



The noise and the KISS in the cancer stem cells niche



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HIGHLIGHTS

- Possible explanation for wide variability observed in cancer stem cells frequency.
- Plasticity is necessary for maintenance of cancer stem cell populations.
- Cell population may exhibit a noise-induced transition.

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ABSTRACT

There is a persistent controversy regarding the frequency of cancer stem cells (CSCs) in solid tumors. Initial studies indicated that these cells had a frequency ranging from 0.0001% to 0.1% of total cells. Recent studies have shown that this does not seem to be always the case. Some of these studies have indicated a frequency of 40%. Through a simple population dynamics model, we studied the effects of stochastic noise and cellular plasticity in the minimal path size of a cancer stem cells population, similar to what is done in what is sometimes called the Kierstead–Skellam–Slobodkin (KISS) Size analysis. We show that the possibility of large variations in the results obtained in the experiments may be a consequence of the different conditions under which the different experiments are submitted, specifically regarding the effective cell niche size where stem cells are transplanted. We also show the possibility of a noise induced transition where the stationary probability distribution of the CSC population can present bimodality.

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1. Introduction

In recent years there has been increasing evidence for the *Cancer Stem Cell* (CSC) hypothesis (Reya et al., 2001; Clarke and Fuller, 2006; Vermeulen et al., 2008; Dalerba et al., 2007), according to which tumor formation is a result of genetic and epigenetic changes in a subset of stem-like cells, also known as *tumor-forming* or *tumor-initiating* cells (Bomken et al., 2010). Cancer stem cells were first identified in various leukemias and, more recently, in several solid tumors such as brain, breast, cervix and prostate tumors (Dalerba et al., 2007).

It has been suggested that these are the cells responsible for initiating and maintaining tumor growth. In this paper, we study a model for tumor growth that assumes the existence of *cancer stem cells* (CSCs), or *tumor initiating cells*.

The conceptual starting point relevant to CSC theory is constructed from the known heterogeneity of tumors. We now know

that cells in a tumor are not all identical copies of each other, but that they display a striking array of characteristics (Denison, 2012; Tian et al., 2011; Shackleton et al., 2009; Marusyk and Polyak, 2010; Marusyk et al., 2012). CSC theory recognizes this fact and develops its consequences. And one of the most immediate implications for clinical practice is that conventional treatments can generally attack the wrong cell type. The appeal of the CSC idea can be described by the following analogy: just as killing the queen bee leads to the demise of the hive, destroying cancer stem cells, should, in theory, stop a tumor from renewing itself. Unfortunately, things are never that simple. In the hive, workers react quickly to the death of the queen by replacing her with a new one. And there is some evidence (Welte et al., 2010; Rapp et al., 2008) to suggest that could also happen in tumors due to a phenomenon known as *cell plasticity*, which allows normal tumor cells to turn into cancer stem cells, should the situation call for it. One goal of this study is to evaluate the possible effects of this plasticity. Analogies with superorganisms such as bee colonies are taken much more seriously in Grunewald et al. (2011).

Stem cells in general (the same applies to CSCs) tend to be found on specific areas of a tissue where one particular

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microenvironment, called *niche* (Lander et al., 2012), promotes the maintenance of its vital functions. This niche has specialized in providing factors that prevent differentiation and thus maintain the stemness of CSCs and, ultimately, the tumor's survival. Stem cells and niche cells interact with each other via adhesion molecules and paracrine factors. This complex network of interactions exchanges molecular signals and maintains the unique characteristics of stem cells, namely, pluripotency and self-renewal.

Given the extreme complexity of the cellular microenvironment in general and of the niche in particular (Iwasaki and Suda, 2009; Lander et al., 2012), we will formulate an effective stochastic theory for the population dynamics of CSCs. We are especially interested in investigating a controversy related to the frequency with which CSCs appear in various tumors (Ishizawa et al., 2010; Stewart et al., 2011; Vargaftig et al., 2011; Sarry et al., 2011; Zhong et al., 2010; Baker, 2008a,b; Johnston et al., 2010). In the initial version of CSC theory, it was believed that these cells were a tiny fraction of the total, ranging from 0.0001% to 0.1% (Schatton et al., 2008; Quintana et al., 2008). However, more recent studies have shown a strong dependence on the number of stem cells present in a tumor with the xenograft experimental model used. In explicit contrast to what was previously thought, in Quintana et al. (2008) a CSC proportion of approximately 25% was observed. Other studies have confirmed this observation (Kelly et al., 2007; Williams et al., 2007; Schatton et al., 2008), with the proportion potentially reaching 41% (Boiko et al., 2010). In Gupta et al. (2009) the authors provide evidence that this discrepancy may be caused by the possibility of phenotypic switching between different tumor cells. By phenotypic switching we mean that a more differentiated cancer cell can, under appropriate conditions, de-differentiate into a cancer stem cell. This is the cellular plasticity mentioned above.

In Zapperi and La Porta (2012), it is suggested that inconsistencies in the numbers of cancer stem cells reported in the literature can also be explained as a consequence of the different definitions used by different researchers. Different assays will give different numbers of cells, which can be orders of magnitude away from each other.

In this paper we are also interested in knowing what are the possible effects of cells diffusion in space. For this, we constructed bifurcation diagrams that show how the population size of CSCs varies when the size of the niche cells changes. We consider the effects that the plasticity phenomenon as well as spatio-temporal noise can have in these diagrams. Finally we studied the effects of the spatial distribution of cells in stationary probability distributions.

The paper is organized as follows: in Section 2 we explain the basic assumptions of our model of CSC population dynamics. In Section 3 we describe the set of reactions we use in the models. The effects of inclusion of spatial structure in the analysis are considered in Section 4. Section 5 closes the paper with conclusions.

2. Assumptions

Mathematical modeling has made significant contributions to our understanding of the biology of cancer since the pioneering work of Nordling (1953) and Armitage and Doll (1954), in which the authors proposed that multiple mutations may explain the data on the incidence of cancer and its correlation with age (Chen et al., 2005; Horov et al., 2009). For historical reviews on the subject, see McElwain and Araujo (2004) and Byrne et al. (2006).

In the model used in this paper, cancer stem cells can perform three types of divisions, according to Morrison and Kimble (2006):

- *Symmetric self-renewal*: Cell division in which both daughter cells have the characteristics of the stem cell mother, resulting in an expanding population of stem cells.

