

A Possible Explanation for the Variable Frequencies of Cancer Stem Cells in Tumors

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Abstract

A controversy surrounds 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 the total cells. Recent studies have shown that this does not always seem to be the case. Some of these studies have indicated a frequency of 40%. In this paper we propose a stochastic model that is able to capture this potential variability in the frequency of CSCs among the various type of tumors. Considerations regarding the heterogeneity of the tumor cells and its consequences are included. Possible effects on conventional treatments in clinical practice are also described. The model results suggest that traditional attempts to combat cancer cells with rapid cycling can be very stimulating for the cancer stem cell populations.

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Introduction

In recent years there has been increasing evidence for the *Cancer Stem Cell* (CSC) hypothesis [1–4], 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 [5]. *Cancer stem cells* (CSCs) were first identified in leukemia and more recently in several solid tumors such as brain, breast, cervix and prostate tumors [4]. It has been suggested that these are the cells responsible for initiating and maintaining tumor growth [6]. In this paper, we study a model for tumor growth assuming the existence of cancer stem cells, or *tumor initiating cells* [6–8].

The conceptual starting point relevant to the CSC theory is constructed from the known tumor heterogeneity. We now know that cells in a tumor aren't all identical copies of each other, but that they display a striking array of characteristics [9–13]. The CSC theory recognizes this fact and develops its consequences. And one of the most immediate consequences for clinical practice is that conventional treatments can attack the wrong cell type. The appeal of the CSC idea can be described through the following analogy: just as killing the queen bee will lead to the demise of the hive, destroying cancer stem cells, should, in theory, stop the tumor from renewing itself. Unfortunately, things are never that simple. In the hive, workers react quickly to the death of queen by replacing her with a new one. And there is some evidence [8,14] suggesting that the same may occur in a tumor due to a phenomenon known as *cell plasticity*, which allows differentiated tumor cells to turn into cancer stem cells, should the situation call for this. One goal of the present study is to evaluate the possible effects of this plasticity. Analogies with super organisms such as bee colonies are taken much more seriously in [15].

Stem cells in general (the same applies to CSCs) tend to be found on specific areas of a tissue where one particular microenvironment, called *niche* [16,17], promotes the maintenance of their vital functions. Such a niche is 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 through 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.

In this paper, we are interested in investigating a controversy related to the frequency in which CSCs appear in various tumors [18–25]. In the initial version of the CSC theory, it was believed that these cells were a tiny fraction of the total, ranging from 0.0001 to 0.1 % [26]. However, more recent studies have shown a strong dependence of the number of CSCs present in the tumor with the experimental xenograft model used. In explicit contrast to what was previously thought, in [27] a proportion of CSCs of approximately 25% was observed. Other studies have confirmed this observation [26,28,29] with the possibility of a proportion of up to 41% [30]. In [31] the authors provide evidence that this discrepancy may be due to the possibility of phenotypic switching between different tumor cells. Phenotypic switching is interpreted as the possibility of a more differentiated cancer cell being able to, under the appropriate conditions, dedifferentiate into cancer stem cell. This is the cellular plasticity mentioned above.

In [32] 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. Articles [31] and [32] provide different explanations for the discrepancy in

the frequency of CSCs. Our arguments are consistent with the results of [31].

Considering that the complexity of the cellular microenvironment can be modeled by the insertion of a Gaussian noise into the equation that describes the population dynamics, we show that a noise-induced transition occurs. That corresponds to the emergence of a bimodal stationary probability distribution. This happens when the noise intensity σ exceeds a critical limit value σ_{cr} .

In this paper we show that *cell plasticity* [14,33,34], combined with a complex network of interactions modeled as noise, can induce discrepant (too small or too large) stationary CSC populations. Effects related to tumor heterogeneity and clinical treatments will be discussed at the end, occasion in which the model parameters possess the appropriate biological interpretations.

