Trends in Cancer Research
Vol. 6, 2010

Review

Brain tumor growth models

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ABSTRACT

Primary brain tumors, benign and malignant, constitute a great number of very different tumors from the point of view of pathology and neuro-oncology. Astrocytomas are the most frequent ones, with various grades of malignacy, from pilocytic astrocytoma (grade I) to glioblastoma (grade IV), the most malignant brain tumor. The incidence of brain tumors has been increased, and no cure exists for them. The use of mathematics and computer models is useful for hypothesis generation on cancer etiology, evolution and prognosis. In this review we try to analyze some of the different growth models applied from mathematics to the biology of brain tumors, like continuum models, the cellular automaton model and the agent-based model.

KEYWORDS: brain tumor, tumor growth model, continuum models, cellular automaton, agent-based model

1. INTRODUCTION

The incidence of primary brain tumors is about 8-10/100.000 people per year. Despite all the efforts to understand the characteristics of brain tumors, their incidence has not been reduced nor has the median survival time. Glioblastoma multiforme is one of the deadliest tumors, with a median survival time of 8-10 months. Due to the invasive nature of these tumors, after surgical removal, the remaining tumor cells in the surrounding brain parenchyma cause tumor recurrence. These tumor cells usually develop resistance to the therapies.

There are many advantages using mathematical and computing models in biology. A mathematical model combined with computational technologies is useful for hypothesis generation and data integration. In addition, the *in silico* experiments are cheaper than the *in vivo* or *in vitro* ones, and they also have faster results. In this review we try to analyze some of the different growth models applied from mathematics to the biology of brain tumors.

2. Continuum models

The first models developed for describing tumor growth were continuum models. They used differential equations to describe the volume or the cell density. A general expression to describe the growth of a biological organism was proposed by Ludwig von Bertalanffy. The idea is that the volume of the organism depends on the rate of growth and the rate of degradation. When we talk about tumor growth, the rate of growth can be described by proliferation and synthesis and the rate of loss can be described by death and degradation. The equation is in the form:

$$\frac{(dV)}{(dT)} = aV^{\alpha} - bV^{\beta}$$

Where V is the tumor volume, a is the rate of growth and b is the rate of degradation. From this

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general equation, two particular cases have been successfully used to describe the tumor growth: The logistic growth equation (α=1; β=2) and the von Bertalanffy growth equation (α=1; β=2) (Figure 1).

In 1825, Gompertz described a new model, currently one of the most often used. The Gompertz equation can be written as:

$$\frac{dV}{dT} = aV - bV\ln V$$

From 1995, a number of papers have been published using the reaction-diffusion equations to describe the glioma growth [1-3]. The equation used by these models can be written:

$$\frac{\delta c}{\delta t} = \nabla (D(x) \nabla c) + \rho c$$

This equation describes how the tumor cell concentration (c(x,t)) changes because of the proliferation (ρ) and the diffusion coefficients (D(x)), the last one representing the motility of the tumor cells.

More recently, Swanson *et al.* [4] have used the same model, with the particularity that they have taken into account the heterogeneity of the brain tissue. Particularly, grey and white matter. They have defined the same net proliferation rate for both grey and white matter, but the diffusion coefficient is larger in white than in grey matter. The scenery of the model is a 3-dimensional representation of the human brain defined by the BrainWeb Atlas (http://www.bic.mni.mcgill.ca /brainweb). They assumed that the tumor is detectable when it has reached a size equivalent to a sphere, with an average diameter of 3 cm and that death occurs when the volume reaches an average diameter of 6 cm.

