Cancerous tumor: The high frequency of a rare event

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(Received 6 September 2000; published 18 April 2001)

A simple model for cancer growth is presented using cellular automata. Cells diffuse randomly on a two-dimensional square lattice. Individual cells can turn cancerous at a very low rate. During each diffusive step, local fights may occur between healthy and cancerous cells. Associated outcomes depend on some biased local rules, which are independent of the overall cancerous cell density. The models unique ingredients are the frequency of local fights and the bias amplitude. While each isolated cancerous cell is eventually destroyed, an initial two-cell tumor cluster is found to have a nonzero probabilty to spread over the whole system. The associated phase diagram for survival or death is obtained as a function of both the rate of fight and the bias distribution. Within the model, although the occurrence of a killing cluster is a very rare event, it turns out to happen almost systematically over long periods of time, e.g., on the order of an adults life span. Thus, after some age, survival from tumorous cancer becomes random.

DOI: 10.1103/PhysRevE.63.051907 PACS number(s): 87.17.−d

I. INTRODUCTION

In the past decades a tremendous amount of experimental effort has been devoted to the study of cancerous tumors. There have been also many attempts to provide some kind of an abstract model. However, theoretical work is difficult due to the highly complex biological mechanisms involved [1]. Modeling usually requires rather drastic oversimplifications, necessary in order to derive any analytical solution for the proposed mathematical equations at hand. Not long ago, complex numerical simulations of cancer spreading, and also of possible immunity, have been attempted [2,3]. Very recently the concept of a phase transition was used to reproduce some qualitative features of cancer dynamics [4]. However, at this stage, while substantial progress has been accomplished in the medical treatment of the illness, the conditions for the appearance, along with the associated spreading dynamics, of a cancerous tumor still resist an overall explanation. Indeed, a thorough theoretical understanding of tumor dynamics is as yet lacking [5].

In this work, somewhat at odds with biological approaches which focus on describing minute details of specific phenomena, we adopt a reductionist point of view. The goal is to provide a simple model which can embody some basic features of a tumor spreading phenomena, although most of the biological components involved will not be included.

We do not claim any exact solution to the problem. Instead we are presenting a model of the occurrence and growth of cancer from an initial, very small, compact cancerous cluster within a healthy system. A simple, local mechanism is suggested to describe the conditions which may lead a small cancerous tumor to either an explosive growth or a complete remission. In other words we study the dynamics associated with a rare event within a given framework [6,7]. Although naive, the model might provide some insights into the understanding of the dynamics involved in a real biological process.

The outline of this paper is as follows. The model is presented in Sec. II together with the rules governing the dynamics. In Sec. III we give details of simulations, and in Sec. IV results are presented. Conclusions are given in Sec. V.

II. MODEL

Let us start from a two-dimensional square lattice system, with periodic boundary conditions. Initially, at every node there is a healthy cell. During the system evolution all cells diffuse randomly on this grid, by moving to one of the nearest neighbor sites, under only the constraint of preserving one cell per node. There are many ways to model a physical diffusion of cells. One could be by introducing empty sites on a lattice to facilitate the cell's movement. However, in tissue, cells are undergoing apoptosis and division all the time. In modeling, the death of any cell on a lattice would mean that at a given node there is an empty place. Thus a division of any of the neighboring cells, producing two identical daughter cells, has a chance to fill such a void. In effect, any subsequent train of consecutive death and division events can randomly transport a functionally equivalent cell to any place on a lattice, allowing for both cell diffusion and exchange. The diffusive dynamics is monitored by nearest neighbor pair exchanges.

One simulation cycle corresponds to an exchange of all cells within a full lattice coverage. In parallel, at each time unit, we attach a very low individual probability for a healthy cell to spontaneously turn cancerous. While there seems to be a growing consensus about the mostly genetic background for cancer origin at a single cell level, the detailed mecha-

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nism by which this might happen does not concern us here. We just account for it existence.

The probability of such an event can be as low as, for instance, $p=10^{-6}$ per unit of time. As soon as a cancerous cell appears, it starts to diffuse in exactly the same way as healthy cells do. In a tissue, cancerous and healthy cells interact via a very complex system of biological mechanisms. One of the best understood is, e.g., competition for nutrients [4]; however, there are many others. To embody part of the biological and chemical complexity which control the cancer spreading, we make two assumptions.