Methods

Model Assumptions

In the model used in this paper, cancer stem cells can perform three types of divisions, according to [35]:

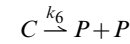
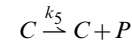
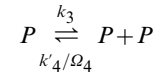
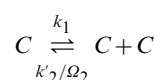
- **symmetric self-renewal:** cell division in which both daughter cells have the characteristics of the mother stem cell, resulting in an expanding population of stem cells;
- **symmetric differentiation:** a stem cell divides into two progenitor cells;
- **asymmetric self-renewal** a cancer stem cell (denoted by C) is generated and a progenitor cell (mature cancer cell, denoted by P) is also produced;

We have 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. We assume, therefore, that besides the three described types of division, 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 dedifferentiated CSC. This hypothesis has experimental support [36]. These dedifferentiated cells do not become cancer stem cells, but rather develop CSC like behavior by re-activating a subset of genes highly expressed in normal hematopoietic stem cells [14]. The biological mechanisms underlying this transformation are described in [31], for example. As mentioned previously, we refer to this process as *cell plasticity*. Finally, we assume that cells are well mixed, so that we can ignore spatial effects.

The model proposed is a natural extension of what is proposed in [37]. We also incorporates the possibility of competition between CSCs and between the progenitor cells in order to limit the exponential growth of the linear model in [37]. This is described in the next subsection.

The basic model

We assume that the dynamics of cancer stem cells (C) and progenitor cells (P) are governed by the following reactions:



The first and second reactions, in the forward sense, models cell proliferation, which occurs at a rate of k_1 and k_3 , respectively. The constants k_2 and k_4 are associated with the reverse process and describe the intensity of competition between the CSCs and progenitor cells, respectively, and prevents their unlimited exponential growth. Many studies, experimental and theoretical, justify this approach [38–47]. As long as no mechanical nor nutritional restrictions apply, the tumor cells go on replicating with a constant duplication time. After a while, however, several constraints force the development of a necrotic core, and growth slows down towards some asymptotic level of saturation. Ω_2 and Ω_4 are constants related to the carrying capacity of the model. The third reaction involving k_5 originates from the asymmetric transformation of CSCs in CSC daughter and progenitor cell types. The reaction involving the k_6 rate is related to a symmetrical division of the stem cell, which gives rise to two progenitor cells. The penultimate reaction is associated with the progenitor cell's death at rate k_7 . Finally, k_8 is the rate of dedifferentiation. All rates have dimension $(\text{time})^{-1}$. The specific time unit (months, quarters, years, etc.) will depend on the type and aggressiveness of the tumor.

Using the law of mass action, we can write

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

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 $C = \Omega_C x$, $P = \Omega_C \sqrt{k_9/k_2} y$ and $t = \tau/k_6$, equation (2) can be written as (see Appendix S1)

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

with

$$\begin{cases} A \equiv \frac{k_1}{k_6} \\ B \equiv \frac{\sqrt{k_8 k_9}}{k_6} \\ E \equiv \frac{k_3}{k_6} \\ F \equiv \frac{\Omega_C}{\Omega_P} \sqrt{\frac{k_9}{k_8}} \\ G \equiv \frac{k_{10}}{k_6} \end{cases} \quad (4)$$

As $\partial f / \partial y = \partial g / \partial x = B$, equation (3) represents a gradient system [48] with potential $V(x, y)$ given by (see Appendix S1)

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

As a consequence [49]:

1. The eigenvalues of the linearization of equation (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).

Sufficiently small F ($\Omega_P \gg \Omega_C$) implies large differences in C and P equilibrium populations. 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 have $(x_0; y_0) = (82; 6710)$.

Adiabatic elimination

The proposed model in (1) is in fact a general model of stem cells and does not 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 normal, stem cell tissue systems. The features associated with cancer stem cells are related to the large carrying capacity of progenitor cells when compared with the carrying capacity of CSCs. This fact is represented numerically by the choice of model parameters made below and is important because it allows a simplification using the adiabatic approximation.