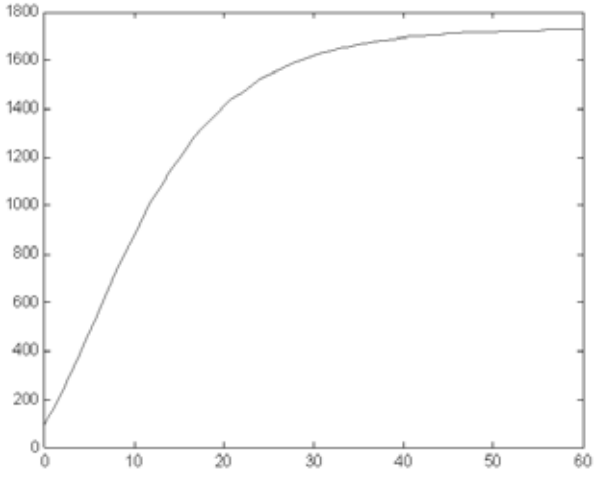

Figure 1. Solution of the Bertalanffy equation with a=4, b=1/3 and V_0=100.

The same group has made improvements on the previous model, concerned by the difficulty of success with chemotherapy in the treatment of gliomas due to the heterogeneity in drug delivery to the different kind of brain tissues [5]. They have started with a model with a homogeneous drug delivery. Here, the chemotherapy is viewed as a loss term, proportional to the number of tumor cells and to the strength or amount of therapy. With this model, they have seen that even with a very effective type of chemotherapy, the tumor continues to grow. To be more realistic, they have implemented another model, taking into account that the drug delivery to the white matter is much less than that to grey matter because of the capillar density. To model it, they implemented the chemotherapy as a function of time and space, making it more efficient in grey matter in proportion to the ratio of capillar density. The result was that the tumor could be eradicated from grey mass while tumor cells in white matter escaped from the chemotherapy, continuing with the tumor growth.

Another example of continuum model can be seen in Kirkby *et al.* [6]. They attempted to create a mathematical model of tumor growth in patients with glioblastoma, in order to predict survival. They wanted to extract biological information from clinical data. They also investigated the effects of the different treatments. Their model represents two kinds of cells: normal and tumor cells. They considered the patient death to be when the number of undamaged normal cells is below a threshold. The rate of damage of normal cells is proportional to the number of normal cells and to the number of tumor cells. The number of normal and tumor cells are modeled by differential equations. To model the radiotherapy, they assumed that a number of exposures are

applied instantaneously and that the same fraction of tumor cells survive each exposure. All the normal cells survive the radiotherapy treatment. The tumor is considered sterilized if the number of tumor cells is less than one after exposure. If the tumor is not sterilized, then the model of tumor growth re-starts with the remaining normal and tumor cells. In order to model a population of patients, they chose the parameters of the model distributed statistically. For each patient, there were 6 parameters to be established: the number of undamaged normal brain cells at presentation, the doubling time of the tumor, the rate constant for damage to normal cells, the delay before treatment is started, the critical size of undamaged brain to die, and the fraction of tumor cells that survive radiotherapy exposure. They selected the patients that were going to be treated, excluding the patients that were deteriorated or that were not going to benefit from the treatment. They calculated the survival time at the moment of the presentation and at the moment of the start of the treatment, and if those times were over a threshold, the patient was selected for treatment. The survival time calculated with their model coincides with the survival data of the Addenbrooke's Hospital.

