

## A Bistable Field Model of Cancer Dynamics

C. Cherubini<sup>1,2,\*</sup>, A. Gizzi<sup>1,3</sup>, M. Bertolaso<sup>4</sup>, V. Tambone<sup>4</sup>  
and S. Filippi<sup>1,2</sup>

<sup>1</sup> *Nonlinear Physics and Mathematical Modeling Lab, University Campus Bio-Medico, I-00128, Via A. del Portillo 21, Rome, Italy.*

<sup>2</sup> *International Center for Relativistic Astrophysics-I.C.R.A., University of Rome "La Sapienza", I-00185 Rome, Italy.*

<sup>3</sup> *Alberto Sordi Foundation-Research Institute on Aging, I-00128 Rome, Italy.*

<sup>4</sup> *Institute of Philosophy of Scientific and Technological Activity, University Campus Bio-Medico, I-00128, Via A. del Portillo 21, Rome, Italy.*

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**Abstract.** Cancer spread is a dynamical process occurring not only in time but also in space which, for solid tumors at least, can be modeled quantitatively by reaction and diffusion equations with a bistable behavior: tumor cell colonization happens in a portion of tissue and propagates, but in some cases the process is stopped. Such a cancer proliferation/extinction dynamics is obtained in many mathematical models as a limit of complicated interacting biological fields. In this article we present a very basic model of cancer proliferation adopting the *bistable* equation for a single tumor cell dynamics. The reaction-diffusion theory is numerically and analytically studied and then extended in order to take into account dispersal effects in cancer progression in analogy with ecological models based on the porous medium equation. Possible implications of this approach for explanation and prediction of tumor development on the lines of existing studies on brain cancer progression are discussed. The potential role of continuum models in connecting the two predominant interpretative theories about cancer, once formalized in appropriate mathematical terms, is discussed.

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\*Corresponding author. *Email addresses:* c.cherubini@unicampus.it (C. Cherubini), a.gizzi@unicampus.it (A. Gizzi), m.bertolaso@unicampus.it (M. Bertolaso), v.tambone@unicampus.it (V. Tambone), s.filippi@unicampus.it (S. Filippi)

## 1 Introduction

The quantitative description of the form development in living beings is a central problem in Biology. The process of animal growth, or morphogenesis, occurs in Nature in a variety of shapes and patterns which seem to have typical regularities, as pointed out one century ago by Darcy Thompson in his classical work "On Growth and Form" [1]. Some biological populations of fungi and amoebae appear aggregated in complicated structures which often have a spiralling shape, but spirals of action potential are experimentally observed also in cardiac cell tissues and even in neural ones [2–5]. In plants complicated morphogenetic processes occur in the developmental process of *kinetic phyllotaxis* [6]. Finally it's worthwhile to notice that spiral waves appear not only in biological systems but also in unanimated ones as the chemical reactions of Zhabotinsky-Belousov type or the gaseous eddies in the atmosphere [4]. All of these different phenomenologies are seen as non-equilibrium thermodynamical processes which can be subject to complicated bifurcations in their dissipative dynamics [7–9] and which can be mathematically described, provided specific technical *caveats* regarding the validity of the continuum hypothesis, by systems of equations of Reaction-Diffusion (RD) class [4]. This type of partial differential equations have represented historically and still represents today a proper tool to deal with non-equilibrium chemical dynamics in fact (in particular when phenomena like oscillations, waves, pattern formation and turbulence occur). Alan Turing in the Fifties formulated an elegant theory for animal coats and morphogenesis using RD equations [10], so it appeared plausible to extend his successful theory to cancer growth processes whose understanding represents still today a major challenge for Biology [11]. Cancer is commonly believed to be a disease that begins at the cellular level. Its development is related with somatic mutations which are transferred from a cell to its progeny, bypassing controls of the immune system and being responsible then for the neoplastic phenotype. Therefore the initiation of cancer is mainly seen as a mutation that involves a set of regulatory genes [12], which either enhance or inhibit malignant properties.

On the other hand, tissues are relatively ordered complex structures which generate forces due to the adhesion between cells, the adhesion between cells and the extracellular matrix that surrounds them and the global property of the tissue itself. These interactions together with biochemical and electrical signals, contribute to the shape of the tissue and can even determine the cellular fate [3]. Cell-to-cell and/or tissue-to-tissue communication represent fundamental aspects which contribute to tissue organization then and their failure can generate cancer [13, 14]. Specific substances (morphostats) analogous to Turing morphogen fields drive this communication: their local concentrations in particular influence the phenotype of neighboring regions of tissue around the specific cell taken in considerations. Some substances which have the properties of the morphostats have been recently identified [15] but it is still unclear their hierarchy, and in particular the way in which they promote carcinogenetic processes. One can interpret these results using the most diffused paradigm in cancer dynamics, the Somatic Mutation Theory (or SMT) which proposes that successive DNA mutations in a single cell cause cancer cell