We can write (2) as (see Appendix S1)

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

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

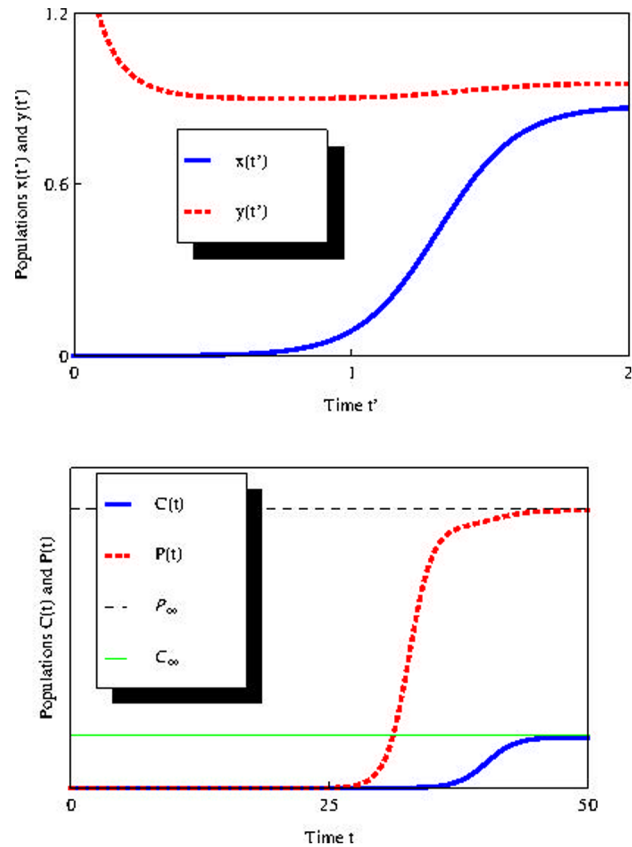


Figure 1. Numerical solutions of differential equations. Top: Numerical solution for rescaled equation (6). Horizontal axis is time t . $x(t)$ and $y(t)$ represent the rescaled population of cancer stem cells and progenitor cells, respectively. **Bottom:** Numerical solution for equation (2). $C(t)$ 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 $C_\infty = 1.8 \times 10^{12}$. $C_\infty / P_\infty = 0.1875$. doi:10.1371/journal.pone.0069131.g001

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

Figure (1) shows the numerical solutions of equations (6, Top) (the rescaled equation) and (2, Bottom) for the parameter values shown in table 1 (which correspond to $A' = 8$, $B' = 5 \times 10^{-4}$, $E' = 10$, $F' = 0.6$ and $G' = 1$, and β is a general parameter with dimension $time^{-1}$ required for dimensional consistency in the following analysis):

Considering the global rate β (we use $\beta \equiv 1$ throughout the text) and assuming $k_5 = r_5 \beta$, $k_6 = r_6 \beta$, we make the usual assumption

Table 1. Parameter Values.

Parameters	k_1	k_2	k_3	k_4	k_5	k_6	k_7	k_8	β
Values	$\beta - k_5 - k_6$	4×10^{-13}	1	10^{-13}	0.1	0.1	0.1	10^{-5}	1

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$r_1 + r_5 + r_6 = 1$ [50] and write $k_1 = r_1\beta = (1 - r_5 - r_6)\beta = \beta - k_5 - k_6$, where r_1, r_2 , and r_3 are probabilities. The values for r_5 and r_6 are consistent with those estimated in [50]. For these parameter values, $\Omega_C \equiv \frac{k_1}{k_2} = 2 \times 10^{12}$ and $\Omega_P \equiv \frac{k_3}{k_4} = 1 \times 10^{13}$ (see Appendix S1). These are rescaled parameters in 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. 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.

Employing standard adiabatic elimination methods, we can write equation (6) as

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

where $\equiv 1/E'$. If we consider $\ll 1$ (this is equivalent to considering the progenitor cell division rate sufficiently large) we can perform adiabatic approximation [51,52] in (8) and, setting $y' = 0$, we obtain the following equation for x , expanding in Taylor series up to first order in :

$$x' = \chi - \mu x + \alpha x(1-x) \quad (9)$$

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

If we set a small enough value for with respect to G', B' and F' , we can further simplify and write $\chi = B'$ and $\mu = 1$. We 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).