Discrete models consider cells individually and can simulate their interactions. As described by Deisboeck *et al*. [7]: "A discrete model is often comprised of several states and a number of transitions...". A hybrid approach, combining continuum and discrete techniques can have all the advantages of both techniques and describe the system at all levels. An example of this is the model developed by Sander and Deisboeck [8]. They combined the two techniques in their model based on their clinical studies. In three-dimensional *in vivo* experiments, they noticed that tumors grow following a pattern. In the model, there is a proliferative core where the tumor cells are born and then they spread to the periphery and become invasive more than proliferative cells. They assume that the motion of the invasive cells is due to the chemotaxis. In their experiment, they model two kinds of chemotaxis: the first one was caused by the different concentrations of nutrients in the tissue, and the second one by the homotype attraction. Therefore, the tumor cells can be attracted by a high concentration of nutrients or by other tumor cells. In order to model the motion of the tumor cells they assumed that in absence of forces, the tumor cells move in a random way; this phenomenon is described by a diffusion equation. In order to model the chemotaxis, they used the Keller-Segel equation. They also modeled the nutrient concentration as a diffusion subtracting the consumption of the tumor cells. The model presents a higher nutrient consumption at the surface of the spheroid that acts as a source of tumor cells due to the high level of proliferation. The mobile tumor cells also act as a source of chemoattractant modeled with a diffusion equation. In their discrete approach, they did not model the homotype chemotaxis with a diffusion equation, they considered that each mobile tumor cell leaves a trail that other cells tend to follow. They implemented this phenomenon by multiplying the probability of an invasive cell to jump to a certain place, if this place had been occupied by another tumor cell before.

3. Cellular automaton model

The cellular automaton is a computer model composed by grids of cells. Each cell can be in a finite number of states. A neighborhood is defined for each cell. The state of a cell at a certain moment is determined by some rules depending on the previous state of this cell and its neighborhood. Kansal *et al*. [9] wanted to investigate the brain tumors as a "self-organizing complex dynamic system". They modeled the Gompertzian growth with a cellular automaton. The volume of the tumor coincided with the Gompertz model on each time point. With the simulation, they could obtain important criteria such as the fraction of tumor which is able to divide, the non-proliferative and necrotic fractions, and the rate of growth. Instead of using square or cubic lattices, they used a Voronoi tessellation (Figure 2A) in order to avoid possible artificial anisotropies. The lattice was designed with a variable grid size and the density change with the radius of the tumor. The sites near the tumor center have higher density than the sites at the edge. It represents an ideal tumor consisting on a spherical mass composed by different shells. The core is composed by necrotic cells, another shell with

cells in the G0 cell-cycle state, and the last shell with proliferative cells (Figure 2B). The proliferative cells are evaluated to decide whether they will divide with certain probability. If the cell is selected to proliferate, there is a search for space for the new cell on the shell for proliferative cells.

In a subsequent paper [10] they have extended their model in order to analyze heterogeneous tumors in which sub-populations possess different growth-rates. This model presents two sub-populations: the primary one, present from the beginning and a secondary one arising from a mutation and with the difference of the cell-doubling time. They aimed to study the probability of survival of the secondary strain depending on the relative advantage in growth rate and its starting volume. The secondary population has a mutation related to the cellular division but the same nutritional needs and response to mechanical pressure. The algorithm of the previous work is used at the beginning until the tumor has a pre-determined radius. Then, a single random surrounding cell is mutated from the primary to the secondary strain. They have also studied the cases when two or more contiguous cells are mutated. The proliferation algorithm is run during a pre-determined number of time steps and the second population is checked to determine the survival.

Six years after, Gevertz and Torquato [11] improved the first model of Kansal *et al*. [9]. They wanted to model the vascular growth of a brain tumor with a cellular automaton model. For the vascularitation, they took into account the state of three proteins: vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2). VEGF is responsible for the formation of an immature vascular network, and Ang-1 acts towards its maturation and stabilization. Ang-2 competes with Ang-1 and is responsible for the vessel regression. Vessels are designed as cylinders of radius one lattice. In order to perform an optimum vessel network and supply the maximum number of cells with the minimum number of vessels, there are 3 rules to construct the network: Vessels at the same angle can not penetrate one in the space of the other. A maximum of 2 vessels can intersect at one lattice (if a third vessel is going to intersect at the same point, the length of the vessel should be truncated). A vessel can not be created if it is not going to supply an unvascularized cell. The places at which to start a vessel are selected randomly,

