality with the quality of the surrounding tissue, a quality which would strongly depend on the way of life.

I. INTRODUCTION

Cancer incidence depends strongly on the tissue considered. For instance, the probability to have lung cancer is nearly the same as to have prostate cancer, twice the probability to have colorectal cancer, four times that of thyroid cancer and ten times to have brain cancer.[1] It was recently asserted that these variations in cancer risk were mostly due to "bad luck," a rather inappropriate way to designate what could explain the occurrence of cancer due to random mutations arising during DNA replication in non-malignant (host) cells.[2,3] This assertion was based on the correlation between the lifetime risk for various cancers and the total stem cell divisions as assessed in the literature. The underlying assumption was that any mutation of a normal cell into a malignant cell during one of the cell divisions has an equal probability to become a growing tumor detected regardless of its microenvironment. This is not justified since it is known that the microenvironment plays a major role in malignant cell proliferation[4] and that only a small fraction of tumor cells initiates a detectable tumor.[5,6] This is mainly due to the fact that tumors result from complex ecologies between numerous cell types[7] and that the microenvironment could revert the malignant phenotype to a non-proliferating one.[8,9]

A first objection to Tomasetti and Vogelstein's approach, according to which, implicitly, the micro-environment does not play any major role, is that assuming that every cell has an equal chance in inducing mutant malignant cells during its division, not only large but also long-lived organisms should present an increased risk for developing a cancer compared to small organisms. Whales are obvious counter examples and, for instance, bowhead whales have 1000 times more cells than humans but do not exhibit a larger lifetime cancer rate,[10,11] thus suggesting that they own natural mechanisms suppressing tumor cells with efficiency more than 1000 times greater than the ones presented by humans. There is therefore no evidence for a correlation between the body size and the lifespan cancer rate.[12] For instance, cancers have been very rarely recorded in blue whales[13] and, in general, whales have a very low lifespan cancer rate.[10] In fact, Keane *et al.* showed that bowhead whales acquired an anti-oncogenic phenotype that was "selected" during millions of years, and which is not found in humans: the long lifespan expectancy of these bowhead whales is also due to a particular immune system.[14] Moreover, Tomasetti and Vogelstein assumed that stochastic errors in DNA replications were the main components for explaining the variations in cancer risk among tissues, but it was recently shown that it resulted from a "logical fallacy" based on ignoring the influence of population heterogeneity in correlations exhibited at the level of the whole population.[15]

Our objective was therefore to take into account the population heterogeneity in a deterministic model describing the interactions between different types of cells involved

in tumor growth. The dynamics governing the interactions between various types of cells is indeed of primordial relevance for tumor growth because it is known that this dynamics is poorly affected by the personal and/or family history, since only less than 10% of cancers could be attributed to hereditary facts.[16] For instance, if some types of cancers (prostate, colorectal, breast,…) can be associated with inheritable factors, there are others (pancreas, stomach, lung, uterus, ovary, bladder,…) for which this is significantly less relevant.[17]

Heredity, for which "chance" or "bad luck" may be evoked because today there is no way to act on it (in a preventive way), is thus only one of the components in tumorigenesis. Indeed, the probability for presenting a mutant cell is not *sensu stricto* the most important component for triggering a detected growing tumor. It is more important that this malignant cell occurs in a nesting tissue where it is able to induce a colony proliferating without too strong barriers.[4] Consequently, the probability to have a given cancer would be more directly related to the strength of the barriers developed by the nesting tissue whose dynamics depends to a limited extent on the inherited genetic background but more strongly on external factors affecting the quality of the micro-environment. In such a case, risk factors for cancers would strongly depend on physical activity, obesity, high consumption of red and/or processed meat, smoking, and moderate to heavy alcohol consumption, that is, the way of life.[18]

All the tissues are not sensitive to the same external factors and the same ways. This could also explain that some cancers are known to be more strongly dependent on external factors of risk than others. For instance, the traditional risk factors associated with oral cancers are alcohol and tobacco,[19,20] although human papillomavirus emerges as an additional risk factor.[21] Although the most important risk factor for gastric cancers is *Helicobacter pylori* infection and host genetic factors,[22] and they are also related to a complex interplay between genetics and the way of life (diet, smoking, etc.) as well as environmental factors (bacterial infections, air pollution, drinking water contamination, etc.).[23–25] One of the most relevant risk factors for breast cancer is mammographic density,[26–28] that is, the state of the host tissue; there is also a known correlation to a family history of breast cancer,[29–31] oral contraceptive usage or hormone replacement therapy,[32–34] However, environmental factors cannot explain the differences observed in organ-specific cancer risk,[2] these differences being far more important than the influence of these factors. Since it is now admitted that the microenvironment is "an integral, essential part of the cancer,"[35] it is therefore necessary to take it into account.

External factors must have a contribution to lifetime risks since most of them could be reduced by changing the lifestyle, behavioural and/or environmental risk factors.[36] The proportion of cancer deaths could be therefore reduced to a theoretical minimum.[37] In that case, it would be useful to take into account the presence or absence of risk factors to determine the cohort of individuals that should be screened for cancer.[38] It is therefore relevant to check whether cancer risks depend on the regeneration rate of the tissue—or in other words, the growth rate of host (normal) cells—in a way that (i) could explain the variations in cancer risk among tissues and (ii) could evidence how external factors can play a significant role in cancer risk.

In order to do that, we used a model for describing the interactions between the populations of host, effector immune and tumor cells at the tissue level.[39] Since this model describes the dynamics in a single site, we used many copies of it that we coupled on a lattice for simulating the spatial growth of tumors.[40] Among the parameter values characterizing the interactions between the populations of cells, that is, the type of tissues considered, we selected those which are the most influent on the dynamics. We used the growth rate of normal cells as the parameter determining the organ tissue. For each type of tissue (organ), we varied some parameter values to take into account how a given type of tissue can be affected by external factors, thus allowing us to construct a cohort of simulated patients with different qualities of the tissue. It is thus possible to compute a probability for an expanding tumor versus the growth rate of host cells.

The subsequent part of this paper is organized as follows. Section II introduces the model describing interactions between different populations of cells. Section III discusses different types of dynamics which can be observed within a single site and explains how the different parameters may influence the dynamics. Section IV describes how copies of our model for one site were coupled on a lattice by a diffusion term of tumor cells. It also shows how the probability of developing a spatially expanding tumor depends on the growth rate of host cells. Section V provides a discussion.