The deterministic equation

For comparison with the stochastic study of the next section, we will briefly review the deterministic analysis of the problem. An analytic solution of Eq. (9) is possible. For the initial condition $x(0) = N_0$, one has

$$x(t) = \frac{1}{2\alpha} \left\{ \delta - \sqrt{\kappa} \text{Tan} \left[\frac{1}{2} t \sqrt{\kappa} + \text{ArcTan} \left(\frac{\delta - 2N_0\alpha}{\sqrt{\kappa}} \right) \right] \right\} \quad (10)$$

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

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

The x scaled population size dynamics can be thought of as analogous to the motion of a particle in a 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 polinomial,

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

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 CSCs population. Such behavior, of course, is expected, since an increase of χ means an increase in frequency in which the induced plasticity mechanism occurs, and an increase of δ is an increase of the symmetric renewal rate of cancer stem cells, both of which increase the population.

Results

Noise in the CSCs niche

Environmental noise. In tumor tissue, the growth rate and other parameters are influenced by many environmental factors, e.g., degree of vascularization of tissues, supply of oxygen and nutrients, immunological state of the host, chemical agents, gene expression, protein synthesis, mechanical stress, temperature, radiation, etc [50,53–55]. Given the many perturbations affecting the CSC niche, we expect parameters such as growth rate to be random, rather than fixed, to give a more reliable description. We propose a simplification in the interaction mechanisms between cancer stem cells and their niche by adding an external Gaussian white noise in an attempt to capture the essential aspects of this complexity in a mathematically tractable way.

It is worth noting that in conjunction with nonlinear interactions, noise can induce many interesting phenomena, such as stochastic resonance [56], noise-induced phase transitions [57], noise-induced pattern formation, and noise-induced transport [51,58].

Including external noise. To model the effect of external noise, focusing initially on the CSCs proliferation rate (by making $\alpha \rightarrow \alpha + \xi(t)$, $\xi(t)$ is the noise with the statistical properties described below), we modify the deterministic equation (9) as follows:

$$x' = \chi - \mu x + (\alpha + \xi)x(1-x) = \chi - \mu x + \alpha x(1-x) + x(1-x)\xi, \quad (12)$$

where $\xi \equiv \xi(t')$ is a Gaussian white noise with statistical properties $\langle \xi(t') \rangle = 0$ and $\langle \xi(t') \xi(t'') \rangle = \sigma^2 \delta(t' - t'')$, σ^2 is the variance of $\xi(t')$. Furthermore, χ is considered a constant related to the plasticity phenomenon and α, μ have interpretations similar to those of equation (9), where α now represents the average symmetric division rate. The noise term in equation (12) represents fluctuations in parameter α , due to the complexity of the microenvironment, as discussed above. We include noise in this

term because it is more important in the CSCs population dynamics, since it is this parameter that regulates symmetric reproduction ($C \rightarrow C + C$). Later on we will add yet another noise in the plasticity constant.

We can write the Langevin equation (12) as a stochastic differential equation (considerations concerning the interpretation of the multiplicative term, *i.e.*, if Itô or Stratonovich or other, will be made below) in the form of

$$dx_t = \zeta(x_t, t)dt + \sigma D(x_t, t)dB_t \tag{13}$$

$$\equiv [\chi - \mu x_t + \alpha x_t(1 - x_t)]dt + \sigma x_t(1 - x_t)dB_t,$$

where we define the drift $\zeta(x_t, t)$ and diffusion $D(x_t, t)$ functions and where dB_t is the Wiener process increment [52,59,60]. The stationary probability distribution $P_{st}(x)$ of the stochastic process defined by (13) is given by [52]

$$P_{st}(x) = N \exp\left(-2 \frac{V(x)}{\sigma^2}\right) \tag{14}$$

where N is a normalization constant and $V(x)$ is the stochastic effective potential defined by

$$V(x) = - \int \frac{\zeta(x)}{D(x)^2} dx + \theta \frac{\sigma^2}{2} \ln[D(x)]. \tag{15}$$

Here $\theta = 1$ refers to the Stratonovich interpretation of (13) and $\theta = 2$ to the Itô version. Substituting the drift and diffusion functions, we get

$$V(x) = \frac{x\mu + \chi - 2x\chi}{x - x^2} + (\alpha - \mu + 2\chi) \ln\left(\frac{x-1}{x}\right) + \frac{\theta}{2} \sigma^2 \ln[x(1-x)] \tag{16}$$

and

$$P_{st}(x) = Ne^{-\frac{2\left(\frac{x\mu + \chi - 2x\chi}{x - x^2} + (\alpha - \mu + 2\chi) \ln\left(\frac{x-1}{x}\right) + \frac{1}{2}\theta\sigma^2 \ln[x(1-x)]\right)}{\sigma^2}}. \tag{17}$$