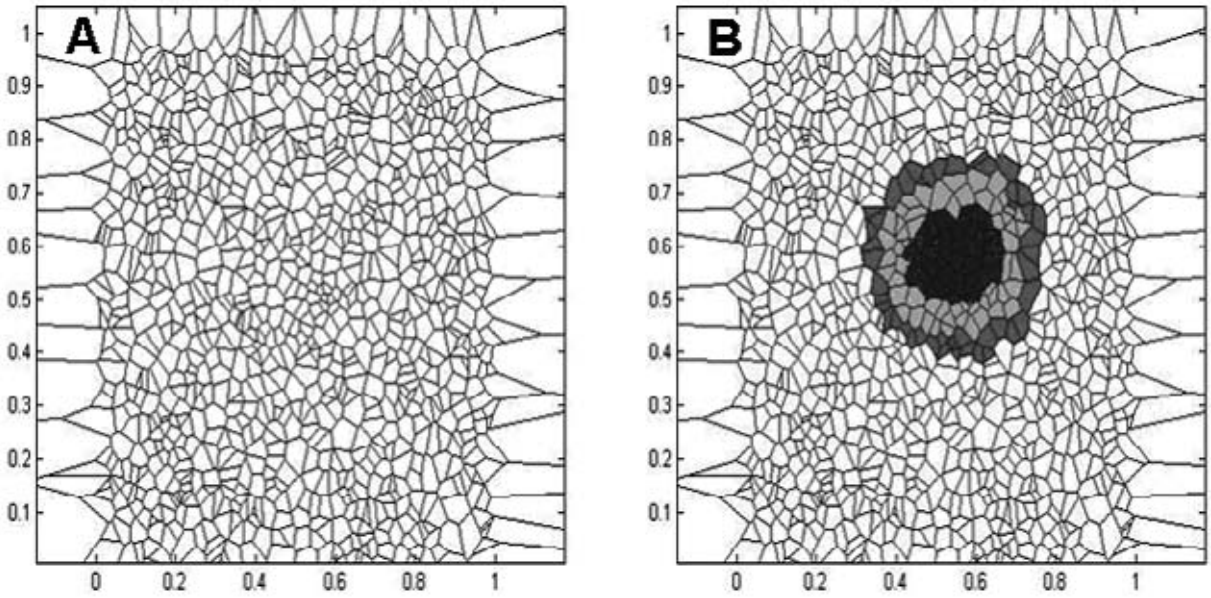

Figure 2. A) Example of a Voronoi Tessellation. B) Representation of a tumor on a Voronoi Tessellation; with a necrotic, a non-proliferative and a proliferative shell.

and a vessel is created at that point unless one of the rules is violated. There are three types of cells: proliferative cells, non-proliferative/hypoxic cells and necrotic cells. Hypoxic tumor cells produce VEGF that is diffused throughout the tissue. Ang-2 is expressed in areas of vascular remodeling, with vessels associated with tumor tissue. Ang-1 is expressed in the healthy tissue. The state and relationships of these proteins are established by differential equations. The main goal was to study the relationship between the levels of the compounds and tumor growth. The levels of VEGF, Ang-1 and Ang-2 are used to decide what happens with the vessels at each lattice vertex. The vessel can regress or sprout in the direction of greatest VEGF concentration.

Schmitz *et al.* [12] attempted to study the treatment resistance in glioblastoma. They have improved the first model of Kansal *et al.* [9]. The original model had 3 parameters: the rate at which the proliferative cells divide, the nutritional needs of the non-proliferative and proliferative cells, and the response of the tumor to mechanical pressure within the skull. In the new model, they have added three more parameters: the sensitivity at each instance of treatment for the proliferative and the non-proliferative cells, and the mutational response of the tumor to treatment. They began the simulation with a spherical tumor of 4 mm radius, representing a glioblastoma after successful surgical resection. The proliferation algorithm was similar to the one in the original paper [9]. The algorithm was performed for 4 weeks of tumor development simulation, and then a treatment algorithm was added. In the treatment algorithm, every proliferative cell was checked to decide whether it had been killed by the treatment with a given probability. If a proliferative automaton cell dies, it is converted into a healthy cell. Then the non-proliferative cells were checked with another probability of being killed by the treatment because it is known that quiescent cells can avoid the effects of chemotherapy. At this step, the non-proliferative cells that survived were checked to see whether they could be converted into proliferative cells. Finally, the proliferative cells were checked to determine whether they would suffer a mutation that changes its treatment resistance.