proliferation placing carcinogenesis at the cellular and subcellular hierarchical levels of biological complexity [16] (a paradigm which in short sounds as "the cell is all"). In some sense this epistemological approach, transferred to the different scenario of Condensed Matter Physics (or Chemistry) could read as "single atoms are everything", which clearly is in contrast with the fact that matter is made by molecules which get organized in larger spatial ordered or disordered structures accounting for very different (and at a first glance unexpected) macroscopic properties. This analogy suggests that in cancer dynamics too spatial organization must be considered. This point of view is taken into account in another paradigm, the Tissue Organization Field Theory (or TOFT) of carcinogenesis and neoplasia. Here in particular carcinogens would act initially by disrupting the normal interactions that take place among cells in the parenchyma and stroma of an organ (the equivalent of the "morphogenetic fields" of developing organisms) [17]: perturbations in a morphostat gradient could initiate then carcinogenesis without any requirement for a mutation [18]. Nevertheless diffusive effects seem to be relevant, from a biological point of view, also at sub-cellular level as recent studies on the telomere dynamics performed in live human cancer cells have shown [19]. In this sense the reaction and diffusion mathematical point of view adopted in this article can be seen as a tool to deal with the same problem observed at different scales (a *multiscale* approach) for which a continuum mathematical theory remains valid. TOFTs main contribution has been to put the question about the right level of inquiry in experimental research and to have proposed one (tissue organization) for the neoplastic phenomenon that seems to be consistent with empirical data and evidences. In this scenario it is possible in any case the epistemological contribution of SMT admitting that a discrete component is also present and active in the dynamics of cancer spread, in this case cells.

We point out that such an idea of a field theory of cancer development is very appealing from the point of view of mathematical modeling. Solid tumor proliferation can be seen in fact as an abnormal morphogenetic process *a la Turing*, consequently it appears straightforward the idea of modeling this nonlinear diffusive biological phenomenon with the RD mathematical theory. On the other hand however SMT view is not absolutely ruled out by this choice when the challenge is to take into account the whole phenomenology of such a complex natural phenomena as cancer is.

As it will appear clear in the following, a reaction-diffusion equation shall account for both the diffusive gradients required by tissue organization previously discussed (clearly evidenced by TOFT) and local reactive cellular dynamics both of genetic (evidenced by SMT) and/or of environmental nature (again stressed by TOFT) performing an integration in this way of different existing theories on cancer [20]. In the simplest scenario a mathematical cancer model should manifest bistability. This is a critical behavior for the dynamics of a system which can choose in its evolution to settle down on one of two possible states. In an elementary picture justifying this choice, there is a threshold of cancer cells density (which should be patient dependent), which locally drives the normal tissue on a cancer cell regime or does not admit cancer to colonize the tissue so that this remains tumor-free (this is, mathematically speaking, a "reaction term"). A diffu-

sive contribution makes cancer cells move around leading to a not only time but also space dependent problem. While continuum models (ordinary, partial or integro-partial differential equations or delay equations) can describe very well this cancer dynamics, also discrete models (cellular automata) seem to lead to positive results towards a possible understanding of carcinogenesis [18]. This is not unexpected in fact because discrete models (as cellular automata are) and continuum diffusion processes share many common features in modeling nonlinear chemical and biological media [21,22]: in particular continuum field theory can be seen as continuum limit of collective discrete behaviors. Mathematical modeling of bistability in cancer dynamics dates back to Lefever and Hors- themke work [23] although in the last thirty years many progresses have been done in this area (see as an example [24] for a recent review on mathematical models). In exist- ing models bistability results as a consequence of complicated non-polynomial reactive terms.

In this article instead we shall introduce and discuss a very basic model of reaction- diffusion bistability based on a cubic nonlinear diffusion equation only. This is inspired by theoretical works calibrated on experimental data of brain tumor (see specifically [3, 25–30]) through a single linear or nonlinear diffusion equation for cancer cells. Assuming a relatively simple mathematical form, these pre-existing studies have shown a great rele- vance for surgery due to the unpleasant and dramatic recurrences of brain tumors. Given a certain volume of brain tissue resection in fact, it is possible to predict the amount of time required by the low density infiltrated tumor cells far afield from the gross tumor site to cause a large cancer again. In this way the surgeon can perform a balanced pre- diction optimizing the amount of tissue removed in union with the quality of life left to the patient. We shall frame our work on the lines of this type of studies then. To this aim however we shall need to introduce a short review of the mathematical aspects of RD processes first, as done in the next section.

## 2 Reaction-Diffusion systems

Reaction-Diffusion equations are mathematical models of parabolic type which describe the nonlinear concentration dynamics of one or more chemical substances. Differently as in standard global chemical kinetic problems, here the model allows the chemical species not only to locally react but also to spatially diffuse one through the others. In a biological context instead RD systems describe fields of activators and inhibitors (in the language introduced by Alan Turing in [10]) which compete to give peculiar patterns (the animal coat pattern theory) or even forms for the living beings (in Turing's original article the problem of gastrulation or of the form of an hydra). Here we present the prototype of reaction-diffusion equations which assumes two variables only together with homoge- neous and isotropic diffusion. The equations in this case result in:

$$\frac{\partial u}{\partial t} = D_1 \nabla^2 u + f(u, v), \quad \frac{\partial v}{\partial t} = D_2 \nabla^2 v + h(u, v), \quad (2.1)$$

where  $f$  and  $h$  can have polynomial form in  $u$  and  $v$ , although more complicated functional dependencies (even on space and time) are allowed. Here  $D_1$  and  $D_2$  are the diffusion coefficients and  $\nabla$  is the gradient operator while  $\nabla^2$  represents the Laplacian one. In general, models with two species only represent a simplification of more realistic situations in which several diffusing and reacting species can interact. Moreover by coupling these models with temperature [31, 32] and mechanical deformations [33, 34] one can match even more the simulations with realistic biological problems. In the past, Turing showed that RD systems can be affected by the so called diffusion-driven instability (or Turing instability) which means that if the homogeneous state is stable against small perturbations in absence of diffusion, it may become unstable if the possibility of diffusion is introduced. This dynamical mechanism generates quasi-stationary spatial patterns although this type of equations can also lead to morphogenetic, chemical or electrophysiological waves [3]. Coming back to the model, an even simpler reaction-diffusion model can be obtained suppressing one of the two species in Eq. (2.1) (say field  $v$ ) and assuming a simple cubic polynomial form for the function  $f(u)$  which could be seen as a Taylor expansion of more complicated functional dependencies, in analogy with FitzHugh-Nagumo type models of electrophysiology and physical chemistry [3, 35]: this is the well-known bistable equation discussed in detail in the following.