- *Symmetric differentiation*: A stem cell divides into two progenitor cells.
- *Asymmetric self-renewal*: A cancer stem cell (denoted by C) is generated and a progenitor cell (mature cancer cell, denoted by P) is also produced.

We developed a simple mathematical model for the stochastic dynamics of CSCs in which the three division types possess intrinsic replication rates, which are assumed to be time-independent. Therefore, besides these division types, we assume that there is also the possibility of a transformation in which a progenitor cell can acquire characteristics of stem cells where, for all practical purposes, we may regard it as having become a de-differentiated stem cell. In mixed lineage leukemia cells, it was recently shown that committed myeloid progenitor cells acquire properties of leukemia stem cells without changing their overall identity (Leder et al., 2010). These cells do not become stem cells, but rather develop stem cell like behavior by re-activating a subset of genes highly expressed in normal hematopoietic stem cells (Rapp et al., 2008). The biological mechanisms underlying this transformation are described in Gupta et al. (2009), for example. As mentioned previously, we refer to this process as *cell plasticity*.

3. Model

This section describes the basic model investigated in this paper. It is based on the cell division mechanism and the plasticity property. We will use the language of stochastic differential equations (Karlin and Taylor, 2000; Schuss, 2010; Oksendal, 2003).

The model is a natural extension of the one proposed in Turner et al. (2009). This extension refers to the inclusion of competition between cells because of the scarcity of resources when populations become large enough. This new possibility in relation to the model proposed in Turner et al. (2009) makes the model nonlinear and prevents that the populations tend to infinity. The model is described in the next subsection.

3.1. The basic model

We assume that the population dynamics of cancer stem cells and progenitor cells are governed by the following reactions:



The first and second reactions, in the forward sense, model cell proliferation, which occurs at a rate k_1 and k_3 , respectively. Constants k'_2 and k'_4 are associated to the reverse process and describe the intensity of competition between the CSC and progenitor cells, respectively, and prevents their unlimited exponential growth; Ω_2 and Ω_4 are constants related to the model's carrying capacity. The third reaction involving k_5 originates from the asymmetric transformation of CSCs in CSC daughter and progenitor cell types. The reaction involving the rate k_6 is related to a symmetrical division of stem cells, which gives rise to two progenitor cells. The penultimate reaction is associated with progenitor cell death at rate k_7 . Finally, k_8 is the de-differentiation rate.

All rates have dimension (time)⁻¹. The specific unit of time (months, quarters, years, etc.) will depend on the type and aggressiveness of the tumor.

Using the law of mass action, we can write

$$\begin{cases} \frac{dC}{dt} = k_1 C - k_2 C^2 - k_6 C + k_8 P \\ \frac{dP}{dt} = k_3 P - k_4 P^2 + (k_5 + 2k_6)C - (k_7 + k_8)P \end{cases} \quad (2)$$

with $k_2 \equiv k'_2/\Omega_2$, $k_4 \equiv k'_4/\Omega_4$. Setting $\Omega_C \equiv k_1/k_2$, $\Omega_P \equiv k_3/k_4$, $k_9 \equiv k_5 + 2k_6$ and $k_{10} \equiv k_7 + k_8$ and making the substitutions $C = \Omega_C x$, $P = \Omega_P y$ and $t = \tau/k_6$, Eq. (2) can be written as (see Appendix A)

$$\begin{cases} \frac{dx}{d\tau} = Ax(1-x) - x + By \equiv f(x, y) \\ \frac{dy}{d\tau} = Ey(1-Fy) + Bx - Gy \equiv g(x, y) \end{cases} \quad (3)$$

with

$$\begin{cases} A \equiv \frac{k_1}{k_6} \\ B \equiv \frac{\sqrt{k_2 k_9}}{k_6} \\ E \equiv \frac{k_3}{k_6} \\ F \equiv \frac{\Omega_C}{\Omega_P} \sqrt{\frac{k_9}{k_2}} \\ G \equiv \frac{k_{10}}{k_6} \end{cases} \quad (4)$$

As $\partial f/\partial y = \partial g/\partial x = B$, Eq. (3) represents a gradient system (Perko, 2000) with potential $V(x, y)$ given by

$$V(x, y) = \frac{1}{6}(3-3A + 2Ax)x^2 - Bxy + \frac{1}{6}(3G-3E + 2EFy)y^2. \quad (5)$$

As a consequence (Hirsch et al., 2004):

1. The eigenvalues of the linearization of Eq. (3) evaluated at equilibrium point are real.
2. If $(x_0; y_0)$ is an isolated minimum of V then $(x_0; y_0)$ is an asymptotically stable solution of (3).
3. If $(x(\tau); y(\tau))$ is a solution of (3) that is not an equilibrium point then $V(x(\tau); y(\tau))$ is a strictly decreasing function and is perpendicular to the level curves of $V(x, y)$.
4. There are no periodic solutions of (3).

Fig. 1 shows the potential function $V(x, y)$. Sufficiently small F ($\Omega_P \gg \Omega_C$) implies large differences in equilibrium populations of C and P . For parameters $A=B=G=1$, $E=3$ and $F=0.01$, $(x_0; y_0) = (8.4; 70.6)$. If we set $F=0.0001$, keeping the other parameters fixed, we get $(x_0; y_0) = (82; 6710)$.

3.2. Adiabatic elimination

The proposed model in (1) is in fact a general model of stem cells and does not even carry any specific characteristic of cancer stem cells. All properties considered, such as plasticity and changes in the microenvironment conditions (to be included later), are also found in stem cell systems of normal tissue. The features associated with cancer stem cells are related to the large carrying capacity of progenitor cells when compared with the carrying capacity of cancer stem cells. This fact is represented numerically by the choice of model parameters made below, which results in this discrepancy.