The maximum x_m of P_{st} , which corresponds to the minimum of $V(x)$, can be obtained from the following equation [61]:

$$\zeta(x_m) - \theta \frac{\sigma^2}{2} D(x_m) \frac{d[D(x_m)]}{dx_m} = 0. \tag{18}$$

We see that for $\sigma = 0$, x_m corresponds to the value given by x^* in eq. (11). From the drift and diffusion functions, we get:

$$-x^3\theta\sigma^2 - \frac{1}{2}x^2(2\alpha - 3\theta\sigma^2) + \frac{1}{2}x(2\alpha - 2\mu - \theta\sigma^2) + \chi = 0. \tag{19}$$

The condition for (19) possessing three real roots (corresponding to the two extremes of P_{st}) is [62]:

$$\frac{1}{16} (2\mu + \theta\sigma^2 - 2\alpha)^2 (4\alpha^2 + 4\theta(\alpha - 4\mu)\sigma^2 + \theta^2\sigma^4)$$

$$+ (2\alpha - 3\theta\sigma^2)(2\alpha^2 + 3\theta(\alpha - 3\mu)\sigma^2)\chi - 27\theta^2\sigma^4\chi^2 > 0. \tag{20}$$

For example, for the parameters values $\theta = 2$, $\alpha = 8$, $\mu = 1$ and $\chi = 0.00045$, the critical value σ_{cr} above which a transition is induced in P_{st} is $\sigma_{cr} = 2.68$.

Figures (2) show, in Stratonovich interpretation ($\theta = 1$), (the results do not change qualitatively if we use Itô. For a discussion quite enlightening about the controversial dilemma Itô/Stratonovich, see [63]) the effect of increasing the noise intensity in the stochastic effective potential $V(x)$ (Top) and in the stationary probability distribution $P_{st}(x)$ (Middle). Below is the $\chi - \sigma$ plane. The shaded region corresponds to high values of σ where P_{st} is bimodal. Note that the presence of plasticity (represented by $\chi > 0$) implies the survival of cells populations regardless of noise intensity. Inclusion of external noise can induces the appearance of a bimodal stationary probability distribution, which leads to a result quite different from the deterministic case: while the population in the deterministic case will necessarily reach the value x^* , in the stochastic case the population is unlikely to reach x^* if σ is above its critical value σ_{cr} . It is much more likely to possess a nonzero (if $\chi > 0$), very small population (left peak of P_{st}) or a very large one (right peak of P_{st}). This peak positioned to the right is associated with a population near the maximum value $x \approx 1$ in the rescaled variable $x = C/\Omega_C$. It stands for the possibility that the population of cancer stem cells possess a value close to $C = \Omega_C x^* \approx 2 \times 10^{12}$. This represents a significant fraction of the population of progenitor cells P , a fraction that depends mainly on the equilibrium value x^* of the deterministic equation given by (11), never exceeding this threshold. When we insert noise in the plasticity χ this is no longer the case.

The inhibition of the host's immune system, which can result in a decrease of the microenvironmental complexity, is equivalent in our model to a decrease of σ . Therefore, a xenograft performed in immunosuppressed mice may, over time, present significantly large CSC populations. This may have been the case for the experiments conducted in [27]. On the other hand, the left peak in P_{st} may represent a tiny fraction of the CSCs population, as commonly reported in the pioneering experiments mentioned in the introduction, in which less immunosuppressed mice were used. If $\chi = 0$ and $\sigma > \sigma_{cr}$, it is much more likely that the population becomes extinct as shown in figure (3).