### 3 A bistable model for cancer cell waves

The most generic one species reaction-diffusion equation is

$$\partial_t c = \underbrace{F(c)}_{\text{Reaction}} + \underbrace{\nabla \cdot (\hat{D} \nabla c)}_{\text{Diffusion}}, \quad (3.1)$$

where we identify for our purposes the field  $c$  with the tumor cell punctual concentration embedded in a pre-existing normal tissue and  $\hat{D}$  is the diffusion tensor which in the most general scenario can depend by time and space (anisotropic and inhomogeneous diffusion). In this article however we shall assume for the sake of simplicity homogeneous and isotropic time independent diffusion first so that we can rewrite

$$\nabla \cdot \hat{D} \nabla c \equiv D \nabla^2 c,$$

where  $D$  is the diffusion constant. The term  $F(c)$  on the other hand takes into account the local dynamical properties of the system (reaction term) although one may extend the treatment assuming  $F = F(c, t, \vec{x})$ , which gives heterogeneities of different physical nature (chemical, biological, physical). Finally one may could have easily added on this reactive term of Eq. (3.1) an external time and space dependent stimulus which in our specific biological problem can account for possible external actions (chemotherapy as an example). We have under-braced explicitly in Eq. (3.1) the reactive and diffusive terms respectively. While the diffusive part can be seen as a typical TOFT quantity, the reactive

one, in the most general heterogeneous externally perturbed scenario, can contain both a genetically driven dynamics and an environmental factor: this modelization meets then both TOFT and SMT points of view about cancer origin. In mathematical terms, in absence of diffusion we have a dynamical system with one degree of freedom (an Ordinary Differential Equation), while the introduction of diffusion leads immediately to an infinite degrees of freedom problem (this is a Partial Differential Equation problem in fact) where the nonlinear parabolic character of the problem accounts for spatial communication and then possible global organization. We are ready now to specialize Eq. (3.1) to a particular case, i.e., the bistable one, which requires for this equation a functional form  $F(c) = k(c - c_1)(c - c_2)(c_3 - c)$ , where  $k$  is a model constant and  $c_1$ ,  $c_2$  and  $c_3$  are constant concentrations which may be genetically determined but also environmentally affected. We assume that a cancer-free tissue must have no cancer cells so we select  $c_1 = 0$ . Quantity  $c_2$  instead represents the cancer generation threshold while  $c_3$  is the maximum value of cancer cells which a tissue can support (possible necrosis effects lowering the tumor cell population are not taken into account here for the sake of simplicity). This equation must be cast now in non-dimensional form: this step is crucial because removes from the model the specifications of the particular tissue and cancer leading to a more general formulation. Following standard Literature [35], we introduce a typical length scale  $L$  of the process in consideration (working for the sake of simplicity in one spatial dimension first) and we define the non-dimensional quantities  $T = tD/L^2$  and  $X = x/L$ . We use moreover the scaling  $c_2 = \alpha c_3$  with  $0 < \alpha < 1$ , adopting a dimensionless concentration  $C = c/c_3$  then and defining the quantity  $a = c_3^2 L^2 k/D$ . The resulting equation is:

$$\frac{\partial C}{\partial T} = \frac{\partial^2 C}{\partial X^2} + F(C), \quad (3.2)$$

with the functional form

$$F(C) = aC(1 - C)(C - \alpha) \quad (3.3)$$

with  $C = 0$  and  $C = 1$  being sinks and  $C = \alpha$  being a source [36]. The process of adimensionalization performed has a great advantage that one can study now the dynamics of the problem forgetting about the physical context we started from. The result obtained with the new compact equations can be later re-converted then to dimensional quantities recovering the contact with experiments. This is a well known point of view adopted both in chemistry and in electrophysiology. In the latter case, as an example, the FitzHugh-Nagumo equation (which is an extension in a two dimensional phase-space of the bistable equation just described), once solved in a specific dimensionless case can be differently framed in the context of heart, nerves or even intestine dynamics [35] through specific dimensional mappings of space, time and action potential. We point out that, all of these examples have different time, space and action potential scales. For this reason, in this article we shall present mainly the general outcomes expected studying the non-dimensional theory, leaving to future studies the accurate analysis of mapping the