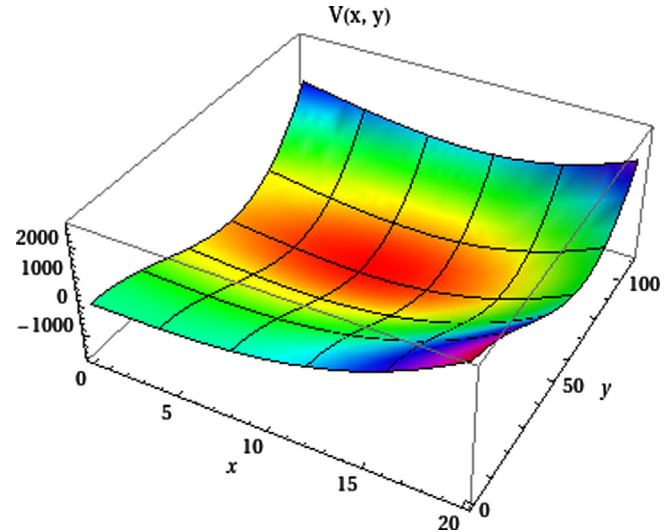


Fig. 1. Potential $V(x, y)$ from Eq. (5) for parameters $A=B=G=1$, $E=3$ and $F=0.01$.

We can write (2) in the form (see Appendix A)

$$\begin{cases} x' = A'x(1-x) - x + B'y \\ y' = E'y(1-F'y) + F'x - G'y \end{cases} \quad (6)$$

with $x' \equiv dx/dt'$, $y' \equiv dy/dt'$, $t' \equiv t/k_6$ and

$$\begin{cases} A' \equiv \frac{k_1}{k_6} \\ B' \equiv \frac{k_2 k_3 k_8}{k_1 k_4 k_6} \\ E' \equiv \frac{k_3}{k_6} \\ F' \equiv \frac{k_1 k_4 k_9}{k_2 k_3 k_6} \\ G' \equiv \frac{k_{10}}{k_6} \end{cases} \quad (7)$$

Fig. 2 shows the numerical solutions of Eqs. (6) (the rescaled equation) and (2) for the following parameter values: $k_1 = 1 - k_5 - k_6$, $k_2 = 4 \times 10^{-13}$, $k_3 = 1$, $k_4 = 10^{-13}$, $k_5 = 0.1$, $k_6 = 0.1$, $k_7 = 0.1$ and $k_8 = 0.00001$.¹ We make the usual assumption $(k_1 + k_5 + k_6)\beta = 1$ (Tomasetti and Levy, 2010), where $\beta \equiv 1$ is a general parameter with dimension time⁽⁻¹⁾ required for dimensional consistency in the following analysis. The values for k_5 and k_6 are consistent with those estimated in Tomasetti and Levy (2010). For these parameter values, $\Omega_C \equiv k_1/k_2 = 2 \times 10^{12}$ and $\Omega_P \equiv k_3/k_4 = 1 \times 10^{13}$ (see Appendix A). These are rescaling parameters for x and y variables, respectively. Stationary values for $P(t)$ and $C(t)$ are $P_\infty = 9.6 \times 10^{12}$ cells and $C_\infty = 1.8 \times 10^{12}$ cells, respectively. By adjusting the k_2 and k_4 parameters we can easily obtain more suitable values for the CSC and progenitor cell equilibrium populations, according to possible new experimental results.

By using standard adiabatic elimination methods, one can write Eq. (6) as

$$\begin{cases} x' = A' \left[x(1-x) - \frac{x}{A'} + \frac{B'}{A'} y \right] \\ \epsilon y' = y(1-y) + \epsilon F' x - \epsilon G' y \end{cases} \quad (8)$$

where $\epsilon \equiv 1/E'$. If we consider $\epsilon \ll 1$ (this is equivalent to considering the progenitor cell division rate sufficiently large) we can perform

¹ These values correspond to $A' = 8$, $B' = 5 \times 10^{-4}$, $E' = 10$, $F' = 0.6$ and $G' = 1$.

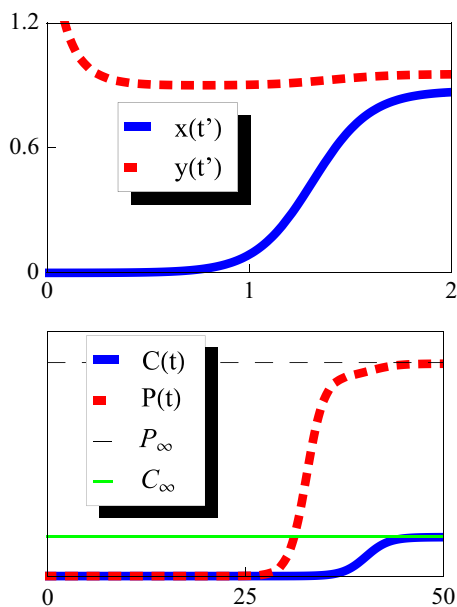


Fig. 2. Top: numerical solution for rescaled Eq. (6). $x(t)$ and $y(t)$ represent the rescaled population of cancer stem cells and progenitor cells, respectively. Bottom: numerical solution for Eq. (2). $C(t)$ and $P(t)$ represent the population of cancer stem cells and progenitor cells, respectively. P_∞ and C_∞ represent the limits of $C(t)$ and $P(t)$ when $t \rightarrow \infty$, respectively. Parameters values: $k_1 = 1 - k_5 - k_6$, $k_2 = 4 \times 10^{-13}$, $k_3 = 1$, $k_4 = 10^{-13}$, $k_5 = 0.1$, $k_6 = 0.1$, $k_7 = 0.1$ and $k_8 = 0.00001$. $P_\infty = 9.6 \times 10^{12}$ and $C_\infty = 1.8 \times 10^{12}$. $C_\infty/P_\infty = 0.1875$.

adiabatic approximation (Berglund and Gentz, 2006; Gardiner, 2009) in (8) and, setting $y' = 0$, we obtain the following equation² for x :

$$x' = \chi - \mu x + \alpha x(1 - x) \tag{9}$$

where $\chi \equiv B'(1 - \epsilon G) = k_8 k_2 (k_3 - k_{10}) / k_1 k_4 k_6$, $\mu \equiv 1 - \epsilon B'F' = 1 - k_8 k_9 / k_3 k_6$ and $\alpha \equiv A' = k_1 / k_6$. Note that χ can be positive or negative depending on the magnitudes of k_3 and k_{10} .

If we consider ϵ to be small enough with respect to G' , B' and F' , we further simplify and write $\chi = B'$ and $\mu = 1$. We can observe that the plasticity phenomenon (associated with k_8) is crucial for the existence of the constant term χ . For this reason, from now on we will consider the parameter χ as representing the plasticity phenomenon in the reduced equation (9).