Figures (4) and (5) show five trajectories of the relevant stochastic process, constructed using the Euler algorithm [64], with initial condition $x(0) = 0.1$, for $\sigma < \sigma_{cr}$ and $\sigma > \sigma_{cr}$, respectively. The black curve represents the solution for $\sigma = 0$. We see in Figure (5) that for high values of σ , some trajectories can exhibit spontaneous regression of the CSCs. This seems plausible in light of the supporting evidence from many clinical reports [65].

Figure (6) shows the effect of α on $V(x)$ (Top) and P_{st} (Middle). Sufficiently small values of α refer to unimodal distributions with left asymmetry (blue curve/dot). Intermediate values correspond to bimodal distributions (shaded area in the $\alpha - \sigma$ plane, red curve/dot). Sufficiently high levels of α correspond to unimodal distributions with right asymmetry (black curve/dot).

We conclude in this section that the cell plasticity phenomenon is necessary for the existence of a cancer stem cell population as a small fraction of total tumor cells. Of course, microenvironmental conditions consistent with high noise levels are also necessary.

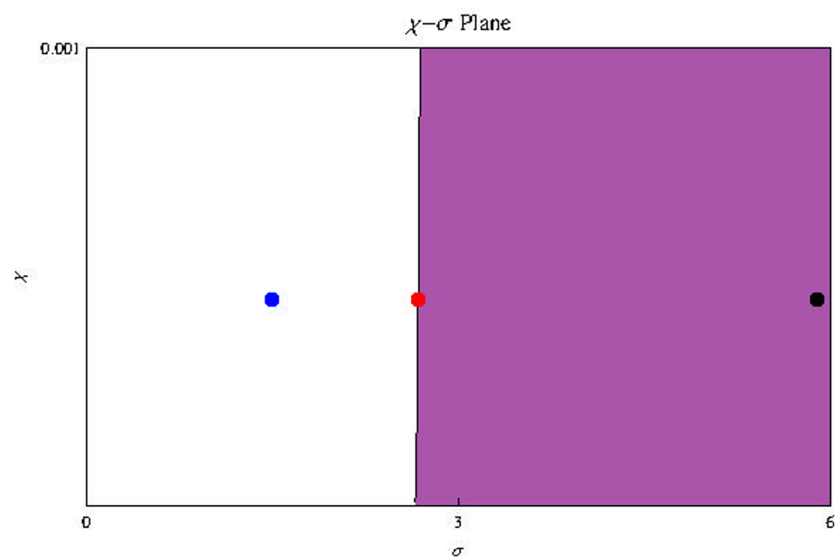
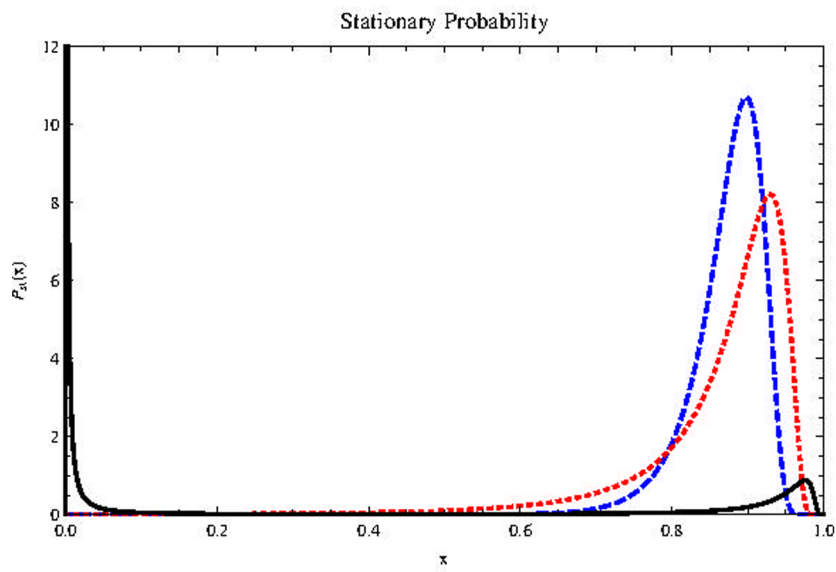
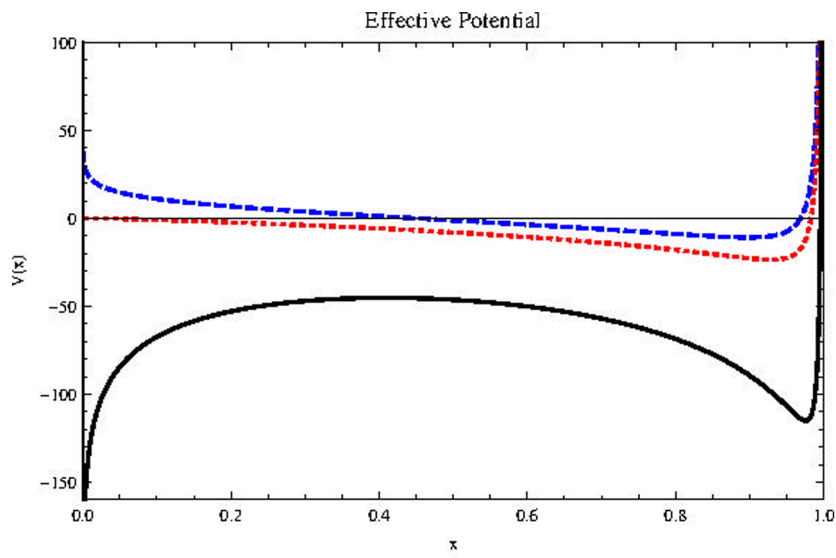