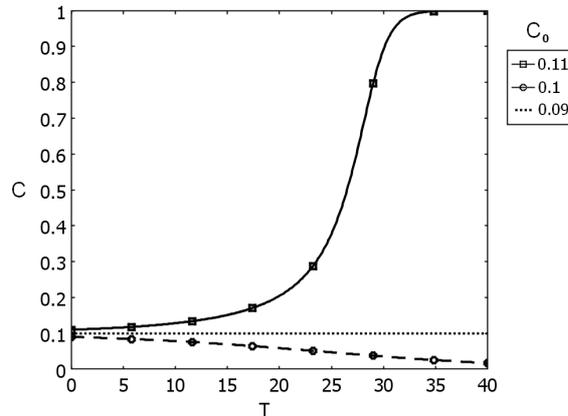


Figure 1: Bistable dynamics of the zero dimensional model with three different initial conditions: i)  $C_0 \equiv C(0) = 0.11$  (above the threshold  $\alpha$  which implies cancer development); ii)  $C_0 = 0.1$  (on the threshold which implies a (metastable) constant in time dynamics) and finally iii)  $C_0 = 0.09$  (below the threshold which implies cancer rejection by tissue).

parameters with specific tumor growth processes and for different tissues. Higher dimensional spatial cases require the addition to this equation of the second derivative terms with respect to  $Y$  and  $Z$ . We point out that our treatment is quite different with respect to the standard Verhulst logistic behavior commonly used to model cell growth [3,24,35,36]: here in fact we have a cubic behavior while in that case a quadratic one is adopted, missing completely the threshold effect. Locally, i.e., neglecting the spatial variations, we obtain the ordinary differential equation  $dC/dT = F(C)$  which is, in the language of dynamical systems, a flow on a line. Such a type of equation cannot have periodic solutions (unless the domain is topologically bent to form a circle [36]) and once integrated (we assume here and in the rest of the paper  $a = 1$  and  $\alpha = 0.1$  which is a typical choice found in the literature of bistable equation simulations [35]) results in three type of possible solutions shown in Fig. 1: i) a solution which starting over the threshold  $\alpha$  reaches asymptotically the maximum value  $C = 1$ , ii) a solution starting on the threshold which is stationary in time and iii) a solution starting below the threshold which asymptotically goes to zero.

Reintroducing diffusion we have a partial differential equation which as discussed before, has infinite degrees of freedom and can lead in fact to more involved situations in which diffusion plays a central role. Manipulations of the one-dimensional diffusing case in Eq. (3.2) lead to the analytical travelling wave solution for the bistable equation associated with specific initial data and boundary conditions (well known in the literature) [35]

$$C(T, X) = \frac{1}{2} + \frac{1}{2} \tanh \left[ \frac{\sqrt{a}(X + VT)}{2\sqrt{2}} \right], \quad V = \frac{\sqrt{a}}{\sqrt{2}}(1 - 2\alpha). \quad (3.4)$$

It is clear the wave type behavior of this solution which travels at constant speed (de-

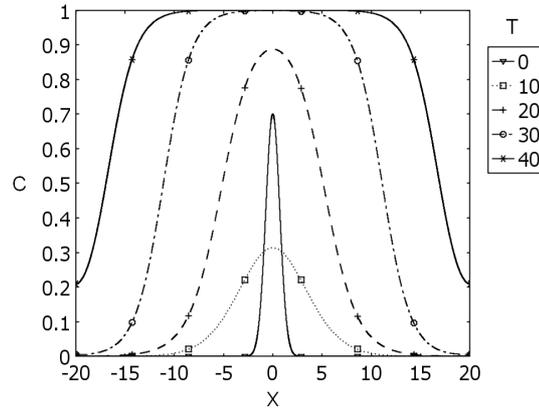


Figure 2: Spatial cancer progression in time on a linear tissue domain (dimensionless units). For the fixed threshold and initial data (see text) cancer front blows down but then recovers and colonizes the entire tissue.

pending by parameters  $a$  and  $\alpha$ ) transferring cancer to not invaded tissue regions. In more general situations associated with complicated initial data and boundary conditions however analytical solutions cannot be found anymore and the equations must be numerically integrated, leading to even more interesting scenarios. To this aim, we have performed an integration of the 1D bistable equation (3.2) on the domain  $X \in [-20, 20]$  (dimensionless units) with Neuman zero flux boundary conditions,  $\alpha = 0.1$ ,  $a = 1$  together with initial data  $C(0, X) = 0.7 \exp(-x^2)$  first. In all the simulations performed we have adopted a finite element scheme using quadratic Lagrange elements with size  $\delta x = 0.005$  together with a direct solver (UMFPACK) running on a parallelized Comsol Multiphysics engine with relative and absolute errors of  $10^{-6}$ . Simulations have been tested also for finer spatial meshing in order to ensure convergence and stability.

In Fig. 2 we show superimposed at different times the behavior of the tumor cell concentration on the line of tissue. At  $T = 10$  the concentration apparently gets lowered but at time  $T = 20$  it starts to rise again. At  $T = 30$  the central part reaches the maximum value of tumor cells and at late times the entire tissue domain gets invaded.

On the other hand starting with a lower initial cancer cell concentration, i.e.,  $C(0, X) = 0.3 \exp(-x^2)$ , the cancer colonization fails (see Fig. 3). It appears clear that such a diffusion driven mechanism is quite delicate in generating a tumor scenario or not, depending in fact on the total (non-dimensional) tumor mass amount  $M = \int C dX$  evaluated on the whole tissue domain at the initial time. The initial conditions which can generate a full tumor outcome represent then a delicate problem to be addressed requiring advanced mathematical methods of dynamical systems (for a specific discussion of this point see [35] on pp. 275). In this article on the other hand we have preferred to study this point by performing selected *ad hoc* numerical simulations which can give us some hint on the role of cancer cells density peaks and in particular of their distance. To this aim we have extended our study to a two dimensional squared domain of  $20 \times 20$  area (in dimensionless units). The code uses similar settings as the one dimensional case but