3.3. The deterministic equation

We will briefly review the deterministic analysis of the problem. An analytic solution of Eq. (9) is possible. For the initial condition $x(0) = N_0$, we get

$$x(t) = \frac{1}{2\alpha} \left\{ \delta - \sqrt{\kappa} \tan \left[\frac{1}{2} t \sqrt{\kappa} + \arctan \left(\frac{-2N_0\alpha + \delta}{\sqrt{\kappa}} \right) \right] \right\} \tag{10}$$

with $\delta \equiv \alpha - \mu$ and $\kappa \equiv -\delta^2 - 4\alpha\chi$. The physically relevant stable fixed point is

$$x^* = \frac{\alpha - \mu + \sqrt{\alpha^2 - 2\alpha\mu + \mu^2 + 4\alpha\chi}}{2\alpha} \tag{11}$$

The x scaled population size dynamics can be thought of as analogous to the particle moving dynamics in an effective potential $V_0(x)$, seeking its minimum point, with $V_0(x) \equiv - \int \zeta(x) dx$ with $\zeta(x) = \chi + \delta x - \alpha x^2$ from (9). Thus, V_0 is given by the cubic

polynomial,

$$V_0(x) = \frac{x^3 \alpha}{3} - \frac{\delta x^2}{2} - \chi x.$$

We see from (11) that by increasing either χ or δ , the minimum x^* of V_0 moves to the right in the potential, thus favoring the tumor stem cell population. Such behavior is, of course, expected, since an increase of χ means an increase of the frequency in which the induced plasticity mechanism occurs, and an increase of δ is an increase of the symmetric stem cell renewal rate, both of which increase the population.

4. Possible consequences of a spatial structure

Traditionally, anti-tumor treatments have targeted the cells directly, removing them with surgery or killing them with radiation. Since these are local treatment methods, they often are not effective in meeting their objectives. The tumors may recur because not all cells were killed or because some cells escaped the primary tumor region where the treatments worked. Since cells compete and/or cooperate with nontumor cells and between themselves, these interactions may be better conceptualized as an evolving ecosystem (Pienta et al., 2008; Kareva, 2011).

One of the possible consequences of this way of seeing the disease is that the destruction of the tumor microenvironment can be much more effective than just extracting or killing the cells that live in it. A prime example of this situation comes from paleontology: studies analyzing the conditions that preceded mass extinctions suggest that they occurred more frequently and were more destructive when pulses of disturbances that cause extensive mortality were accompanied by perturbative pressures such as climate change. This sequence weakened and destabilized populations for several generations (Arens and West, 2008).

Motivated by these considerations, it seems promising to consider mathematical techniques originating in mathematical ecology, a well-developed branch of applied mathematics (Cantrell and Cosner, 2003; Petrovskii and Li, 2005). We are now interested in the possible effects from the incorporation of diffusion in the model. For this, let $u(x, t)$ be a population of CSCs at position x at time t that lives in a one-dimensional domain of length L . By adding a diffusion term in Eq. (9), we get

$$\frac{\partial u}{\partial t'} = D \frac{\partial^2 u}{\partial t'^2} + \chi - \mu u + \alpha u(1 - u) \equiv D \frac{\partial^2 u}{\partial t'^2} + f(u) \tag{12}$$

where D is the cell diffusion coefficient and $f(u) = \chi - \mu u + \alpha u(1 - u)$. This is the deterministic partial differential equation that we will consider first. Later we will consider a stochastic version. This is a reaction diffusion equation that is typical in the population dynamics of species that interact and disperse.

Eq. (12) with $\chi = 0$ is the famous Fisher (1937) equation. In this equation we analyze the effect of plasticity represented by the parameter χ on the patch size to sustain a population, similar to what is sometimes called the Kierstead–Slobodkin–Skellam (KISS) size (Skellam, 1951; Kierstead and Slobodkin, 1953). The main motivation for performing this type of analysis is related to the experimental results obtained in Quintana et al. (2008), where xenografts in immunosuppressed mice sustained surprisingly high populations of cancer stem cells. The idea here, therefore, is to identify some phenomenon related to the size of the CSC niche that may justify this result. The question is: What is the effect of transplanting a cancer stem cell population to an environment where, in theory, they will have more space to live and proliferate?

To formulate the problem mathematically, we can imagine that there is a finite domain available for the cells to develop (their niche). Beyond a certain boundary (i.e. outside the niche), there

² Expanding in Taylor series up to first order in ϵ .

are restrictions (e.g., absence of signaling to support the cancer stem cell phenotype, normoxic conditions incompatible with the state of CSCs, adverse pH conditions, etc.) which make the survival of cancer stem cells unsustainable. Outside the niche, these cells have a tendency to differentiate into progenitor cells. Thinking of the niche as a linear domain of length L , our problem can be mathematically formulated as a boundary value problem with Dirichlet conditions given by (12) and

$$u(0, t') = u(L, t') = 0.$$

Following Méndez et al. (2008), the population density at the steady state is given by $u(x, \infty) \approx u_m \sin(\pi x/L)$, where u_m is the maximum population density at steady state for a given patch size L . In Méndez et al. (2008), for a function $f(u)$ in the form $f(u) = a_1 u + a_2 u^2 + a_3 u^3$, an approximation to u_m is found as the real solution to the equation $\Phi(u_m, L) = 0$ with

$$\Phi(u_m, L) \equiv u_m \left[\frac{3a_3}{4} u_m^2 + \frac{8a_2}{3\pi} u_m + a_1 - D \left(\frac{\pi}{L} \right)^2 \right]. \quad (13)$$

Allowing the possibility of plasticity (represented by χ), we insert a term a_0 in the $f(u)$ function so that $f(u) = a_0 + a_1 u + a_2 u^2 + a_3 u^3$. By performing the calculations as in Méndez et al. (2008), we obtain the new function

$$\Phi_\chi(u_m, L) = \frac{4a_0}{\pi} + u_m \left[\frac{3a_3}{4} u_m^2 + \frac{8a_2}{3\pi} u_m + a_1 - D \left(\frac{\pi}{L} \right)^2 \right]. \quad (14)$$

By solving equation $\Phi_\chi(u_m, L) = 0$, we get three solutions that, when placed on the same figure, make up what we call a bifurcation diagram (if $\chi = 0$).³ For $a_0 = \chi$, $a_1 = \alpha - \mu$, $a_2 = -\alpha$ and $a_3 = 0$, we consider the case of Eq. (12).