Aubert *et al.* [13] studied the diffusion properties of glioma cells during migration. They did a previous *in vivo* experiment with a human glioma cell line (GL15). They took 4 pictures at different stages and studied the density profiles and the velocity and paths of the migrating cells. For the computering model, they chose the hexagonal lattice because of its isotropy. The center of the lattice was occupied by the glioma cell spheroid. From this center, an unlimited number of cells were going to be ejected. When there was a free position in the hexagons surrounding the center, it was occupied by a tumor cell ejected from the center. They did not take proliferation into account because they considered that it was canceled by apoptosis. To model the attraction between tumor cells, they favored the movement to positions adjacent to an occupied cell. They also modeled the effect of the inertia, so the cells had to move in the same direction, allowing only the movement to the three hexagons in the forward direction.

Two years later, they improved their previous model to add some characteristics [14]. They wanted to study the hypothesis given by some studies that the tumor bulk acts as a chemorepellent due to the toxic factors produced by necrotic cells. First of all, they decided to change the tessellation because of the problems of symmetry of the hexagonal one. They wanted to use a Voronoi tessellation but they wanted to preserve the number of neighbors for each cell near to six. The solution was to start with a hexagonal tessellation, and perturb the position of each cell, obtaining a Voronoi tessellation with polygons of comparable size. They modeled the chemorepellent action of the tumor bulk with a central source of toxic and a diffusion coefficient. They assumed that the migration is in the direction of decreasing gradient of the chemo-repellent. The chemorepellent concentration on the place where the cell is, and the concentration on the possible places to go, were evaluated, and the probability of a tumor cell to migrate to that place was proportional to the difference between them. When a cell was selected to move, one of the neighboring places was randomly selected; the cell only moves if this place satisfies the rules of cell interaction and chemorepellent action.

4. Agent-based model

One of the most used hybrid models is the agent-based model. An agent-based model is a computational model used to simulate the interactions between different agents and also between the agents and the environment. Once the characteristics of the environment are defined, the agents can take decisions depending on the environment and on the characteristics of the rest of the agents. With this model, it is easy to see how the actuation of each agent can influence on the whole system fitness. This model has been used in biology to study the behavior of different populations of animals or for epidemics. When this model is used to model the growth of a tumor, each tumor cell is represented by an agent. They can be divided into different subpopulations with different behaviors. With each program iteration, the cell analyzes the environment (nutrients, oxygen or different molecules) and the situation of the rest of the cells, and decides what to do in order to survive in collaboration with the others. For example, the cell can decide to migrate, proliferate, be quiescent or die.

A lot of package software exists for implementing an agent-based model. One of them is Netlogo. In this program we can find an example of tumor growth model. The model starts with a stem cell represented in black color (Figure 3A). The stem cell can be divided into two stem cells or into one