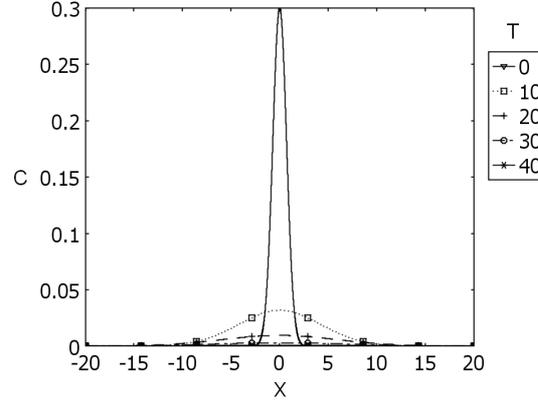


Figure 3: Spatial cancer no-progression in time on a linear tissue domain (dimensionless units). For the fixed threshold and initial data (see text) cancer front blows down and tissue remains cancer cell free.

regarding the meshing we have adopted squared sized (side length  $\delta x = 0.25$ ) Lagrange cubic elements.

Results of the simulations are shown in Fig. 4. We have taken an initial data adding several distorted Gaussian functions centered at different points. In this approach, for a fixed choice of model constants  $\alpha$  and  $a$ , there are clearly three critical parameters which can affect the entire dynamics: the Gaussian peak amplitudes, their widths and finally their distance. In our case we have chosen specifically:

$$C_0 = 0.8e^{-0.1(x-1)^2 - 0.3(y-3)^2} + 0.75e^{-0.25(x-10)^2 - 0.15(y+9)^2} + 0.6e^{-0.2(x+3)^2 - 0.5(y+4)^2} + 0.5e^{-0.25(x+5)^2 - 0.3(y-1)^2} \quad (3.5)$$

and left it free to evolve. The remaining panels of Fig. 4 show the cancer spread and finally a large scale invasion dynamics. We have performed also a more simplified study in order to understand if two over-threshold cell colonies of Gaussian form may lead to a tumor progression or extinction scenario depending on the distances of their peaks only. To this aim we have taken as initial data

$$C_0 = 0.61e^{-0.1(x-4)^2 - 0.3y^2} + 0.61e^{-0.1(x+4)^2 - 0.3y^2}, \quad (3.6)$$

which has lead to a final tumor progression as shown in Fig. 5.

On the other hand the initial data

$$C_0 = 0.61e^{-0.1(x-6)^2 - 0.3y^2} + 0.61e^{-0.1(x+6)^2 - 0.3y^2} \quad (3.7)$$

has not given any tumor progression as shown in Fig. 6. These results suggest that the nonlinear interaction of the two waves leads to a critical configuration which has cancer as an outcome, while if the two distorted Gaussian colonies are slightly more distant, the nonlinear mechanism is not sufficient to maintain the developmental process and the

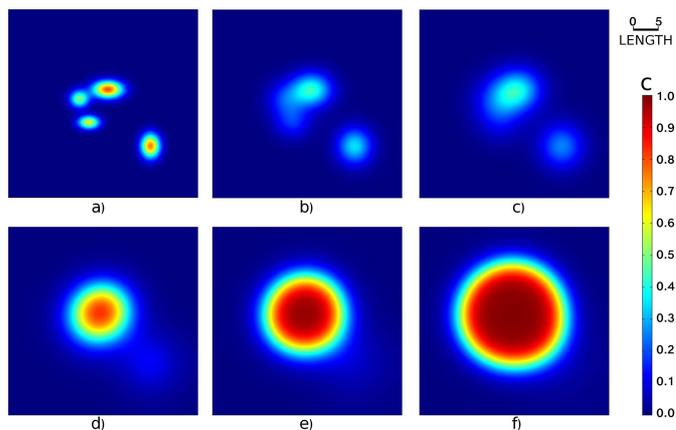


Figure 4: Spatial cancer progression at different times on a two-dimensional tissue domain (dimensionless units). Labels a) to f) stand for snapshot times of  $T = (0, 2, 6, 15, 21, 27)$ . Starting from a relatively irregular inhomogeneous initial data (see text), some cancer regions tend to blow down, but at the end one of the peaked populations is able to colonize the entire tissue.

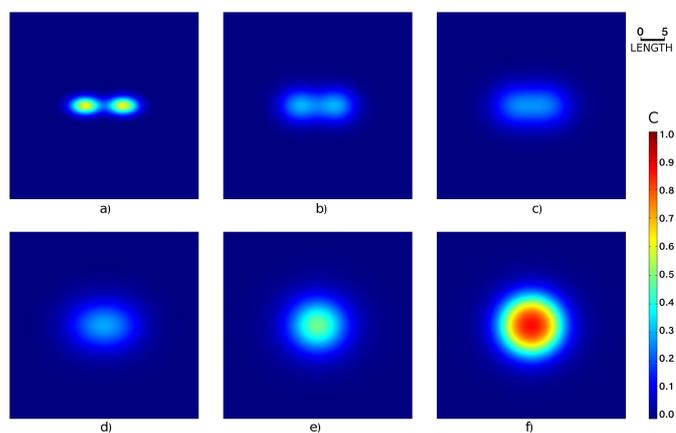


Figure 5: Spatial cancer progression at different times on a two-dimensional tissue domain (dimensionless units) for two distorted Gaussian populations with close peaks. Labels a) to f) stand for snapshot times of  $T = (0, 3, 6, 11, 23, 30)$ : in this scenario cancer cells are able to colonize the entire tissue due to their nonlinear interaction.