Figure 2. Effects of noise intensity on $V(x)$ and $P_{st}(x)$. Effect of σ on $V(x)$ (on the top) and $P_{st}(x)$ (in the middle) for parameters $k_1 = 1 - k_5 - k_6$, $k_2 = 4 \times 10^{-13}$, $k_3 = 1$, $k_4 = 10^{-13}$, $k_5 = 0.1$, $k_6 = 0.1$, $k_7 = 0.1$ and $k_8 = 0.00001$. Horizontal axis represents population size x . Blue, dashed curve: $\sigma = 1.5$. Red, dotted: $\sigma = 2.68$. Black, thick: $\sigma = 5.9$. Below we also show the $\chi - \sigma$ plane with σ in the horizontal axis.
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Colorful background noise

We can ask ourselves what effects the variability induced by noise in P cells produce in the C population. In equation (9), reminiscences of the presence of P cells are manifested by the presence of χ . We can imagine this term as representing a source of background noisy for C cells. The question that immediately arises is: what are the effects of a noise on the proliferation rate α combined with other noise related to the plasticity in constant χ ?

To answer this question, let's add the noise $\xi(t)$ and $\eta(t)$ as $\chi \rightarrow \chi + \xi(t)$ and $\alpha \rightarrow \alpha + \eta(t)$ and write the equations

$$\begin{aligned} \dot{x} &= \chi - \mu x + \alpha x(1-x) + \xi(t) + \eta(t)x(1-x) \\ &\equiv h(x) + g_1(x)\xi(t) + g_2(x)\eta(t) \end{aligned} \tag{21}$$