(1) First, to account in the simplest possible way for the interactions whose outcome governs tumor growth dynamics, we introduce local fights between four neighboring cells. This is an arbitrary choice, to illustrate the model most clearly, the qualitative results do not depend on this. However, the existence of even configurations (two healthy cells against two cancerous cells) is instrumental in monitoring the richness and fragility of real interactions. We assume the fighting not to be systematic. It does not occur everywhere, and at each diffusive step. The frequency of fights is controlled by the parameter k, which defines, at each time step, the probability of a local fight to occur on a particular node. That is, cells of any given neighborhood will either diffuse or fight depending on the current value of k, which is stochastically controlled. Therefore, a local fight occurs with a probability k, or diffusion occurs with a probability $1-k$. When there is one different cell and three identical ones, a simple majority rule is used—all four cells become identical. Such a choice produces a definite advantage for a current cell majority.

(2) To account for some local defficiency of the organism, as well as its current, overall state of stress, some very small, qualitative advantage may be given to cancerous cells when an even configuration of cells occurs (two against two, a tie). To implement this effect, we define a local bias, controlled by another parameter β, which can vary from -1 to 1. Then, in a tie situation, the outcome of a fight becomes probabilistic. Two regimes are considered.

(a) The unfair regime. For the unfair regime only cancerous cells might have a probabilistic advantage in the case of a tie. We pick a random number δ. For a fixed value of β, if $\delta \leqslant \beta$ the cancerous cells win. Otherwise nothing happens. Indeed healthy cells win only when they have a majority, i.e., three against one. In contrast, cancerous cells also win at two against two, but with probability β.

(b) The fair regime. In the fair regime the case of a tie is decided either in favor of the healthy cells or the cancerous cells according to another probabilistic rule. Here, for a random number $\delta<\beta$, the cancerous cells win, while for $\delta>\beta$ the opposite is true. In the relatively rare case $\delta=\beta$, nothing happens; that is, a tie situation is propagated to the next time step with no change of the sick to healthy cell ratio. In other words, the fair regime is symmetric with respect to the bias, while the unfair regime slightly favors cancerous growth.

A similar model was previously used to study the emergence dynamics of new species [8]; however, the bias was deterministic and always in favor of a minority. To survive, a new species has to start from above some critical threshold of the overall population density, which can vary between 10% and 23%, depending on k. Recently, in the same model but at one dimension, it was shown that, even at zero density, there exist some compact clusters which lead to the final overcoming of the indigenous species [9].

III. SIMULATION

From the local fight rules above, any isolated cancer cell will eventually be destroyed, independently of the overall cancer cell density. Therefore, we focus on the dynamics and the final fate of the smallest possible initial cancerous cluster, i.e., two nearest neighbor cells.

We now describe the simulation. First a two-cell cancerous cluster is randomly placed (either horizontally, vertically, or diagonally) on a system grid. The whole ranges of both k and β are systematically explored by repetitively performing the following steps.

For a given $N\times N$ lattice we randomly choose a node. At each time cycle this choice predefines a fixed grid of 2×2 tiles, giving $(N/2)\times(N/2)$ four-cell neighborhoods. Due to randomness, at each cycle this tilling is different. Then, in accordance with current values of δ, k, and β, a fight or diffusion takes place for this specific neighborhood, which is subsequently marked as visited.

Next, again randomly, another node is selected, and so on, until all neighborhoods have been visited. The whole sequence is then repeated until all nodes on the lattice are either healthy or all are tumorous. The number of time cycles necessary to reach one of these two final states is stored, together with the corresponding values of k and β. As the tilling scheme adopted here is somewhat arbitrary, we have also performed other simulations with different four-cell neighborhood topologies, but the qualitative results obtained were always very similar.

IV. RESULTS

At first sight, although cancerous cells are produced at some given, but rather low, rate (for instance $p=10^{-6}$), they do no harm at all, being systematically neutralized—in both simulation regimes, fair and unfair. Fight rules imply that, in order to have a chance to win a single local fight, the cancerous cells must form at least a packed cluster of two (nearest neighbors) cells.