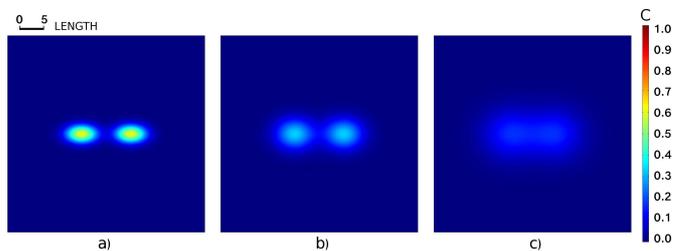


Figure 6: Spatial cancer progression at different times on a two-dimensional tissue domain (dimensionless units) for two distorted Gaussian initial populations with distant peaks. Labels a) to c) stand for snapshot times of  $T = (0, 2, 8)$ : in this scenario cancer colonization fails and the tumor cells decay very fast towards null concentration.

total cancer cells density vanishes in time. This model generalized in three dimensions (blocks of tissue) has to be calibrated on experiments, in order to estimate a realistic initial data, the diffusion coefficient and the physiological threshold  $\alpha$  which could be patient dependent and possibly genetically and/or environmentally ruled [37].

Clearly stochastically induced mutations as well as instabilities driven by diffusion, angiogenesis and so on must play an important role in cancer development (see [24] and the more recent [38] for a discussion on the role of field theories in carcinogenesis). On the other hand, as anticipated already, an active field of research in tumor modeling adopts a *single* reaction-diffusion equation (see [3, 25–30] for details) to model solid cancer growth in anatomically correct 3D brain geometry (as already analyzed in [39] by some of the authors).

#### 4 Bistable dynamics with ecological dispersal effects

We can now extend in a novel way the theory previously introduced, borrowing from the ecological models the possibility to have population dispersal. Discrete models [40] have been proposed to reproduce these properties. In this work we propose a continuum approach instead. The starting point of such a formulation is the experimental evidence that populations of animals in a territory diffuse with a certain (mean) speed depending by the density of animals in that region. Stated in a more straight way, if there are too many individuals in certain region, they tend to exhaust rapidly the local food supplies so that they should abandon the area as soon as possible. If their concentration is not so high on the other hand, they could spread around more slowly. Clearly such a point of view should work correctly also for bacteria, viruses and other microorganisms as well as for solid cancer cells, which in this simplified scenario would migrate because of the ecological pressure. Clearly this is a very basic starting point for more refined modelizations which should take into account also the role of chemotaxis and angiogenesis [3] together with advective effects for oxygen and nutrients and the importance of the immune system in these matters. Anyway this simplified point of view makes the formulation non-trivial because it requires mathematically to have a diffusion coefficient which depends by the local concentration of the diffusing field, i.e., in our case  $\hat{D} = \hat{D}(c)$ . Borrowing again from ecological models the theoretical formulation, we assume the isotropic power law functional dependence  $\hat{D} = D \cdot [c(t, \vec{x}) / c_{ref}]^m \hat{I}$ , where  $D$  is the diffusion constant,  $c_{ref}$  is a reference constant concentration, here introduced for dimensional analysis reasons,  $m$  is a non negative real number and  $\hat{I}$  is the identity matrix. Rewriting  $c_{ref} = \sigma c_3$  with  $\sigma > 0$ , and adopting the same non-dimensional quantities previously discussed, we finally arrive to the dimensionless equation

$$\frac{\partial C}{\partial T} = \sigma^{-m} \nabla \cdot (C^m \nabla C) + F(C), \quad (4.1)$$

which in the limit  $m \rightarrow 0$  reduces to the standard bistable equation previously discussed (in 1D Eq. (3.2)) while if  $F(C) = 0$ , becomes the porous media equation which has an-

alytical solutions in one dimensions [3]. Eq. (4.1) in 1D can be studied with the usual procedure adopted to find travelling wave solutions. Requiring  $C = C(X+VT) \equiv C(\xi)$  (here  $V$  is the constant velocity of the pulse), it becomes

$$\sigma^{-m} \frac{d}{d\xi} \left( C^m \frac{d}{d\xi} C \right) - V \frac{dC}{d\xi} + F(C) = 0, \quad (4.2)$$

which could be possibly studied in search of analytical solutions or numerically as a boundary value problem for the allowed values of the constant  $V$ , again. Although this would lead to an interesting mathematical problem, from the physical point of view, such travelling waves of constant velocity  $V$  should be regarded in the best case as asymptotic states in time of more complicated solutions which already in the 1D case do not travel always at constant speed. The reason for this is that the dimensionless velocity of the standard bistable pulse in Eq. (3.4), once rewritten in dimensional variables, gives a velocity which grows linearly with the (constant) diffusion coefficient. The addition of dispersal implies a non constant diffusion coefficient (monotonically increasing with field concentration) so that, if one assumes a very slow growth of the density, the speed of the pulse too should change analogously and a constant speed travelling wave would not be possible. However, once the system reaches its highest asymptotic concentration value due to the bistable dynamics, practically a constant diffusion coefficient occurs so that constant speed travelling wave appears. In order to prove this scenario and have a complete view of the real dynamics of this extended model, we have studied Eq. (4.1) adopting the same codes for the numerical simulation previously discussed in the simple bistable case, requiring for the sake of simplicity  $\sigma = 1$  and  $m = 1$  (a linear growth for diffusion in function of concentration which is in agreement with the literature [3]).