II. THE MODEL

Among the very rare models taking into account the environment in the interactions between different populations of cells at a tumor site, the model proposed by de Pillis and Radunskaya[39] is particularly interesting because it is able to reproduce some relevant clinical features.[41] This model describes the interactions between host (normal), effector immune (natural killer) and tumor cells in a single tumor site. The host cells correspond to healthy cells which are structuring the considered organ. The effector immune cells are cytotoxic lymphocytes that can kill the tumor cells. The system is adimensionalized in such a way that all populations are within the unit interval (a population equal to 1 thus saturates the site at its carrying capacity). Without any interaction between them, the populations x of host cells and z of tumor cells are governed by logistic functions depending on the growth rates ρ_h and ρ_t, respectively. Host and tumor cells are in competition for space, oxygen and nutrients, as evidenced by the negative coupling term $-\alpha_{ht}xz$, where α_{ht} is the death rate of host cells due to tumor cells reducing the population x and the negative coupling term $-\alpha_{th}zx$, where α_{th} is the death rate of tumor cells due to host cells reducing the population z. Similar terms are used between the population y of effector immune cells and the population z of tumor cells. From that point of view, these last two populations are also in competition. Nevertheless, the growth rate of effector immune cells is governed by a type-II Holling term $\frac{\rho_i yz}{1+z}$; the

proliferation of effector immune cells is therefore induced by the presence of tumor cells. Few lymphocytes T4 and T8 are recruited in lymph nodes by dendritic cells which are in contact with the tumor. Some of those immature lymphocytes migrate toward the tumor site where they are activated. Then, these lymphocytes proliferate, stimulated by lymphocytes T4 and the contact with tumor cells. Consequently, the most important process quantified by parameter ρ_i is the growth rate of immune cells and not the recruitment rate of few of them in lymphatic nodes.

Depending on the parameter values ρ_i and α_it, the coupling term between effector immune and tumor cells can be positive: in that case, according to Hodge and Arthur,[42] the interactions between two populations with one positive term ($\rho_\mathrm{i} \frac{yz}{1+z} - \alpha_\mathrm{it}\, yz$ with appropriate parameter values) and one negative term ($-\alpha_\mathrm{ti}\, zy$) correspond to contramensalism (two populations having opposite effects on each other). Without tumor cells, the population y remains null. The natural death of effector immune cells is taken into account by the term $-\delta_\mathrm{i} y$. At the site S_{ij}, the three populations are thus governed by three differential equations

$$\begin{cases} \dot{x}_{ij} = \rho_\mathrm{h} x_{ij}(1 - x_{ij}) - \alpha_\mathrm{ht} x_{ij} z_{ij} \\ \dot{y}_{ij} = \dfrac{\rho_\mathrm{i} y_{ij} z_{ij}}{1 + z_{ij}} - \alpha_\mathrm{it} y_{ij} z_{ij} - \delta_\mathrm{i} y_{ij} \\ \dot{z}_{ij} = \rho_\mathrm{t} z_{ij}(1 - z_{ij}) - \alpha_\mathrm{th} x_{ij} z_{ij} - \alpha_\mathrm{ti} z_{ij} y_{ij} - \nabla \cdot (K \cdot \nabla z), \end{cases} \tag{1}$$

where $\nabla \cdot K(\cdot \nabla z)$ describes the diffusion of tumor cells from one site to another when the corresponding population exceeds a given threshold value. Our tumor sites are located in a plane (two-dimensional space). Each site is a square whose edges have $\eta = 100\,\mu$m in length. Our two-dimensional tissue is made of a lattice of 10×10 sites. The tissue is thus a square of 1 mm^2. Each site has eight neighboring sites whose location is designated according to N, S, W, E, NE, NW, SE, and SW, where N corresponds to North, S to South, W to West and E to East. For instance, the population of host cells within the site located at the North-East of site S_{ij} will be designated by x_{ik}^{NE}, and so on.

The rate of diffusion is dependent on the parameter K. In this work, for each simulated case, all sites were characterized by the same parameter values: we therefore considered tumor growth in homogeneous tissues. The diffusion of tumor cells is governed by an isotropic Laplacian operator (as done in Refs. 43 and 44) which is discretized on a lattice according to

$$\nabla \cdot (K \nabla z) = \mathcal{H}(z_{ij} - 0.99)\, K \sum_k \left(\frac{z_{ij}^k - z_{ij}}{\beta_k\, \eta^2} \right), \tag{2}$$

where z_{ij}^k with $k = \{\mathrm{N}, \mathrm{S}, \mathrm{E}, \mathrm{W}, \mathrm{NE}, \mathrm{NW}, \mathrm{SE}, \mathrm{SW}\}$ designates the tumor cell density at the kth site around the site (i, j) and the coefficient $\beta_k = \{2, 2, 2, 2, 4, 4, 4, 4\}$. For instance, z_{ij}^{NE} corresponds to the tumor cell density at the site located at the North-East of the site (i, j), that is, at the site $(i + 1, j + 1)$. For all our simulations, we used $K = 10^{-10}$.

III. LOCAL DYNAMICS

The default parameter values (reported in the last column of Table I) correspond to the chaotic attractor shown in Fig. 1 (also investigated in Ref. 41). As shown in Ref. 40, this chaotic regime corresponds to a slowly growing tumor, characterized by a layer of proliferating tumor cells which is rather heterogeneous. Due to the impossibility to estimate all parameter values of such a model *in vivo* or *in vitro*, mostly because of and due to the large differences observed between animal, culture or human models,[45] there are no serious possibilities to accurately assess the parameter values for such a model. Since our objective is not to reproduce quantitatively the dynamics for a given patient but rather to browse qualitatively the different situations which can be observed, parameter values were chosen for browsing different dynamics provided by our model.

When the diffusion parameter K is equal to 0, model (1) has three singular points that are always with positive real coordinates, namely points

$$\mathrm{S}_0 = \begin{vmatrix} x_0 = 0 \\ y_0 = 0 \\ z_0 = 0 \end{vmatrix}, \quad \mathrm{S}_1 = \begin{vmatrix} x_1 = 1 \\ y_1 = 0 \\ z_1 = 0 \end{vmatrix} \quad \text{and} \quad \mathrm{S}_2 = \begin{vmatrix} x_2 = 0 \\ y_2 = 0 \\ z_2 = 1 \end{vmatrix}.$$

Point S_0 corresponds to a state where there is no living cell; typically, it is stable when the site corresponds to a necrotic layer. Point S_1 is saturated with host cells and is thus associated, when it is stable, with a healthy tissue with strong barriers against tumor progression. Point S_2 is saturated with tumor cells and, when it is stable, corresponds to a site in a layer of strongly proliferating tumor cells.