Fig. 3 shows the bifurcation diagram for $\chi = 0$ (blue curve) and the curves $u_m(L)$ for $\chi = 0.1$ (dotted red curve) and $\chi = 0.01$ (black dashed curve). We find that the inclusion of plasticity allows small cancer stem cell populations to survive even in very small niches. Above a certain approximate critical minimum value for patch size (KISS size $L_c = \pi\sqrt{D/a_1}$), the population undergoes an abrupt increase in its size. If a small cell niche is abruptly increased to a value significantly greater than L_c , the CSC population will be absurdly high. This may have been the case for the xenograft cancer stem cells in immunosuppressed mice reported in Quintana et al. (2008). This may also be an answer to the question raised above.

4.1. Effect of noise on the bifurcation diagram

4.1.1. Noise in the cancer stem cell niche

Cells growing in a tissue are not alone: they are constantly communicating with one another by sending signals through tissue that are picked up and transmitted by other cells in the medium. When thousands of cells are together, there are hundreds of thousands of these signals present every minute, all competing to be heard. All this complexity induces stochastic fluctuations in population dynamics that will hereafter be called noise.

A growing body of evidence indicates that noise is generally not detrimental to biological systems, but can be employed to generate behavioral diversity (Samoilov et al., 2005; Fange and Elf, 2006). Mechanisms involving noise are important in the development of organisms (Arias and Hayward, 2006; El-Samad and Khammash, 2006), a fact supported by experiments showing that noise is down-regulated in embryonic stem cells (Zwaka, 2006) and that fluctuations of the Nanog transcription factor predispose these cells towards differentiation (Chambers et al., 2007; Kalmar

³ Naturally, the name bifurcation diagram only makes sense in the absence of plasticity. This is due to the critical nature of L_c , which exists only for $\chi = 0$. When $\chi \neq 0$, the equivalent in figures will be called $u_m(L)$ curves.

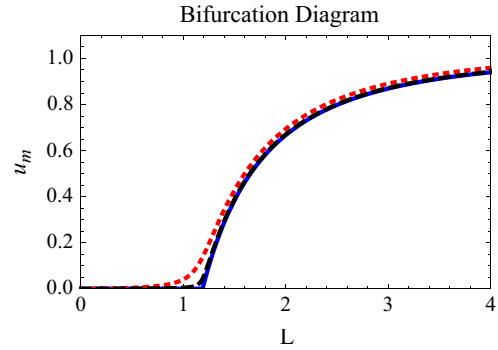


Fig. 3. Bifurcation diagram obtained from $\Phi_\chi(u_m, L) = 0$ with $\Phi_\chi(u_m, L)$ given by Eq. (14) with $\chi = 0.0$ (blue, thick line), $\chi = 0.1$ (red, dotted line), $\chi = 0.01$ (black, dashed line), $\mu = 1$, $\alpha = 8$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

et al., 2009). In Hoffmann et al. (2008) it was suggested that the regulation of noise can be an effective strategy in stem cell differentiation. The results of the present paper suggest that high levels of noise can stimulate the development of cancer stem cells.

4.1.2. Modeling noise in a spatial environment

We will now reformulate the population dynamics in terms of a stochastic reaction–diffusion equation and reduce it to a deterministic equation that incorporates the systematic noise contributions (Santos and Sancho, 2001). Let us first formulate the problem in a general way and then use our model as an example.

Consider the following stochastic partial differential equation (SPDE) in the Stratonovich interpretation, with both additive and multiplicative noises:

$$\frac{\partial \phi}{\partial t} = D \nabla^2 \phi + f(\phi) + \epsilon^{1/2} g(\phi) \eta(x, t) + \xi(x, t). \quad (15)$$

In the above equation, ϵ is an explicit measure of the noise strength given by $\eta(x, t)$, $\phi(x, t)$ is a field (scalar or vector) that describes the state of the system (the number of CSCs in our context) at a spatial location x at time t , and D is the diffusion coefficient. The additive noise $\xi(x, t)$ is Gaussian and white in both space and time, with zero mean and correlations given by

$$\langle \xi(x, t) \xi(x', t') \rangle = 2\gamma^2 \delta(x - x') \delta(t - t').$$

The multiplicative noise $\eta(x, t)$ is Gaussian, with zero mean and correlation

$$\langle \eta(x, t) \eta(x', t') \rangle = 2c(|x - x'|) \delta(t - t')$$

with $c(|x - x'|)$ as the spatial correlation function. A crucial feature of (15) is that while $\eta(x, t)$ has zero mean, our new noise term $g(\phi)\eta(x, t)$ does not. If $g(\phi)$ is constant, Eq. (15) has only additive noise. In our case however, noise is coupled to the system through function g .

4.1.3. Effective deterministic model

As mentioned above, the new noise term has nonzero mean. We define it as follows:

$$\epsilon^{1/2} \langle g(\phi) \eta(x, t) \rangle \equiv \Psi(\phi). \quad (16)$$

Adding and subtracting $\Psi(\phi)$ in (15) lead to an equivalent equation, but with zero mean noise term R

$$\frac{\partial \phi}{\partial t} = D \nabla^2 \phi + f(\phi) + \Psi(\phi) + R(\phi, x, t) \quad (17)$$

where

$$R(\phi, x, t) = \epsilon^{1/2} g(\phi) \eta(x, t) - \Psi(\phi) + \xi(x, t). \quad (18)$$

$R(\phi, x, t)$ is related to the nonsystematic noise effect. This effect will

be neglected (Santos and Sancho, 2001), thus leading to an effective deterministic equation

$$\frac{\partial \phi}{\partial t} = D \nabla^2 \phi + f(\phi) + \Psi(\phi) \tag{19}$$

with an effective reaction term $f(\phi) + \Psi(\phi)$. $\Psi(\phi)$ can be calculated using Novikov's (1965) theorem producing

$$\epsilon^{1/2} \langle g(\phi) \eta(\mathbf{x}, t) \rangle = \epsilon c(0) \langle g'(\phi) g(\phi) \rangle. \tag{20}$$