Having a probability $p\to 0$ to obtain one cancerous cell, the probability to obtain two adjacent is p^2, a much smaller value of 10^{-12}. However, it is worth stressing that in a living organism, the number of cells can be about 10^9. This will result, on an average, in the probability to form a two-cell cluster of 10^{-3}. Now, in one year there are 3×10^7 or so seconds. Making one diffusive step associated with one second, for 30 years there will be 10^9 diffusive steps, resulting, again on an average, in 10^6 such clusters.

Therefore, we may assume that over an adult life span, the probabity of obtaining one two-cell cancerous cluster is a rather certain event. This corroborates the empirical observation that most often cancerous tumors are detected at adult or

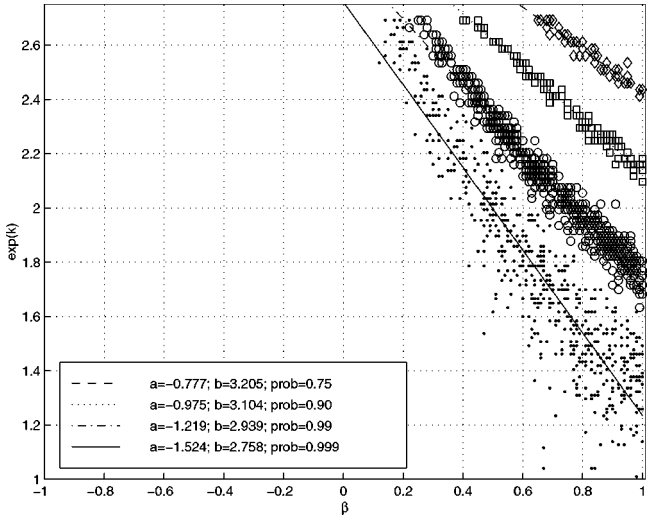

FIG. 1. Probability isolines for survival in the fair regime at (from top) 0.75 (dashed line, diamonds), 0.90 (dotted line, squares), 0.99 (dot-dashed line, circles), and 0.999 (solid line, dots).

older ages. On this basis, we now concentrate on the minimal viable settings, i.e., starting from an initial cancerous tumor of two cells.

For such a cluster, the conditions for its growth are in a very subtle balance, depending on values of both parameters k and β. Obviously, the cancerous cells ''benefit'' from more aggressiveness than diffusion, while the healthy system should conversely ''favor'' diffusion over fights.

Systematic results of our simulation are shown in Figs. 1 and 2 for fair and unfair regimes, respectively. The whole ranges of $0<k\leqslant 1$ and $-1\leqslant\beta\leqslant+1$ are explored. For each pair of parameters k and β, we run $M=1000$ simulations in both regimes, fair and unfair, counting how many times the two-cell starting cancerous cluster wins over the whole system. The sum of such victories, divided by M, gives the associated probability for an organism to die.

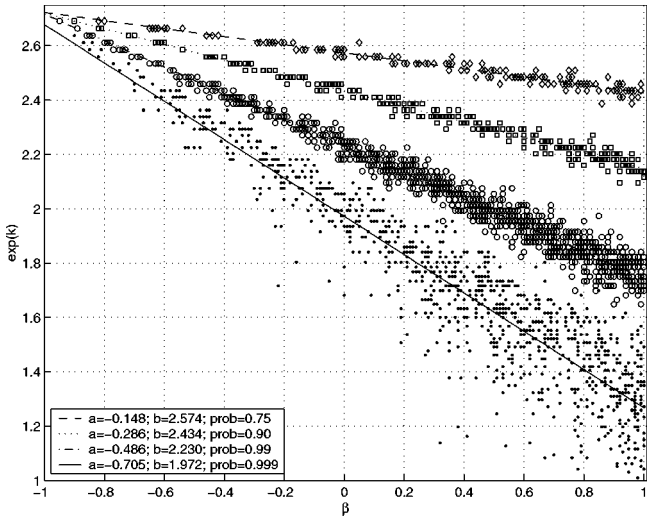

FIG. 2. Probability isolines for survival in the unfair regime at (from top) 0.75 (dashed line, diamonds), 0.90 (dotted line, squares), 0.99 (dot-dashed line, circles), and 0.999 (solid line, dots).