The other singular points are

$$\mathrm{S}_3 = \begin{vmatrix} x_3 = \dfrac{\rho_\mathrm{t}(\rho_\mathrm{h} - \alpha_\mathrm{ht})}{\rho_\mathrm{t}\rho_\mathrm{h} - \alpha_\mathrm{th}\alpha_\mathrm{ht}} \\ y_3 = 0 \\ z_3 = \dfrac{\rho_\mathrm{h}(\rho_\mathrm{t} - \alpha_\mathrm{th})}{\rho_\mathrm{t}\rho_\mathrm{h} - \alpha_\mathrm{th}\alpha_\mathrm{ht}} \end{vmatrix},$$

$$\mathrm{S}_{4,5} = \begin{vmatrix} x_{4,5} = 0 \\ y_{4,5} = \dfrac{\rho_\mathrm{t}}{\alpha_\mathrm{ti}}(1 - \chi_\pm) \\ z_{4,5} = \chi_\pm \end{vmatrix}$$

TABLE I. Parameters of model (1) used for describing the interactions between the populations of host (x), effector immune (y) and tumor (z) cells. The values (or the interval over which they are varied) used in our simulations are also reported. Default values correspond to the chaotic attractor shown in Fig. 1.

Symbol	Meaning	Range	Default
ρ_h	growth rate of host cells	[0; 1]	0.518
ρ_i	growth rate of effector immune cells	[0.1; 6]	4.5
ρ_t	growth rate of tumor cells	$2\rho_\mathrm{h}$	1.0
α_ht	death rate of host cells by tumor cells	[0.5; 2]	1.5
α_it	inhibition rate of effector immune cells by tumor cells	[0.1; 3.5]	0.2
α_th	death rate of tumor cells by host cells	[0.5; 2]	1.0
α_ti	death rate of tumor cells by effector immune cells	2.5	2.5
δ_i	natural death rate of effector immune cells	0.5	0.5

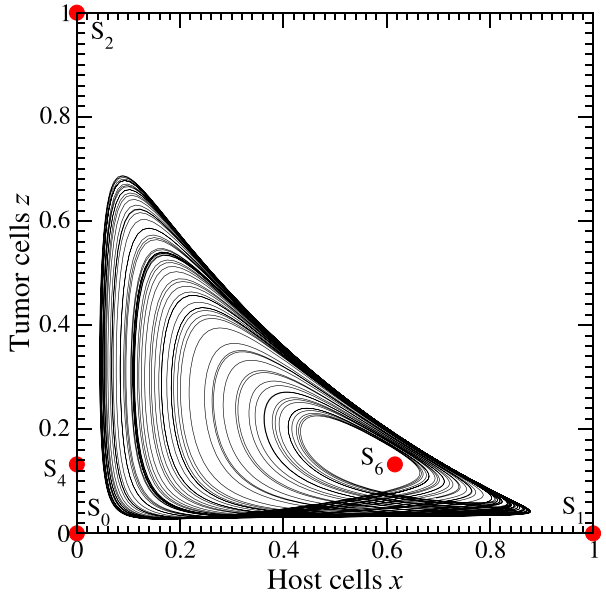

FIG. 1. Chaotic attractor produced by model (1) with the default parameter values as reported in Table I. The singular points with positive coordinates are also shown.

and

$$S_{6,7} = \begin{vmatrix} x_{6,7} = 1 - \dfrac{\alpha_{ht}}{\rho_h}\chi_{\pm} \\ y_{6,7} = \dfrac{\rho_t\,(1-\chi_{\pm}) - \alpha_{th}}{\alpha_{ti}} + \dfrac{\alpha_{th}\alpha_{ht}}{\rho_h\alpha_{ti}}\chi_{\pm} \\ z_{6,7} = \chi_{\pm}, \end{vmatrix}$$

where

$$\chi_{\pm} = \frac{\rho_i - \alpha_{it} - \delta_i \pm \sqrt{(\rho_i - \alpha_{it} - \delta_i)^2 + 4\alpha_{it}\delta_i}}{\alpha_{it}}.$$

Point S_3 corresponds to the coexistence of host and tumor cells without immune cells. When stable, it is associated with a deficient immune system. Points $S_{4,5}$ correspond to the coexistence of sole immune and tumor cells; they are associated with a layer of proliferating tumor cells, but the immune system is still active. Consequently, the tumor growth is slower when the proliferation layer is associated with point S_4 or S_5 than with point S_2. Note that point S_5 has quite rarely (in the parameter space) positive coordinates; moreover, it is most often a saddle. Points S_6 and S_7 correspond to the coexistence of three types of cells. Point S_7 rarely has all its coordinates positive. When stable, point S_6 typically corresponds to a site with a tumor in its early non-vascularized phase. As shown in Fig. 1, the chaotic attractor is structured around point S_6 characterized by a rather large population of host cells and a quite small population of tumor cells, thus explaining why slowly expanding tumors are associated with chaotic dynamics.[40]

In model (1), the growth rate ρ_h of host cells is directly related to the number of stem cell divisions, that is, the rate of regeneration of a tissue. It is known that different "organs have different rates of regeneration."[46] For instance, bone tissues present a long regeneration period and the liver has a high capacity for regeneration. The parameter ρ_h can be thus used for distinguishing organ tissues. To be in agreement with Tomasetti and Vogelstein's data,[2] the probability for detecting an expanding tumor must depend on this parameter of our model. The bifurcation diagram *versus* the growth rate of host cells ρ_h (Fig. 2) is computed by retrieving the minimal and maximal values of the population of tumor cells as defined in Ref. 41. We also plotted points corresponding to a stable singular point. The route to the chaotic attractor shown in Fig. 1 is a period-doubling cascade. Some periodic windows can also be identified as in any chaotic systems. For small values of the growth rate ($\rho_h < 0.38$), the trajectory converges to the singular point S_4 where the population of host cells is zero. For large values of ρ_h, the dynamics is more developed, that is, structured around a larger population of periodic orbits,[47] leading to a chaotic behavior: the tumor is then slowly expanding as discussed in Ref. 40.

To correctly assess the influence of parameter ρ_h on the dynamics of cancer model (1), it is necessary to use the singular points. For instance, let us compare the singular points for $\rho_h = 0.518$ (chaotic behavior) and $\rho_h = 2.0$ (stable singular point). In both cases, points S_0, S_1, S_2, and S_4 are a saddle with a two-dimensional unstable manifold (designated by SD_2), a saddle with a one-dimensional unstable manifold (designated by SD_1), SD_1 and a saddle-focus with a one-dimensional unstable manifold (designated by SF_1), respectively. Points S_3 and S_5 have at least one negative coordinate and do not contribute to the structure of the positive domain of the state space. The main difference between the two cases shown in Fig. 3 is related to point S_6, which is a SF_2 around which sustained oscillations take place for $\rho_h = 0.518$ and a SF_1 for

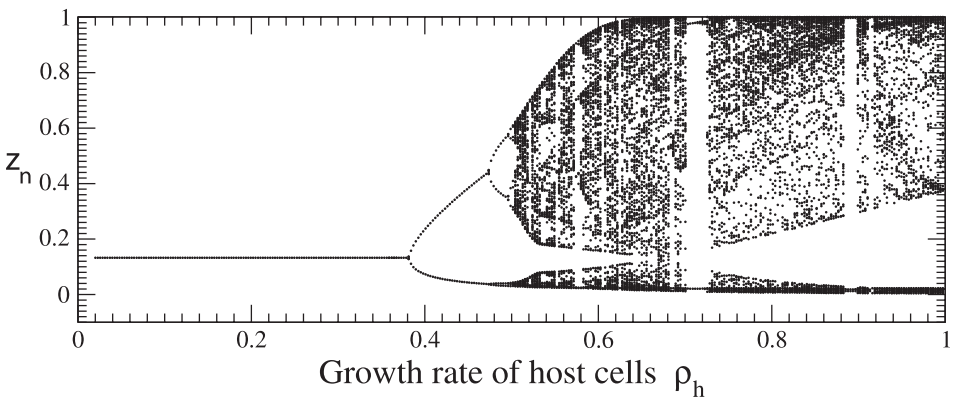

FIG. 2. Bifurcation diagram versus the growth rate of host cells ρ_h when other parameters have the default values reported in Table I.