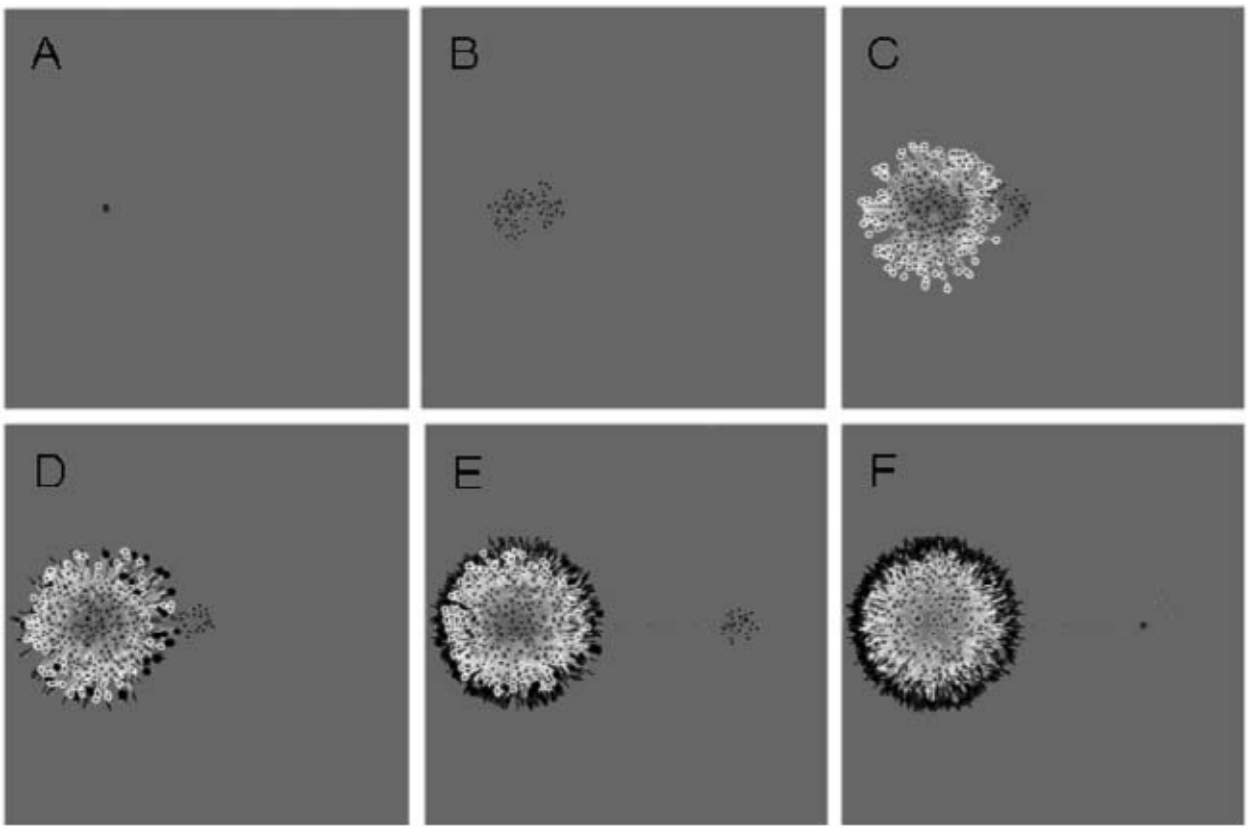

Figure 3. A) First stem cell. B) First tumor stage. C) Evolution of tumor growth. D) First transitory cells start to die. E) A metastatic colony of cells appears. F) The young transitory cells have been killed. The model itself and for the NetLogo software can be checked at: -Wilensky, U. (1998). NetLogo tumor model. http://ccl.northwestern.edu/netlogo/models/Tumor. Center for Connected Learning and Computer-Based Modeling, Northwestern University, Evanston, IL. - Wilensky, U. (1999). NetLogo. http://ccl.northwestern.edu/netlogo/. Center for Connected Learning and Computer-Based Modeling, Northwestern University, Evanston, IL.

stem cell and one transitory cell (Figures 3B and 3C). The transitory cells die at a certain number of divisions. Necrotic cells are represented in black (Figure 3D). They also represent metastasis with a colony of transitory cells advancing to distant places (Figure 3E). You can play with the model by killing transitory or stem cells, modeling processes as chemotherapy, in which transitory cells are killed but stem cells continue expanding the tumor. In Figure 3F, the young transitory cells have been killed.