The deterministic effective model is written as

$$\frac{\partial \phi}{\partial t} = D \nabla^2 \phi + f(\phi) + \epsilon c(0) g'(\phi) g(\phi). \tag{21}$$

4.1.4. Application to our model

Considering the inclusion of a Gaussian noise of intensity σ in parameter α ,⁴ (by the transformation $\alpha \rightarrow \alpha + \sigma W(t)$, $W(t)$ is a Wiener process Oksendal, 2003) we get a model corresponding to Eq. (15) with $f(\phi) = \chi + (\alpha - \mu)\phi - \alpha\phi^2$ (a polynomial of degree two) and $g(\phi) = \phi(1 - \phi)$. Therefore, the effective deterministic model is given by

$$\frac{\partial \phi}{\partial t} = D \nabla^2 \phi + \chi + (\alpha - \mu + \sigma)\phi - (\alpha + 3\sigma)\phi^2 + 2\sigma\phi^3 \tag{22}$$

or

$$\frac{\partial \phi}{\partial t} = D \nabla^2 \phi + \chi + M\phi - N\phi^2 + P\phi^3 \tag{23}$$

with $M \equiv \alpha - \mu + \sigma$, $N \equiv \alpha + 3\sigma$, $P \equiv 2\sigma$ and $\sigma \equiv \epsilon c(0)$. Besides the renormalization in parameters μ and α , the degree of the polynomial function to the right of (22) is lifted from two to three. The systematic contributions of the noise in the proliferation rate give rise to a cubic term in the effective reaction function. Consequently, the validity range of Eq. (23) is restricted to sufficiently small noise strengths or small densities. This does not affect our conclusions, since we are interested in the conditions for extinctions, i.e., situations where the density is indeed small. At higher densities, the model needs to be modified to include higher-order saturation effects.

It is interesting to observe the effect of σ on the effective potential $V_{eff}(\phi)$ associated with the model without diffusion, obtained from $V_{eff}(\phi) = - \int [f(\phi) + \Psi(\phi)] d\phi$.

Fig. 4 shows this effect. Curves in blue, black and red (thick, dashed and dotted, respectively) have $\sigma = 0, 5$ and 10 , respectively. An increase in noise decreases the equilibrium population represented by the minimum of the potential, but this decrease is accompanied by the possibility of the population falling into the hole on the right with no minimum. And the larger the noise intensity, the more likely this is to occur. Cancer stem cells enjoy noise.

The bifurcation diagram: We can now use Eq. (14) to construct the bifurcation diagram corresponding to (23). In this case, we put $a_0 = \chi$, $a_1 = M$, $a_2 = N$ and $a_3 = P$ with $\alpha = 8$, $\mu = 1$.

Fig. 5 shows the bifurcation diagrams for $\chi = 0$ (top of the figure) and curves $u_m(L)$ for $\chi = 0.1$ (bottom). We see clearly that the noise helps cancer stem cells to survive in very small niches. The minimal patch size $L_c = \pi \sqrt{D/(\alpha - \mu + \sigma)}$ needed to sustain cell life is reduced with noise. The price to pay is related to lower values of its stationary population.

⁴ We consider the inclusion of noise in this parameter by its essential importance in the population dynamics, since this parameter is associated with its nonlinear character.

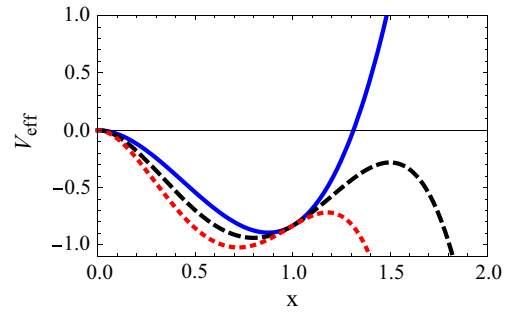


Fig. 4. Effect of σ on V_{eff} with $\chi = 0$, $\alpha = 8$, $\mu = 1$. $\sigma = 0$ (blue, thick line), $\sigma = 5$ (black, dashed line), $\sigma = 10$ (red, dotted line). An increase in the noise intensity decreases the population equilibrium but facilitates the escape of the cells to a situation where population growth is uncontrolled. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

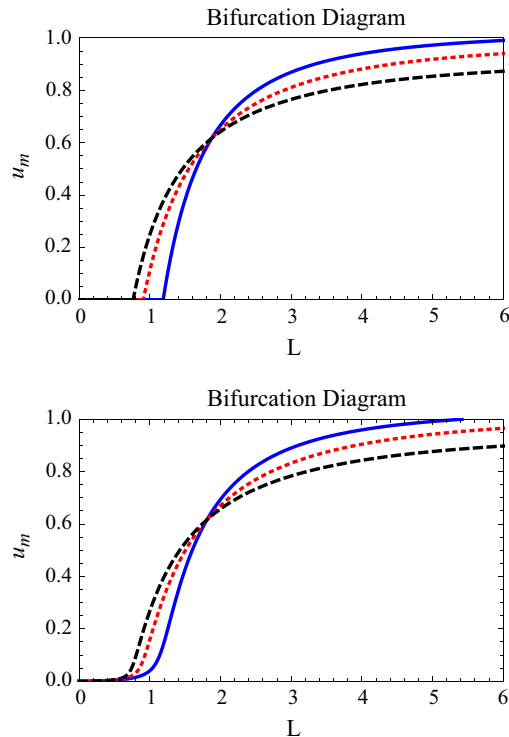


Fig. 5. Bifurcation diagram with $\chi = 0.0$ (top) and $\chi = 0.1$ (bottom), $\sigma = 0.0001$ (blue, thick line), $\sigma = 5$ (red, dotted line), $\sigma = 10$ (black, dashed line), $\mu = 1$, $\alpha = 8$. Noise enables the survival of CSCs in very small niches. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

4.2. The effect of diffusion in the stationary probability distribution

In this subsection we estimate the effects induced by diffusion on the stationary distribution. Let us consider the tumor as a spatially continuous medium as in the previous section, described by field variables obeying partial differential equations. We consider the reaction–diffusion equations

$$\frac{\partial \phi(\mathbf{x}, t)}{\partial t} = f(\phi(\mathbf{x}, t)) + D \nabla^2 \phi(\mathbf{x}, t) \tag{24}$$

where $\phi(\mathbf{x}, t)$ is a field (scalar or vector) that describes the state of the system at a spatial location \mathbf{x} at time t . A discretization procedure is commonly used to transform the continuous partial differential equation to be analyzed into a set of coupled ordinary differential equations, after approximating the continuous space by a lattice (García-Ojalvo and Sancho, 1999). In the case of

Eq. (24), for example, assuming a regular Cartesian lattice, the discretization leads to

$$\frac{d\phi(t)}{dt} = f(\{\phi_i\}) + \frac{D}{\Delta x^2} \sum_{j \in n(i)} (\phi_j - \phi_i) \tag{25}$$

where the sum term, which runs over the set of nearest neighbors of i , represents a possible choice for the discrete version of the Laplace operator and Δx denotes the lattice spacing. The relation between the discretized field and the real one is $\phi_i(t) = \phi(i\Delta, t)$, where $i = (i_1, i_2, \dots, i_d)$ and d is the space dimension.