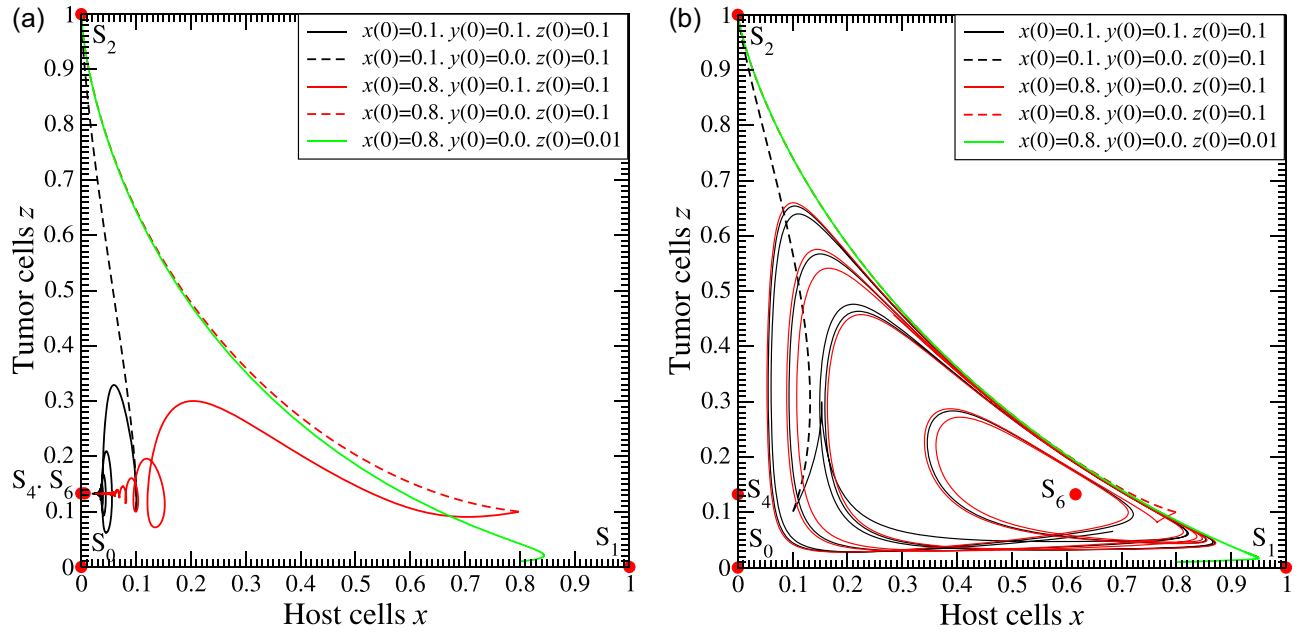

FIG. 3. Phase portrait produced by cancer model (1) under five different initial conditions for two different types of tissues. (a) Slowly regenerative tissue: $\rho_h = 0.2$ (b) Moderately regenerative tissue: $\rho_h = 0.518$.

$\rho_h = 0.2$ around which damped oscillations are observed. In both cases, as shown in Fig. 3, the point S_6 is the one which mainly organizes the trajectories when the immune system is active ($y \neq 0$).

For tissues with a low growth rate of host cells ρ_h, that is, tissues with a long regeneration period, the population of tumor cells remains at very low values ($z \approx 0.13$); the tumor starts to colonize the site only when there is a deficiency of the immune system (an episode during life at which $y(t) = 0$) and then to spatially expand. In the case of rather large values of the growth rate ρ_h, there are large amplitude oscillations, and the population of tumor cells can take quite a large value ($z \approx 0.7$) for short durations. This leads to slowly expanding tumors as explained in Ref. 40. As observed for tissues with slow regeneration, when the immune system presents a deficiency, there is a rapid saturation of the site by tumor cells and the tumor starts to expand. This feature explains how a temporary deficiency of the immune system can lead to tumor expansion as shown in Fig. 4, where $y = 0$ for $160 < t < 200$ a.u.t. In this model, the process is reversible because model (1) does not take into account the irreversible degradation of the tissue by tumor progression and treatment.[48] The bifurcation diagram (Fig. 2) shows that until the immune system is active, faster the regeneration of the tissue (larger growth rate ρ_h), larger the population of tumor cells can be and, consequently, faster the tumor progression is.

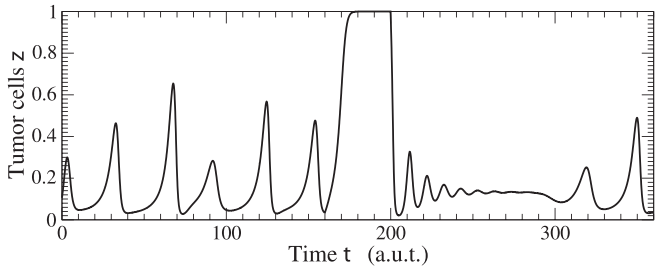

FIG. 4. Time evolution of the population of tumor cells for a tissue with a moderate regeneration duration (moderate growth rate, $\rho_h = 0.518$). Other parameters have the default values reported in Table I. The deficiency of the immune system occurs at $t = 160$ a.u.t. ($y = 0$); its action is recovered at $t = 200$ a.u.t. ($y = 0.1$).

The growth rate ρ_t of tumor cells is related to the growth rate ρ_h, since ρ_t is always greater than the growth rate of cells ρ_h from which mutated, malignant cells most often proliferate:[49,50] we therefore choose to use $\rho_t = 2\rho_h$ in the subsequent simulations. The bifurcation diagram *versus* ρ_t is shown in Fig. 5(b). There is a threshold value for this growth rate ($\rho_t \approx 0.95$), under which the population of tumor cells remains 0. There is a chaotic regime followed by a sequence of reverse bifurcations leading to an inverse cascade of period-doublings, and then the point S_6 becomes a stable node-focus ($\rho_t \approx 1.25$).