One of the first studies of cancer using an agent-based model was developed by Maley and Forrest [15]. Based on the idea that different cancers come from a different set of mutations in the cells, they saw each tumor as unique, thereby needing a specific treatment. With their agent-based model they aimed to study the probability of developing a cancer and to also present a hypothesis regarding the genetic nature of cancer. They studied two important characteristics of cancer: genetic instability and uncontrolled proliferation. They developed a two-stage model (precancerous and malignant), so they needed at least six rate parameters: the rate of cells changing from normal state to precancerous state, the rate of reproduction of precancerous cells, the rate of loss of precancerous cells, the rate of cells changing from precancerous to malignant state, the rate of reproduction of malignant cells, and the rate of loss of malignant cells. They chose a two-dimensional, discrete-event model; each cell was represented by an agent and stored the following information: the number of selective mutations it has suffered, the number of neutral mutations, whether or not it has suffered a mutation that increases its mutation rate, and the number of time steps until it divides. On each iteration, approximately half a day, the population of cells was updated serially. The proliferation has a normal probability distribution with a mean of 8 time steps (4 days) and standard deviation of 2 time steps (1 day). Each selective mutation has the effect of increasing the replication rate of the cell. They simulated 74 years, approximately a human life and corrected the parameters until the model fitted with the real probabilities for humans to develop a cancer in their life.

Mansury *et al*. [16] wanted to study the spatio-temporal migrations in a brain tumor due to the importance of tumor cell invasion that makes it impossible to remove all of the tumor, with bad consequences for patient diagnosis. They developed an agent-based model in which tumor cells are agents interacting each other and with the environment. This model aims to simulate the behavior of small tumor cell colonies undetectable by a microscope. They developed a previous *in vitro* assay in order to assess the behavior of the tumor cells in the presence of a heterotype attractor. Their observations were used to model the capabilities of the *in silico* cells in the agent-based model by giving them the ability to recognize the best place to live depending on the environment characteristics such as blood vessels or toxic metabolites. The proliferation is modeled as an stochastic process in order to represent the fact that a favorable location is not enough of a condition for proliferation. They also modeled the mechanical resistance of the tissue for the cells to migrate. The environment is a 2D torus of grid lattice that contains 50x50 locations to represent a ‘‘2D’’ virtual brain tissue slice. At the beginning, the nutrients are distributed as a gaussian distribution and they are non-replenished. At the initial state, the model has 10 agents representing tumor cells. These cells are placed on the quadrant opposite to the maximum level of nutrients. At each moment, the level of nutrients is decreased proportionally to the number of cells at each location. A level of toxicity metabolites is also represented at each location and is increased proportionally to the number of cells at that location. The tissue presents a mechanical confinement, representing the energy that a cell consumes migrating through the tissue, and it is different at each point, resembling a gaussian distribution with the maximum resistance at the maximum level of nutrients. At each iteration, a cell is selected and evaluated for performing three possible actions: migration, proliferation or death. Cell death has a probability distribution proportional to the level of toxicity at its location. If the cell is not selected to die, then the cell is evaluated to proliferate with a probability that increases with higher levels of nutrient, but only if the cell is part of a cluster and if it is on the surface of the cluster. If a cell is selected to proliferate, then a daughter is created and posed in the same location. If the cell is not selected to

proliferate, then it is evaluated to migrate, only if it is placed on the surface of a cluster. To find the best location to migrate, the cell implements two different algorithms. A global algorithm evaluates every position in the tissue, depending on the number of cells in that location (cells prefer to be with other cells because tumor cells produce protein growth factors, but they avoid a location that is overcrowded), the number of cells in the current location, the distance between the two locations, and the energy costs of going from one point to the other depending on the mechanical confinement. The other algorithm is local and evaluates only the cell neighborhood in order to find the exact location to move to. The evaluation is based on the nutrients, toxicity, mechanical resistance and the number of tumor cells in the current and the new location to migrate.