A lattice will be used so that the state of the system is described by a set of scalar variables $\{x_i\}$, $i = 1, \dots, L^d$ defined on a d -dimensional cubic lattice with lattice points i . Suppose that the dynamics of the variables x_i can be described by the following stochastic differential equation in the Stratonovich sense:

$$\dot{x}_i = f(x_i) + g(x_i)\xi_i - \frac{D}{2d} \sum_{j \in n(i)} (x_i - x_j). \tag{26}$$

$n(i)$ is the set of the nearest $2d$ neighbors of site i , and $\{\xi_i(t)\}$ are Gaussian white noises in time and space with zero mean and an autocorrelation function given by

$$\langle \xi_i(t)\xi_j(t') \rangle = \sigma^2 \delta_{ij} \delta(t-t')$$

and D is the diffusion coefficient. The functions $f(x_i)$ and $g(x_i)$ are $f(x_i) = \chi - \mu x_i + \alpha x_i(1-x_i)$ and $g(x_i) = x_i(1-x_i)$. Following Van den Broeck et al. (1994), and using a mean-field approximation, the stationary probability distribution at site i is given by

$$P_{st}(x) = \frac{1}{Z} \exp \left[\frac{2}{\sigma^2} \int_0^x dy \frac{f(y) - \frac{\sigma^2}{2} g(y)g'(y) - D(y - \mathbb{E}(y))}{g(y)^2} \right] \tag{27}$$

where Z is a normalization constant and

$$\mathbb{E}(y) = \langle v_i | v_j \rangle = \int y_i P_{st}(y_j | y_i) dy_j \tag{28}$$

represents the steady state conditional average of y_j at neighboring sites $j \in n(i)$, given the value y_i at site i . Using the Weiss mean-field approximation, neglecting the fluctuation in the neighboring sites, i.e., $\mathbb{E}(y) = \langle x \rangle$, independent of y , and imposing the self-consistent

requirement, we obtain

$$\langle x \rangle = \int_{-\infty}^{\infty} dx x P_{st}(x) = F(\langle x \rangle). \tag{29}$$

We are interested in the effect of the diffusion coefficient D in the stationary probability distribution of the site i . The maxima of $P_{st}(x)$ are obtained from $f(y) - (\sigma^2/2)g(y)g'(y) - D(y - \mathbb{E}(y)) = 0$, or

$$x^3 + \frac{x^2(2\alpha - 3\sigma^2)}{2\sigma^2} + \frac{x(2D - 2\alpha + 2\mu + \sigma^2)}{2\sigma^2} - \frac{Dm + \chi}{\sigma^2} = 0 \tag{30}$$

where we put $\mathbb{E}(y) = m$. We see that $D > 0$ raises the coefficient of the linear term in x and the constant term. For the cubic equation $x^3 + Bx^2 + Cx + F = 0$, the condition for having three real roots is given by (Kavinoky and Thoo, 2008)

$$\Delta \equiv \frac{q^2}{4} + \frac{p^3}{27} < 0 \tag{31}$$

with $p = C - B^2/3$ and $q = 2B^3/27 - BC/3 + F$. For $3\sigma^2 > 2\alpha$ ($B < 0$) and $0 < m < 1$, an increase of C and F increases the value of Δ so that condition (31) is more difficult to achieve. In Fig. 6 (lower row) we see that an increase in the diffusion constant D has the effect of hampering the transition from a unimodal to a bimodal distribution. There is competition between σ and D . Fig. 6 (top left) shows the effect of increased σ for $D=0.1$ and Fig. 6 (top right) shows the effect of χ for $\sigma = 1.5$ and $D=1$.

We see in Fig. 6 (top left) that for sufficiently large values of σ bistability can occur. This bistable state can lead to the coexistence of two separate phases in space. In Zhong et al. (2008) the authors show that this type of bistability can be associated with noninfiltrative growth of a benign tumor, a case that corresponds to small noise, as well as an infiltrative type of malignant growth corresponding to intense noise. While increases in σ stimulate bistability, increases in D discourage it, as shown in Fig. 6 (bottom row).

5. Conclusion

We proposed a model to describe population dynamics of CSCs. Our analysis allows us to address a controversy related to the frequency of such cells in tumors. Initially, it was thought that these cells were relatively rare, comprising at most ~1% of the