Among the six remaining parameters of model (1), the natural death rate of effector immune cells δ_i is commonly considered as being non-patient dependent.[51,52] We therefore left this parameter to its default value. The bifurcation diagrams versus each of the five free parameters are shown in Fig. 5. No bifurcation is observed in the diagram versus the death rate of tumor cells by effector immune cells α_{it} [Fig. 5(f)], meaning that the value of this parameter has no effect on the dynamics: this parameter is therefore kept at its default value. The other four parameters can be grouped into two classes. Increasing the parameters ρ_i and α_{th} contribute to the reduction of the population of tumor cells; the former by increasing the efficiency of the immune system and the latter by increasing the barrier against tumor progression provided by the nesting tissue. Parameters α_{ht} and α_{it} promote the proliferation of tumor cells, the former by inhibiting the immune system and the latter by reducing the barriers provided by the host cells. Note that what is important in these bifurcation diagrams is not how the dynamics is developed (the population of periodic

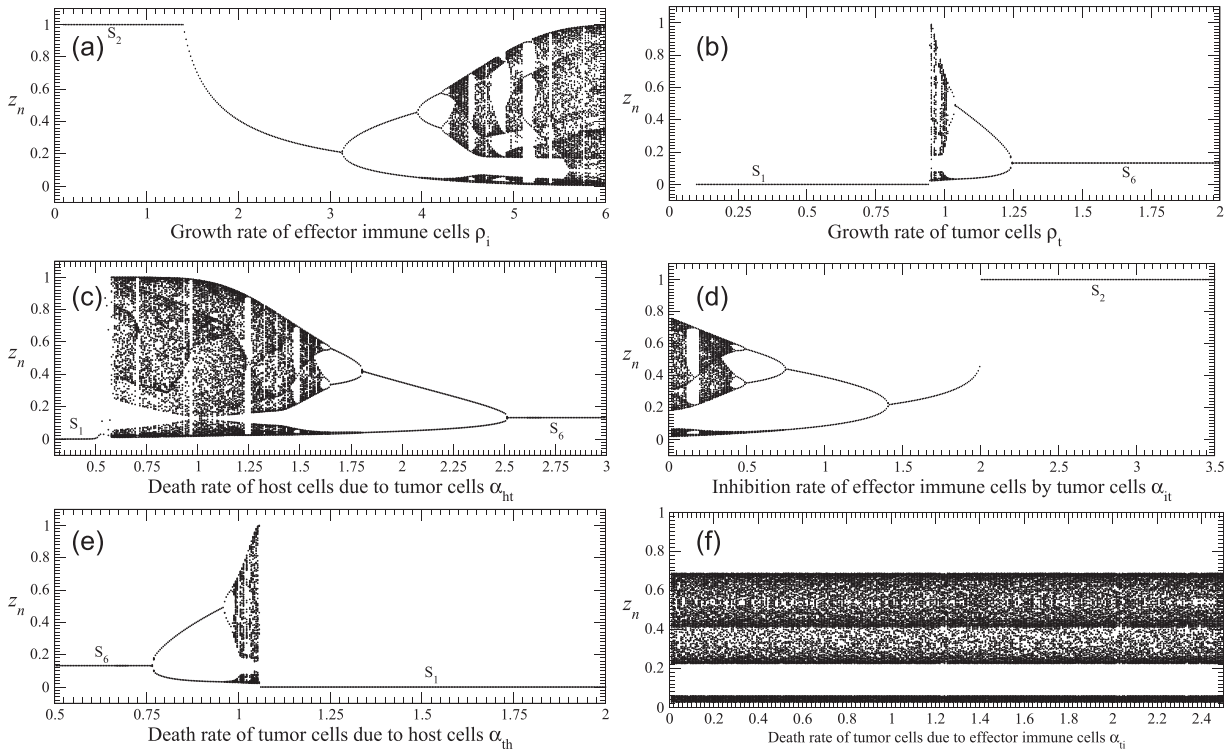

FIG. 5. Bifurcation diagrams versus different parameters of the cancer model for an isolated site (the diffusion term is cancelled). (a) Growth rate of immune cells ρ_i (b) Growth rate of tumor cells ρ_t (c) Death rate α_{ht} of host cells by tumor cells (d) Inhibition rate α_{it} of immune cells by tumor cells (e) Death rate α_{ht} of tumor cells by host cells (f) Death rate α_{it} of tumor cells by immune cells.

orbits as easily shown by the cascade of period-doublings), but rather the transition between the attractors at the two ends of the diagram, which are most often stable singular points. For instance, promoting the tumor cells is observed by switching from point S_1 to S_6 or toward point S_2. Reducing the proliferation of these cells is associated with the transition from point S_2 to chaos (or point S_1, if ρ_i is increased up to 7.0) or from S_6 to S_1. We have therefore an aggressive tumor for low values of ρ_i and α_{th}, and large values of α_{ht} and α_{it}. We have therefore various configurations for which the tumor can remain under the clinical level of detection, can slowly grow (for instance, when there is a chaotic regime) or can present a fast expansion. These four parameters are therefore useful for distinguishing how the tumor micro-environment can provide barriers against tumor progression or not.

Let us now discuss six typical cases of dynamics which can be encountered. These simulations were performed with the initial conditions $(x(0), y(0), z(0) = (0.1, 0.1, 0.01)$. Parameter values are reported in Table II with the types of eight singular points.

In case I, the trajectory converges quite quickly to point S_2, which is a stable node [Fig. 6(a)], meaning that the site provides an environment in which tumor cells very quickly proliferate.

In case II, point S_2 is also a stable node, but there are three additional singular points compared to the previous case [Fig. 6(c)]. Points S_3 and S_4 are such that $y_4 > y_3$ and $z_4 > z_3$. Point S_4 is therefore associated with larger populations of immune and tumor cells compared to point S_3. Point S_5 is associated with three non-zero populations of cells; the population of tumor cells being the largest ($z_5 > 0.5$), therefore, corresponds to a rather deleterious configuration (tumor cells proliferate very quickly). Point S_6 corresponds to a site where the host cells are most numerous ($x_6 > 0.5$) and thus where there are strong barriers against tumor proliferation. The direct effect of these additional singular points is a longer transient regime before reaching the stable node point S_2. Obviously, this transient regime is very sensitive to initial conditions as shown in Fig. 6(b) (the second set of initial conditions is such that $(x(0), y(0), z(0)) = (0.6, 0.1, 0.2)$,

TABLE II. Parameter values for the six cases whose dynamics is explicited. The singular points of the system are also reported with their type. The subscripts indicate the dimension of the unstable manifold. Other parameter values: $\alpha_{ti} = 2.5$ and $\delta_i = 0.5$.