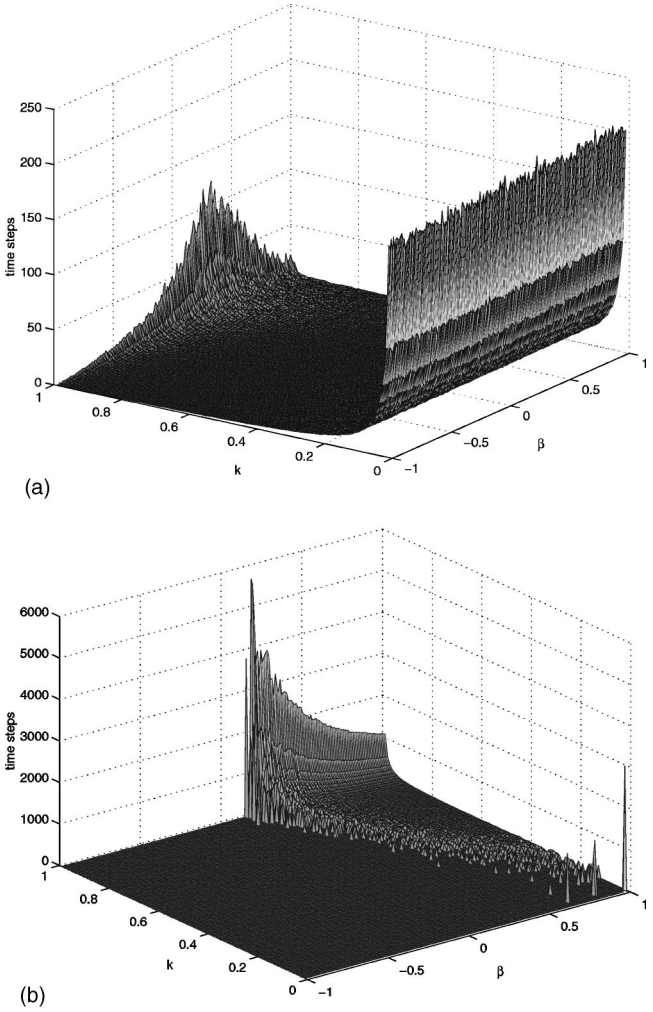

FIG. 3. Number of the time cycles necessary to arrive at one of the two final states in the fair regime: (a) a completely healthy system, and (b) a completely tumorous system.

From a set of points sharing the same value it is possible to interpolate the probability. Our figures show the probability isolines at 0.75, 0.90, 0.99, and 0.999, obtained as an exponential-linear fit $[f(\exp(x))\equiv a*x+b]$ for respective sets of points sharing a given probability. Although the change of conditions from fair regime to the unfair regime is rather slight, it nevertheless produces striking differences (cf. Figs. 1 and 2). It can be seen that in the fair case, cancerous cells always fail with a probability 1 for $\beta<0$. This is not the case for the unfair regime.

If, instead of a two-cell starting cluster, the initial size was increased to three or four cells, the corresponding probability isolines are all shifted diagonally toward smaller values of both k and β. As the observed changes are of only a quantitative nature, and the direction of such a shift is intuitively obvious, we do not describe them here in more detail.

We also calculated the number of time cycles necessary to arrive at a final, stable state, either a totally healthy one or a dead one. The associated three-dimensional phase diagrams are shown in Figs. 3 (fair regime) and 4 (unfair one). In cases when the tumor completely overwhelms the system [Figs.