Four years later, Mansury *et al*. [17] improved their model by introducing the evolutionary game theory. The game theory studies the strategies in a situation when the decision of an agent influences the fitness of the others. This theory was applied to biology with the name of "evolutionary game theory". John Maynard Smith won the Crafoord prize for his work in this field. In this model, there are two types of tumor cells. Type A are more proliferative cells and type B are more migrative cells, although type A cells can also migrate and type B cells can also proliferate. These cells must cooperate when they are in a group in order to be stronger but at the same time, they have to compete for the locations with more nutrients. The interactions among cells means different benefits or losses (payoffs) depending on the type of cells that are interacting. They define three kinds of payoffs: proliferative capability, cell-cell gap-junction communication (GJC), and migratory capability. According to *in vivo* experiments, they knew that interactions among proliferative cells involve stronger gap-junction communication, so they modeled the highest levels of communication when there was an interaction between type A cells followed by an interaction between type A and type B, and finally type B with type B. They also know that when there are strong GJC levels, proliferation is reduced. It means that an interaction with a type A cell will end in a high reduction of its proliferation. For a study on the relationship between GJC and migration, they also know that the fastest cells are the ones with least connexion. According to these statements, they have defined the payoffs of the interactions of each kind of cells in terms of connexion, proliferation and migration, and they have incorporated these payoffs into the probabilities of proliferation and migration in the decisions made by the agent-based model.

Zhang *et al*. [18] implemented a multiscale agent-based brain tumor model, not only in the cellular but in the molecular scale. Each cell is equipped with an epidermal growth factor receptor (EGFR) network in order to study whether or not it could be responsible for the decision of a cell to migrate or proliferate by activating the signaling protein phospholipase Cγ (PLCγ).

It is a three-dimensional model: a grid with 100x100x100 points each one with a level of TGFα, glucose and oxygen tension. The TGF and glucose are consumed by the cells and replenished depending on their diffusion coefficient. There can be only one cell in each grid position. The model is initialized with five hundred tumor cells at the center of the cube opposite to the one with the highest level of glucose, TGFα and oxygen tension. To describe the EGFR network, each tumor cell has four layers: the external space, the cell membrane, the cytoplasm, and the nucleus. The EGFR network is modeled by differential equations. As a result of the interactions in the network, a level of concentration of PLCγ is obtained, and depending on whether it excesses a threshold or not, the cell decides to migrate, proliferate or be quiescent coinciding with the results from previous works. Cells enter the reversible quiescent state if they do not find a location to migrate or proliferate, or depending on the levels of glucose concentration and Phosphorylated active dimeric TGFα-EGFR cell surface complex.

In 2009, the same group extended the three-dimensional multiscale model [19]. The environment represents a slice of brain tissue by a 100x100x100 lattice, with a replenished nutrient source as a blood vessel that supplies glucose, TGFα and oxygen. At the beginning, these chemo-attractants are dispersed by normal distribution. There can be five different cell clones, whose

difference is their EGFR receptor density, for modeling some results observed from their experimental data. They have observed that cell clones with higher EGFR receptor density are more aggressive and they can move faster along the environment's least resistance because of higher search precision. They also demonstrated that cell clones with high EGFR receptor density have a lower proliferation rate. Depending on the concentration level of TGFα at the cell location, the cell can move to a different defined neighborhood, increasing the spatial permission with higher levels of TGFα concentration. It reflects the progressive loss of tumor cell adhesion. Each cell clone type can mutate only to the next type with higher EGFR receptor density.

ACKNOWLEDGEMENTS

Authors are grateful to Laura Stokes for help with editing the manuscript. MP Arrastia was a fellow of the Departamento de Innovación, Empresa y Empleo del Gobierno de Navarra, Pamplona, Spain. JS Castresana is funded by the Departmento de Salud del Gobierno de Navarra, Caja Navarra, and Fundación Universitaria de Navarra, Pamplona; and by the Fondo de Investigación Sanitaria, Madrid, Spain.

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