Case	I	II	III	IV	V	VI
ρ_h	0.8	0.65	0.75	0.75	0.75	0.75
ρ_i	0.1	5.344	6.0	6.0	5.344	6.0
ρ_t	1.6	1.3	1.5	1.5	1.5	1.5
α_{ht}	2.0	0.833	1.00	1.166	0.53	0.833
α_{it}	2.366	2.366	1.988	1.611	1.23	1.988
α_{th}	0.5	1.166	1.333	1.5	1.83	1.333
S_0	SD_1	SD_1	SD_2	SD_2	SD_2	SD_2
S_1	SD_2	SD_2	SD_1	SN	SN	SD_1
S_2	SN	SN	SD_1	SD_1	SD_2	SD_1
S_3	…	NF_0	…	…	…	…
S_4	…	SF_1	SF_1	SF_1	SF_1	SF_1
S_5	…	SD_2	…	…	…	…
S_6	…	SF_2	SF_2	SF_2	…	NF_0
S_7	…	SD_1	…	…	…	…

SD ≡ saddle point, SN ≡ stable node point, SF ≡ saddle-focus, and NF ≡ node-focus.

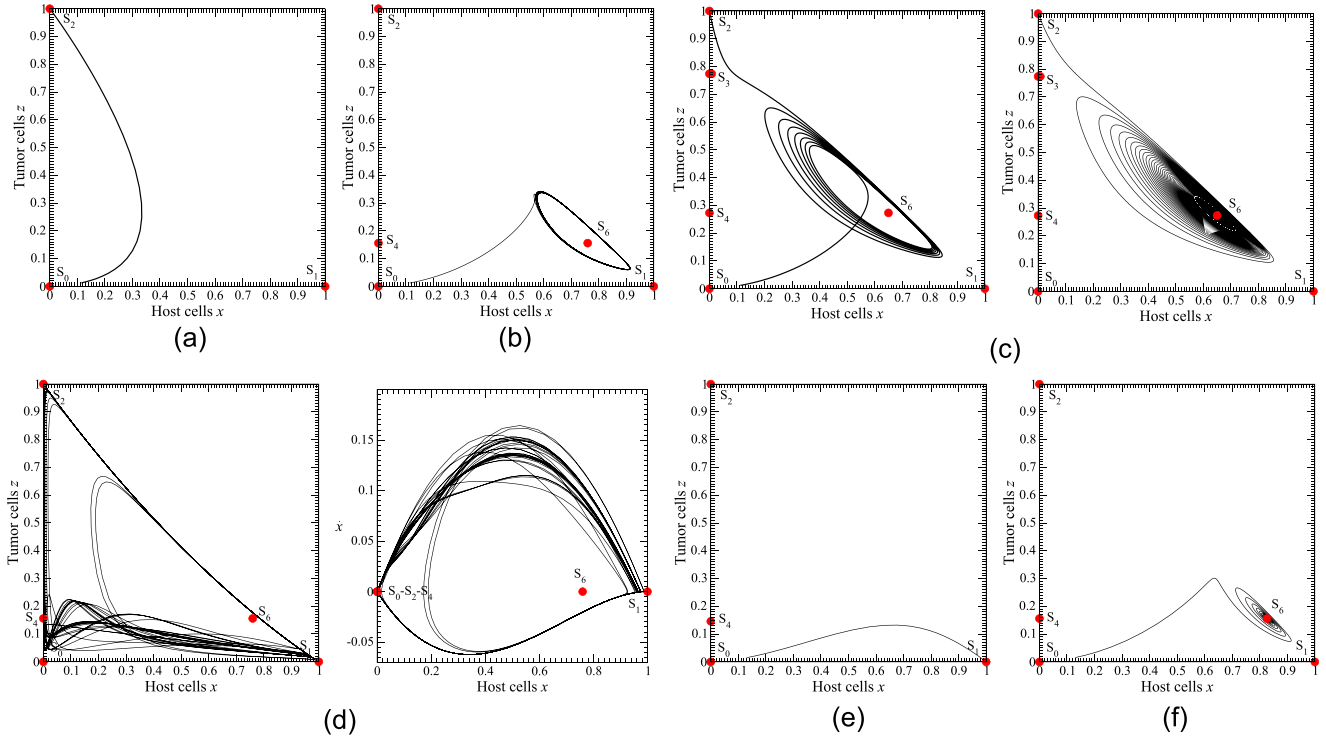

FIG. 6. Phase portraits of the dynamics produced by a single isolated site for the six different cases whose parameter values are reported in Table II. (a) Case I, (b) Case III, (c) Case II, (d) Case IV, (e) Case V, and (f) Case VI.

that is, quite close to point S_6, thus trapping the trajectory in the slowly divergent spiral around it). The tumor thus starts to grow slowly and then presents a fast growth. This is what is clinically observed very often since when its growth is initiated, a tumor commonly remains too small to be detected by routine imaging for several years. This initial prevascular phase corresponds to a slowly expanding tumor;[53] it is then followed by a second phase during which the tumor is neovascularized and grows rapidly,[54] with the size exceeding 2 mm, therefore becoming clinically detectable by routine imaging. The volume of the tumor can then easily reach 1 l, that is, a diameter of about 10 cm.

In case III, points S_3 and S_5 are no longer with real positive coordinates. Point S_2 is no longer a stable node. Points S_4 and S_6 are two saddle-focus points: point S_6 is associated with the eigenvalues

$$\begin{cases} \lambda_{1,2} = 0.0014 \pm 0.2423\, i \\ \lambda_3 = -0.8308\,; \end{cases} \tag{3}$$

the small real part of the two complex conjugated eigenvalues indicate that this point is close to a Hopf bifurcation which occurs, for instance, for $\rho_i \approx 5.979$ and $\alpha_{th} = 1.333$ or $\rho_i = 6.0$ and $\alpha_{th} \approx 1.339$. This Hopf bifurcation is investigated in more detail in Ref. 55. Consequently, the asymptotic behavior is a limit cycle around point S_6 [Fig. 6(b)]. There are small oscillations with a rather large population of host cells (and a small tumor cell population). The tumor therefore does not grow and remains limited to a single site. In case IV, compared to case III, point S_1 is no longer a saddle, and now has a two-dimensional stable manifold and a marginal stability in the third direction. This means that the trajectory may visit the neigborhood of this point. This lead to a chaotic attractor as shown in Fig. 6(d), where the transient regime is removed. The trajectory oscillates between the neighborhoods of points S_2 and S_1. This particular structure squeezes the trajectory in the upper part of the attractor (in the plane x–$\dot{x}$ projection). This attractor has a very particular structure as evidenced by the Poincaré section

$$\mathcal{P} \equiv \left\{ (\dot{x}_n, y_n) \in \mathbb{R}^2 \,|\, x_n = 0.5, \dot{x}_n > 0 \right\} \tag{4}$$

shown in Fig. 7. Such a "snail" structure was observed in the "funnel" Rössler attractor.[47] Nevertheless, the structure is not fully equivalent since we were not able to obtain a multimodal map as in the Rössler attractor. This case would correspond to a slow tumor growth as shown in Ref. 40.