In Fig. 7 (to be compared with Fig. 2) we show the evolution of the tumor at different times with initial data  $C(0,x) = 0.7\exp(-x^2)$  again. Notice the sharp interface of the cell front with the zero tumor region, which is totally absent in the simple diffusive case. The inclusion of the porous medium term in fact leads to a quasilinear partial differential equation, eliminating the unpleasant regularizing effect of the heat operator which generates a nonzero concentration in the entire domain (infinite propagation velocity).

In Fig. 8 (to be compared with Fig. 3) we can see that, differently than in the diffusive case, the smaller initial data  $C(0,x) = 0.3\exp(-x^2)$  leads in any case to tumor cell progression which has a different propagation velocity in time. In fact by focusing on the  $X$ -axis, one can see that at equidistant time intervals, the interface covers different spaces manifesting the expected concentration-dependent velocity of propagation which, once the upper concentration limit is reached, becomes approximately constant, confirming the physical scenario previously hypothesized.

A space-time diagram of the latter simulation shows this effect quantitatively as shown in Fig. 9 where there is a strong change in the slope (so in speed) due to the change of concentration. In Fig. 10 we present instead the space-time diagram for the interaction of the two initial data just discussed by assuming  $C(0,X) = 0.7\exp(-(x-10)^2) + 0.3\exp(-(x+10)^2)$ . We point out the change in slopes of the smaller distorted Gaussian in comparison

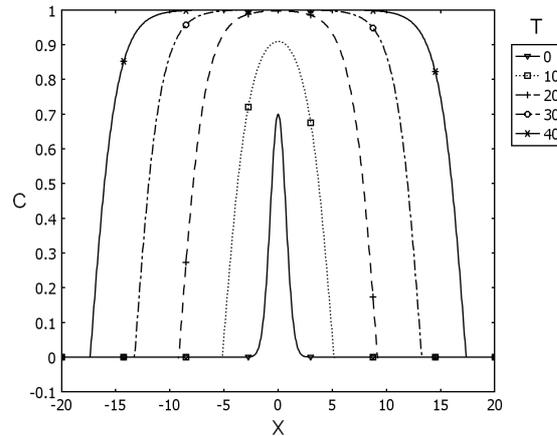


Figure 7: Spatial cancer progression in time on a linear tissue domain (dimensionless units) in the case of population dispersal for initial data  $C(0,x)=0.7\exp(-x^2)$ .

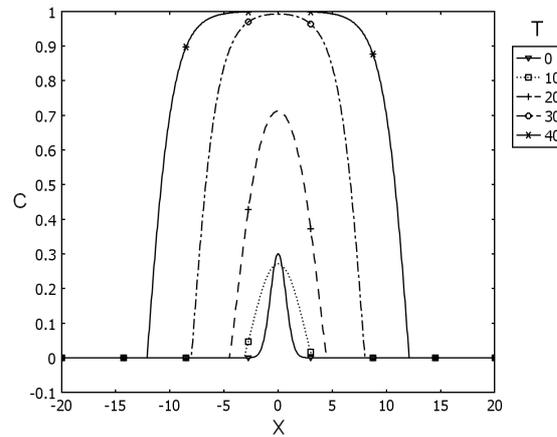


Figure 8: Spatial cancer progression in time on a linear tissue domain (dimensionless units) in the case of population dispersal for initial data  $C(0,x)=0.3\exp(-x^2)$ . Differently as in the simpler reaction-diffusion theory, here even smaller initial data can lead to tumor progression.

with the higher one and the nonlinear interaction on the collision area.

We can now analyze the dynamics in higher dimensional cases. In three dimensions, assuming a purely radial dynamics, one starts from cartesian coordinates, adopts the same non-dimensional notations as in the one-dimensional case, and passing to dimensionless spherical coordinates  $(R,\theta,\phi)$ , finally obtains:

$$\frac{\partial C}{\partial T} = \frac{\sigma^{-m}}{R^2} \frac{d}{dR} \left( C^m R^2 \frac{d}{dR} C \right) + F(C). \tag{4.3}$$

This spherical scheme shall have relevance for realistic NMR imported 3D brain geometries, on the lines of precedent studies of some of the authors [39], performing a fine

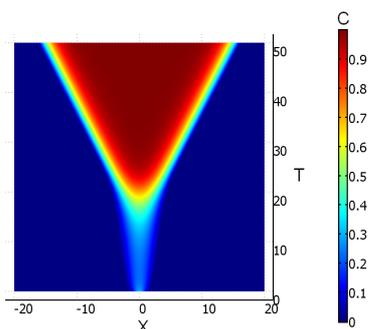


Figure 9: Space-time diagram of cancer progression in time on a linear tissue domain (dimensionless units) in the case of population dispersal for initial data  $C(0,x) = 0.3\exp(-x^2)$ . Notice the change of slope meaning a change of tumor progression speed.

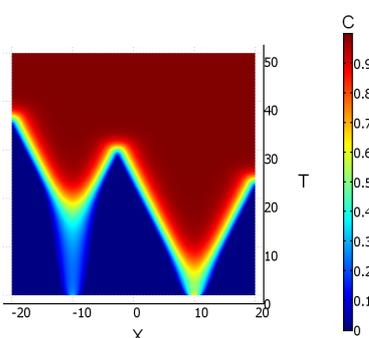


Figure 10: Space-time diagram of cancer interaction for the initial data  $C(0,X) = 0.7\exp(-(x-10)^2) + 0.3\exp(-(x+10)^2)$ . Due to the dispersal term the various populations interact nonlinearly with different speeds.