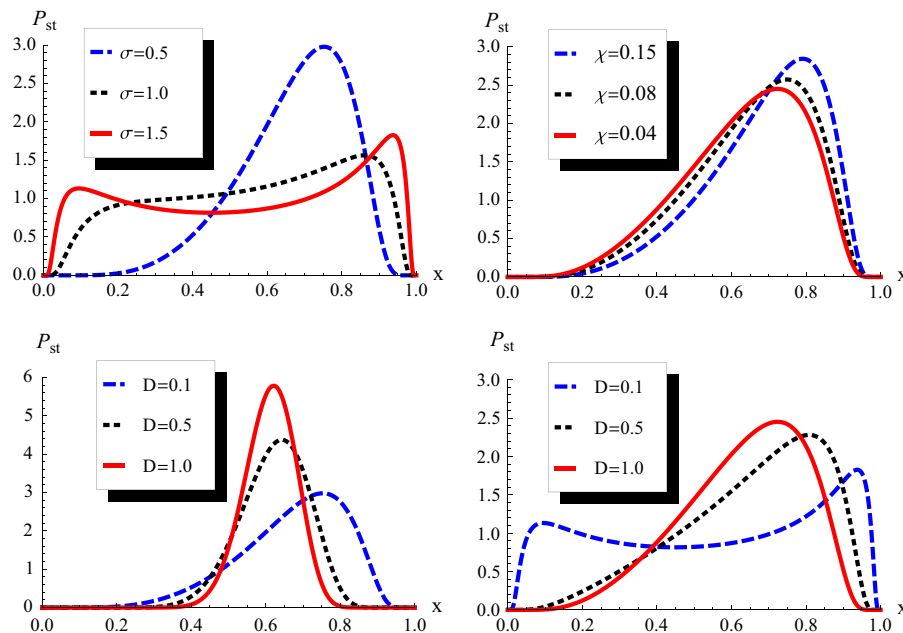


Fig. 6. Top left: effect of noise strength on P_{st} for parameters $\alpha = 0.04$, $\mu = 0.06$, $D = 0.1$ and $\chi = 0.04$. Top right: effect of χ on P_{st} for parameters $\alpha = 0.04$, $\mu = 0.06$, $D = 1$ and $\sigma = 1.5$. Bottom left: effect of D on P_{st} for parameters $\alpha = 0.04$, $\mu = 0.06$, $\chi = 0.04$ and $\sigma = 0.5$. Bottom right: effect of D on P_{st} for parameters $\alpha = 0.04$, $\mu = 0.06$, $\chi = 0.04$ and $\sigma = 1.5$.

cancer cell population. More recent experiments, however, suggest that the CSC population need not be small.

When considering the spread possibility of CSCs, we estimate the conditions to support themselves in a niche with hostile boundary conditions. Without plasticity, there is a threshold of the niche size below which the population cannot be sustained. With plasticity, this threshold is lost and cells can survive in niche, even in small populations. The inclusion of noise in case of no plasticity decreases the minimum required niche size, conspiring again in favor of CSCs.

We briefly considered a simplified model with spatial distribution in a lattice. The possibility of a bimodal stationary probability distribution was observed. Using mean-field theory, we demonstrated that diffusion (D) competes with noise (σ) in the construction of this bimodality. We showed that the discrepancy observed in the frequency of these cells is entirely consistent with the original hypothesis of the existence of cancer stem cells, as long as favorable conditions related to the complexity of the microenvironment are met.

Appendix A. Rescale transforms

In this appendix we detail the rescales made throughout the main text. The first refers to Eq. (6) and the second refers to Eq. (3). The general model written in terms of the reactions is



Using the law of mass action we have

$$\begin{cases}
 \dot{C} = k_1 C \left(1 - \frac{C}{\Omega_C}\right) - k_6 C + k_8 P \\
 \dot{P} = k_3 P \left(1 - \frac{P}{\Omega_P}\right) + k_9 C - k_{10} P
 \end{cases}
 \tag{A.2}$$

with $k_9 \equiv k_5 + 2k_6$, $k_{10} \equiv k_7 + k_8$, $\Omega_C \equiv k_1/k_2$, $\Omega_P \equiv k_3/k_4$ and $k_2 \equiv k'_2/\Omega_2$, $k_4 \equiv k'_4/\Omega_4$. Using the rescale $C \equiv \Omega_C x$ and $P \equiv \Omega_P y$

$$\begin{cases}
 \dot{x} = k_1 x(1-x) - k_6 x + \frac{k_8 \Omega_P}{\Omega_C} y \\
 \dot{y} = k_3 y(1-y) + \frac{k_9 \Omega_C}{\Omega_P} x - k_{10} y
 \end{cases}
 \tag{A.3}$$

Using $t \equiv k_6 t'$ and $\Omega \equiv \Omega_P/\Omega_C$

$$\begin{cases}
 \frac{dx}{dt'} = \frac{k_1}{k_6} x(1-x) - x + \frac{k_8 \Omega}{k_6} y \\
 \frac{dy}{dt'} = \frac{k_3}{k_6} y(1-y) + \frac{k_9}{k_6 \Omega} x - \frac{k_{10}}{k_6} y
 \end{cases}
 \tag{A.4}$$

or

$$\begin{cases}
 x' = Ax(1-x) - x + By \\
 y' = Ey(1-y) + Fx - Gy
 \end{cases}
 \tag{A.5}$$

with $x' \equiv dx/dt'$, $y' \equiv dy/dt'$ and

$$\begin{cases}
 A \equiv \frac{k_1}{k_6} \\
 B \equiv \frac{k_2 k_3 k_8}{k_1 k_4 k_6} \\
 E \equiv \frac{k_3}{k_6} \\
 F \equiv \frac{k_1 k_4 k_9}{k_2 k_3 k_6} \\
 G \equiv \frac{k_{10}}{k_6}
 \end{cases}
 \tag{A.6}$$

A.1. Gradient system

Starting from (A.2) and carrying out the transformation $S = s_1 c$, $P = s_2 p$ and $t = s_3 \tau$, we can write

$$\begin{cases}
 \frac{dc}{d\tau} = k_1 s_3 c \left(1 - \frac{s_1}{\Omega_C} c\right) - k_6 s_3 c + \frac{k_2 s_2 s_3}{s_1} p \\
 \frac{dp}{d\tau} = k_3 s_3 p \left(1 - \frac{s_2}{\Omega_P} p\right) + \frac{k_9 s_1 s_3}{s_2} c - k_{10} s_3 p
 \end{cases}
 \tag{A.7}$$

Imposing $k_2 s_2 s_3/s_1 = k_9 s_1 s_3/s_2$, $k_6 s_3 = 1$ and $s_1 = \Omega_C$, we obtain $s_1 \equiv k_1/k_2$, $s_2 \equiv \Omega_C \sqrt{k_9/k_2}$ and $s_3 = 1/k_6$.

In this way we obtain

$$\begin{cases}
 \frac{dc}{d\tau} = \frac{k_1}{k_6} c(1-c) - c + \frac{\sqrt{k_2 k_9}}{k_6} p \\
 \frac{dp}{d\tau} = \frac{k_3}{k_6} p \left(1 - \frac{\Omega_C}{\Omega_P} \sqrt{\frac{k_9}{k_2}} p\right) + \frac{\sqrt{k_2 k_9}}{k_6} c - \frac{k_{10}}{k_6} p
 \end{cases}
 \tag{A.8}$$

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