Cases V and VI correspond to a situation for which the microenvironment provides strong barriers against tumor growth, the former due to the singular point S_1 that is a stable node (only the host cells colonize the site) and the latter due to the singular point S_6 which is a stable node-focus point at which there is a very large population of host cells with the small ones of immune and tumor cells. In these two cases, there is no tumor (the tumor cells are not sufficiently numerous to form an expanding colony).

With these six cases, we depicted all possible cases we can have from the tumor growth point of view. Cases III, IV, V and VI produce a colony confined in a single tumoral site. Cases I and II are shown in Fig. 8 at time $t = 8000\,dt$. Case I is clearly the situation in which the tumor growth is the fastest.

IV. SPATIAL DYNAMICS

Many genomic changes occur simply in a random way during DNA replication. We considered that the endogenous

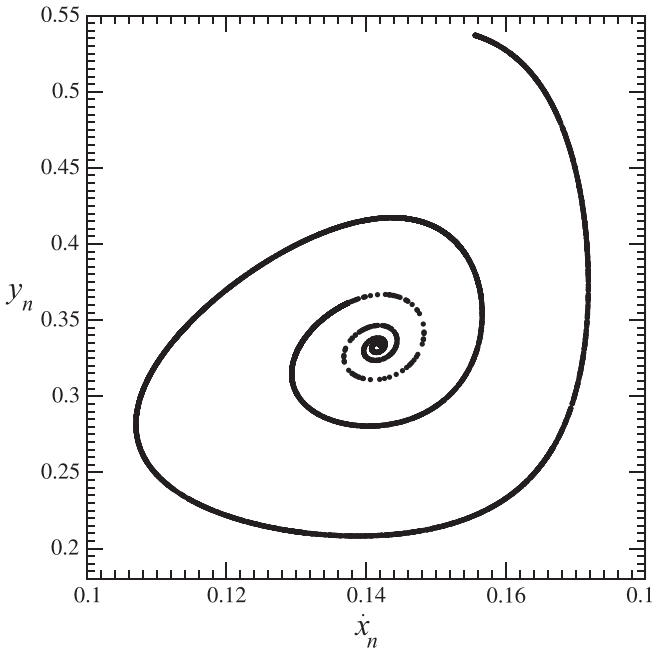

FIG. 7. Poincaré section $\mathcal{P}$ of the chaotic attractor produced by an isolated system (1) with the parameter values of Case IV.

mutation rate of all types of human cells is nearly the same[56,57]—as also considered in Ref. 2. Nevertheless, we considered that the apparition of a malignant cell is sufficiently frequent that the key factor is not this mechanism, but rather the occurrence of a nesting tissue in favor of an expanding colony of tumor cells, the time state being characterized by the parameter ρ_i, α_{ht}, α_{it}, and α_{th}. Variations in the values of these four parameters allow one to take into account how the spatial growth of the tumor mass mainly depends on carcinogenic factors such as pesticides, benzene, light particles, tobacco, quality of food, etc.[58,59] It is not our purpose here to relate directly how a given carcinogenic factor affects a given parameter. Typically, a set of parameter values providing a fast expanding tumor would correspond to a tissue which was degraded by carcinogenic factors.

The central site ($i = 5$ and $j = 5$) is such that, at time $t = 0$, it contains a small colony of tumor cells. This site is thus initialized with $x_{5,5}(0) = 0.6$, $y_{5,5}(0) = 0.1$, and $z_{5,5}(0) = 0.2$. In all other sites, at time $t = 0$, the population y_{ij} of effector immune cells is null, since there is no tumor cell in them. These sites are thus considered to be filled only with host cells. Initial conditions for sites S_{ij} ($i \neq 5$ and $j \neq 5$) are therefore $x_{ij}(0) = 1.0$, $y_{ij}(0) = 0$, and $z_{ij}(0) = 0$. When there are some tumor cells which diffuse at time $t > 0$ into one of these sites, the population y_{ij} of that site is set to a non-zero value ($y^k_{ij}(t) = 0.1$ for $k = \{\text{N, S, W, E}\}$ and $y^k_{ij}(t) = 0.05$ for $k = \{\text{NE, NW, SE, SW}\}$).

Each of the four parameters α_{ht}, ρ_i, α_{it}, and α_{th} was varied by using ten values equidistributed over the intervals reported in Table I. This was therefore 10^4 different sets of parameter values which were investigated for each value of the growth rate ρ_h of host cells. We thus considered a given tissue (organ) in 10 000 different states from the cell interaction point of view. Since each patient has a tissue in a particular state, each tissue state can be interpreted as representing a given patient. This is thus a cohort of 10 000 different simulated patients which was considered.

Our simulations using 100 coupled copies of model (1) were performed using a fourth-order Runge-Kutta scheme for 50 000 time steps ($dt = 5 \times 10^{-2}$ arbitrary units of time). Such a duration is large enough to allow a significant spatial growth of the tumor mass, provided that the diffusion of tumor cells occurs. In order to determine whether there is a spatial growth at the end of each simulation, we checked whether the population of tumor cells is such that $z_{8,5}(50\,000) \neq 0$, that is, whether tumor cells are detected at a distance greater than 300 μm from the initial location. With 10 000 different simulated patients in our cohort, we can detect up to 10 000 expanding tumors for each ρ_h-value. The probability P_{gt} for a growing tumor is therefore the number of sets of parameter