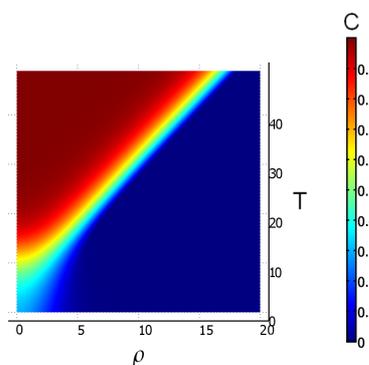


Figure 11: Space-time development of cancer growth in the cylindrical (planar radial) self-diffusing case for initial data  $C(0,\rho) = 0.3e^{-0.1\rho^2}$ .

tuning of the model parameters with radiological data taken at different times. Another possible field of application of this modelization is in the context of cancerous cell cultures. In circular dimensionless cylindrical coordinates  $(\rho, \phi, Z)$ , assuming purely radial

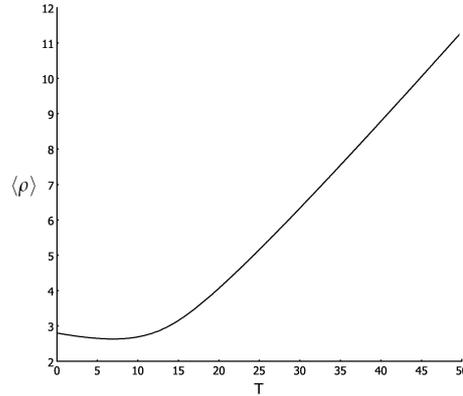


Figure 12: Mean value of tumor radius versus time in the case of Fig. 11.

diffusion (typical of cell cultures situations which are almost planar) we obtain instead

$$\frac{\partial C}{\partial T} = \frac{\sigma^{-m}}{\rho} \frac{d}{d\rho} \left( C^m \rho \frac{d}{d\rho} C \right) + F(C). \tag{4.4}$$

Taking as initial data  $C(0, \rho) = 0.3e^{-0.1\rho^2}$  and zero flux again as boundary conditions [41], we obtain the spacetime diagram in Fig. 11.

In Fig. 12 we have plotted instead the mean radial distance of the cancer population from the origin versus time (see [3] pp. 553 for this definition), i.e.,

$$\langle \rho \rangle = \frac{\int_0^{\rho_0} \rho^2 C(\rho, T) d\rho}{\int_0^{\rho_0} \rho C(\rho, T) d\rho}, \tag{4.5}$$

where  $\rho_0$  represent the outer boundary of the Petri dish which in our case has value twenty space dimensionless units. On page 555 of [3], based on experimental results by [42], an estimate, *in vitro*, of an (approximate) value of the mean radius versus time for an anaplastic astrocytoma, a mixed glioma and a glioblastoma multiforme cultures growing can be found. More in detail it is approximated by

$$\langle \rho \rangle \simeq \frac{\int_{\lambda^2}^{\rho_0} \rho(\rho - \lambda) C(\rho, T) d\rho}{\int_{\lambda^2}^{\rho_0} \rho C(\rho, T) d\rho}, \tag{4.6}$$

where  $\lambda^2$  represents the uniform steady state of the cell distribution. Scaling the variables it is possible to obtain a growing trend for the tumor mean radius in qualitative agreement with some of these experiments, in particular in the case of the mixed glioma. The two other types of tumors on the other hand manifest a different regime so our model should be fine tuned also in the functional form of  $D(c)$  in order to fit these data. A set of parametric simulations in which  $(m, \sigma, a, \alpha)$  are varied shall improve the agreement of the model with experiments, especially for values of  $m$  close to zero (i.e., standard diffusion). We plan to perform all of these works in future studies in union with additional experimental data [37].

## 5 Conclusions

In this article we have introduced and discussed a very basic model of cancer spread which grasps the main feature of solid cancer progression in tissues, i.e., the possibility for the tumoral cell colonization to occur or the blocking action of this process due to different biological reactions of the organism. The model is based on the bistable equation, which can be seen as a polynomial approximation [36] for many different more complicated biological scenarios making the formulation very general. The inclusion of dispersal effects makes the formulation absolutely nontrivial but much more interesting because of the possibility to have different propagation speed in association with different cancer cells densities in the tissue. It is important to remark also that this modelization could play a central role not only in the field of cell growth modeling but also in the field of computational electrophysiology where reaction-diffusion theory with simple diffusion (and not with porous medium term) is commonly adopted to study electrochemical waves in biological media.

This article is a starting point for a field theoretical approach of cancer progression formulated in terms of very basic but at the same time very general equations aiming to extend in future the successful experimental and theoretical works regarding brain cancer [3, 25–30] with the techniques on real brain geometries developed by some of the authors in the past. The hope is to find, through mathematical modeling, some general behaviors which could be extrapolated from the patient dependent specific scenario, in analogy with other branches of Theoretical Physics in which apparently different systems simplify towards a common description once well expressed in mathematical terms. Such a formalization of cancer spread can bridge the requirements of the major existing interpretative theories. Nevertheless, any methodological approach needs a greater awareness of the complexity of the organism, which appears nowadays more and more evident, in order to develop consistent mathematical tools for modeling.

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