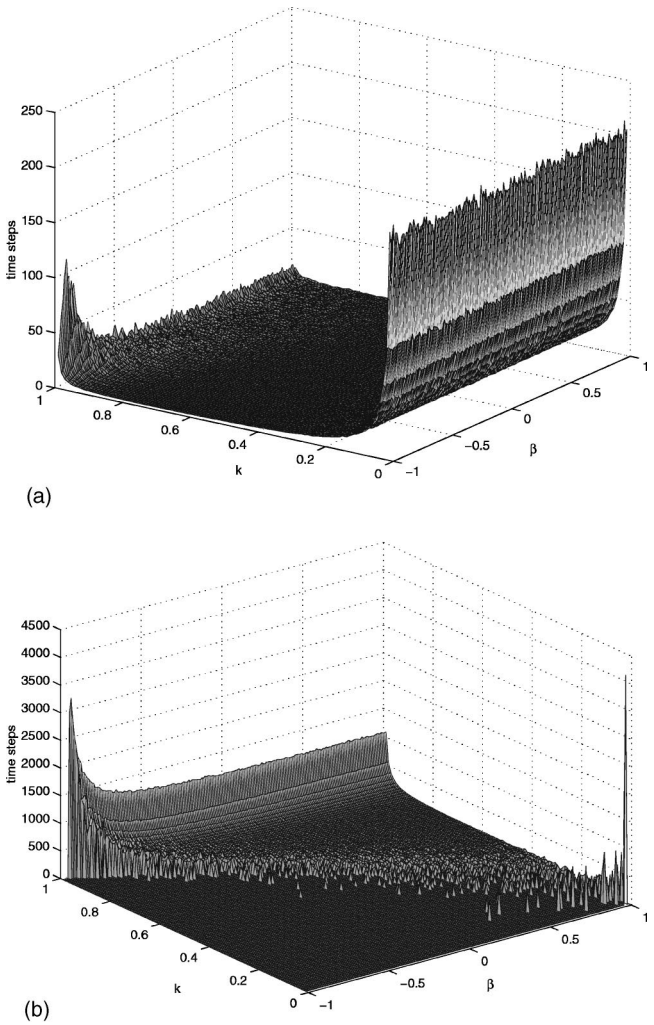

FIG. 4. Number of the time cycles necessary to arrive at one of the two final states in the unfair regime: (a) a completely healthy system, and (b) a completely tumorous system.

3(a) and 4(a)], many more cycles are necessary than in the reverse situation of successful defense [Figs. 3(b) and 4(b)]. At the extreme (the low-k and high-β regions), the isolated events of tumorous victory are not only very improbable, but at the same time the ensuing fight for survival is also an extremely long one [e.g., as shown in Fig. 4(b), longest of all]. For very small values of k, when there is almost no diffusion, the time needed to recover a completely healthy system is also rather long, and it depends strikingly only slightly on the β value [Figs. 3(a) and 4(a)].

A very interesting region lies at the border zone in a vicininty of the 0.999 probability line. If we consider the number of time cycles necessary for complete remission [e.g., Fig. 3(a)], in this area, especially at the high values of diffusion and in the fair regime, there is a symmetric peak present. Due to the complete symmetry inherent in the fair regime, the number of time cycles leading to any of the two final states decays roughly symmetrically on both sides of the border line. Such a symmetry is missing, however, in the corresponding plot of dying systems [cf. Fig. 3(b)]. Thus, for a system almost wholy dominated by tumorous cells, it may be enough to shift values of k or β very slightly in order to arrive at a completely different outcome.

V. CONCLUSIONS

We have presented a simple diffusive model for a cancerous tumor growth. The unique ingredients are biased local fights and the frequency of these fights. While each individual cancerous cell is eventually destroyed, the occurrence of a two-cell tumorous cluster was found to jeoperdize chances of survival. Indeed the system capability to win becomes probabilistic. The associated full phase survival diagram was obtained using large scale simulations ($M = 1000$).

The very simple, naive model presented here shows that tumor dynamics appear to be in a rather delicate equilibrium during most of a tumors' presence. For instance, a high value of k turns out to have varying effect on cancer growth depending on the initial tumor size.

In parallel, the effect of diffusion is also not linear. A high diffusion rate acts against a cancerous tumor, and eventually leads to its destruction only when the size is relatively small. For a larger tumor, the same diffusion rate will produce an enhancement of its growth. Moreover a few percentages of randomly distributed sick cells have no chance to produce a spreading tumor. On the opposite side, just one unique small compact cluster may lead to an invading tumor.

In conclusion, our model should not be taken as a description of a real biological system, but rather as an oversimplied tool to mimic a complex dynamics of either the irreversible spreading or the total remission of a cancerous tumor. At this stage, we conclude that tumor spreading is of a more probabilistic than chaotic character. Nevertheless, it is worth stressing that a final outcome we observe for a given pair of fixed β and k values is of a somewhat static nature. However, in a real organism actual values of the associated β and k pairs are likely to fluctuate widely with time, due to e.g., the general health of the whole system, the size of the tumor, and many other factors. Thus this shifts the overall tumor dynamics more and more toward a chaotic behavior. To study associated phenomena in more detail is our next goal.

ACKNOWLEDGMENTS

We would like to thank Yonathan Shapir, Suzana Moss, and Dietrich Stauffer for discussions and stimulating comments. J. P. R. was partially supported by KBN Grant No. 115/E-343/S/UM-1010/2000/ICM.

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