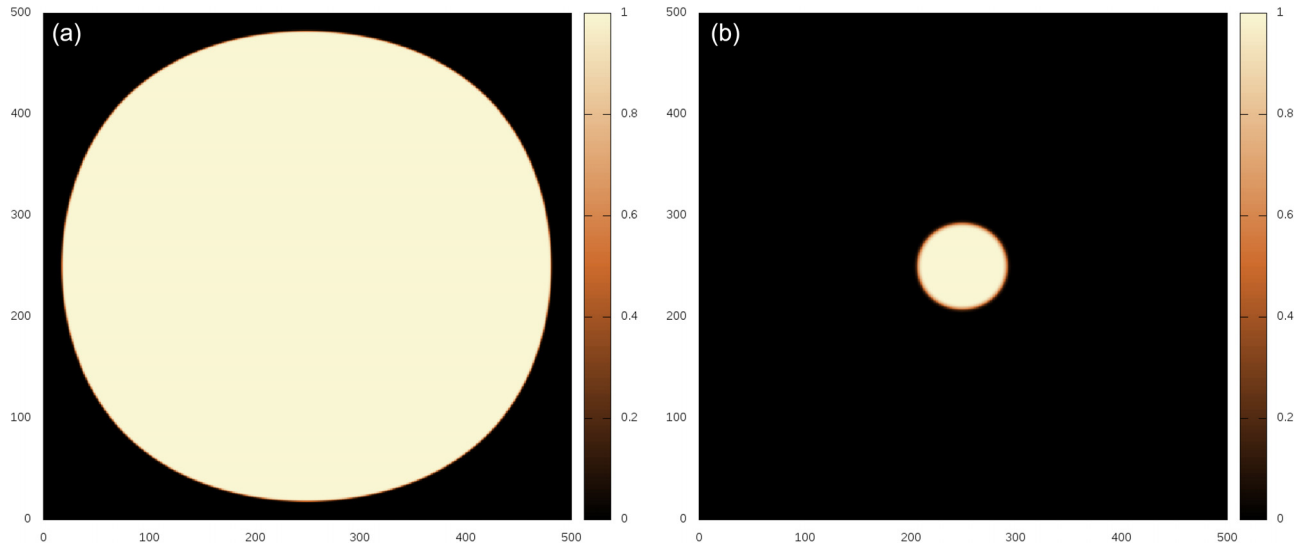

FIG. 8. Size of the tumor at time $t = 8000\ dt$ for the two cases in which there is a detected tumor growth. Parameter values as reported in Table II. (a) Case I and (b) Case II.

values ($\alpha_{ht}, \rho_i, \alpha_{it}, \alpha_{th}$) leading to an expanding tumor divided by 10,000. This probability was thus computed for each value ρ_h (varied from 0 to 1 by a step d $\rho_h = 0.05$). By plotting the probability P_{gt} versus the growth rate ρ_h (Fig. 9), we show that the probability P_{gt} is highly significantly correlated ($r = 0.99$, $p < 10^{-6}$) to the growth rate ρ_h. This curve shows that tissues with fast regeneration more often lead to an expanding tumor than those with slow regeneration. This is equivalent to the relationship between the number of stem cell divisions in the lifetime in a given tissue and the lifetime risk of cancer in that tissue which was obtained by Tomasetti and Vogelstein (see Fig. 1 in Ref. 2). From that point of view, our model is validated by the clinical data obtained by these authors.

V. DISCUSSION

With our purely deterministic model, we were able to show that the lifetime risk is strongly correlated with the total number of divisions of the normal self-renewing cells. Nevertheless, contrary to what was asserted by Tomasetti and Vogelstein,[2] the random mutations arising during DNA replication do not play any role in our approach since we here considered any case with an initial small population of tumor cells (a mutation that occurred in each case). Indeed, the correlation we obtained between the probability for a growing tumor and the growth rate of host cells results from the variations in the parameter values of model (1) describing the inter-patient variability related to the interactions the tumor cells have with the surrounding micro-environment. For instance, the smallest growth rate ρ_h (0.15) of host cells for which the number of detected growing tumors is non-zero would correspond to osteocarcoma of the pelvis in the work of Tomasetti and Vogelstein[2] and the largest one (1.0) to the basal cell cancer. This shows that the variations in the probabilities for an expanding tumor are fully explained by the nesting tissue state mostly affected by the way of life and external factors. We therefore provided with our simulations a new argument against Tomasetti and Vogelstein's interpretation (see Refs. 15, 35, and 60–62 for other critics). Our explanation offers a fully deterministic relationship between the lifetime risks for cancer and the way of life.

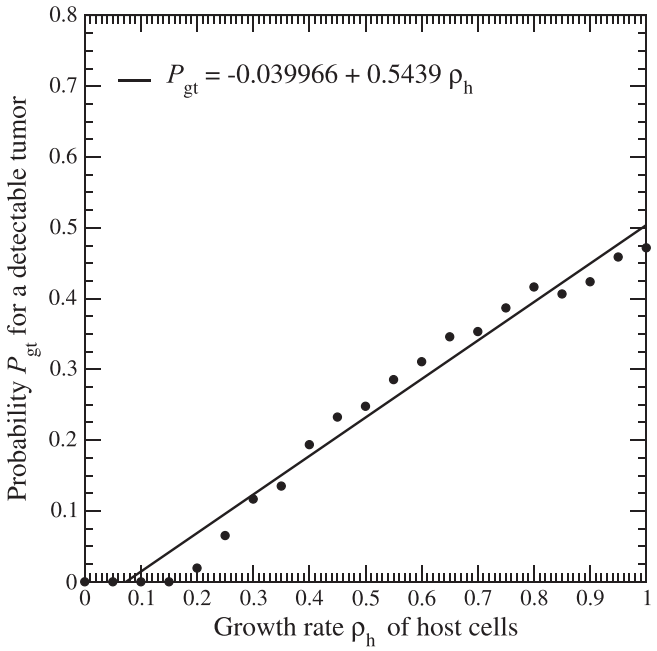

FIG. 9. The relationship between the probability P_{gt} for detecting a growing tumor after 50 000 arbitrary units of time *versus* the growth rate ρ_h of host cells.

Our simulations clearly show that the state of the surrounding tumor tissue is preponderant in the evolution of a cancer. Since the state of the nesting tissue is only related to 10% to the heredity,[63] this state necessarily results from the way of life and external factors as the quality of the air breathed, working conditions, sleep quality, exercise, etc. The optimal functioning of a given body with its genetic properties is only governed by the way of life. For instance, obesity induces a high level of saturated fatty acids in blood which, in turn, promotes inflammation. Such a feature has a direct consequence on the parameter values governing the interaction of immune and host cells with tumor ones. Obesity increases the rate of IGF1 that directly affects the growth rate of tumor cells.[64] We could also mention the level of exercise performed by patients: exercise is known for improving the response of the immune system and increasing the rate of intra-cellular glutathione.[65] Exercise therefore affects the values of parameters ρ_i, α_{it} and α_{ti}. Smoking, alcohol drinking, and ingesting anti-oxidant agents also influence these parameter values. Our results therefore confirm that preserving the tissue, where mutations always occur, in good condition, could be an efficient strategy to reduce cancer risks.

Consequently, cancer risks are not seen as resulting from "bad luck". It might be not useless to recall how Laplace was considering "randomness":[66]

> "All events, even those which on account of their insignificance do not seem to follow the great laws of nature, are a result of it just as necessarily as the revolutions of the sun. In ignorance of the ties which unite such events to the entire system of the universe, they have been made to depend on final causes or on hazard, according as they occur and are repeated with regularity, or appear without regard to order, but these imaginary causes have gradually receded with the widening bounds of knowledge and disappear entirely before sound philosophy, which sees in them only the expression of our ignorance of the true causes."

What was designated by "bad luck" therefore would be the way of life and external factors that can affect the complex system made of a tumor and its environment, and certainly not the random mutation occurring in cell divisions. The way such an environment—the organ tissue—is affected by the way of life (food, drink, air pollutant, tobacco, stress, overtiredness, exercise…) is only very partially understood. With our model, we showed that it might be of primary importance to keep our tissues in good condition. Prevention in favor of a good way of life could thus reduce cancer risk.

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