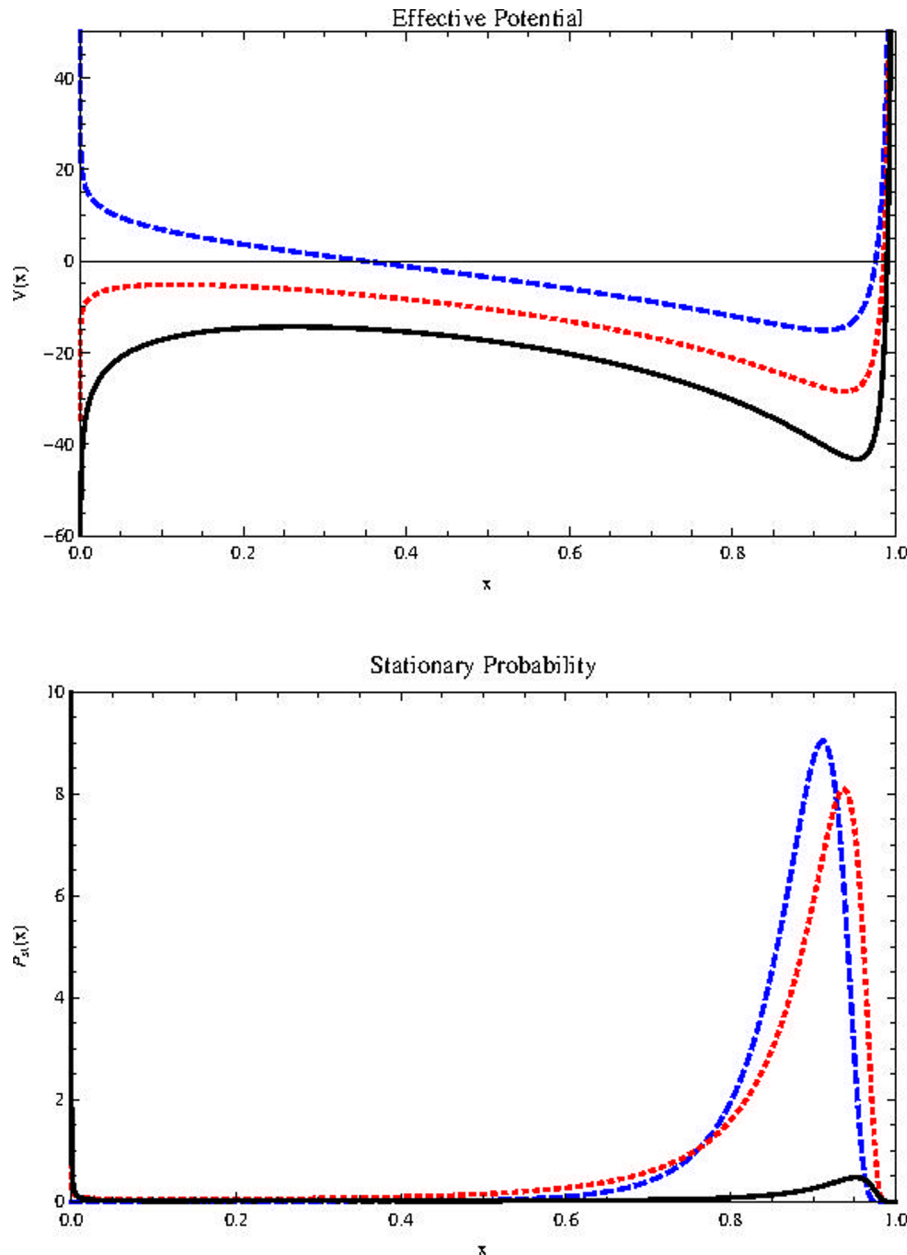


Figure 3. Effects of noise intensity on $V(x)$ and $P_{st}(x)$. Effect of σ on $V(x)$ (on the top) and $P_{st}(x)$ (at bottom) for $\chi=0$. Horizontal axis represents population size x . Blue, dashed curve: $\sigma = 2$. Red, dotted: $\sigma = 3$. Black, thick: $\sigma = 3.74$. Other parameters are as in figure (2). For sufficiently high values of σ , the CSCs population is extinguished.
doi:10.1371/journal.pone.0069131.g003

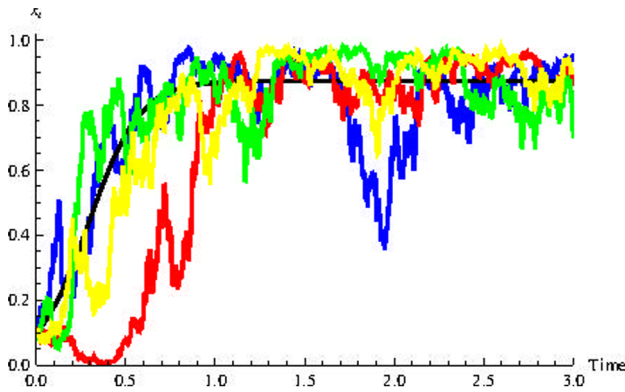


Figure 4. Some possible trajectories for the population dynamics with weak noise. The rugged curves show four realizations of stochastic process (13) with $\sigma=1.0$. The black curve shows the deterministic case, $\sigma=0$.
doi:10.1371/journal.pone.0069131.g004

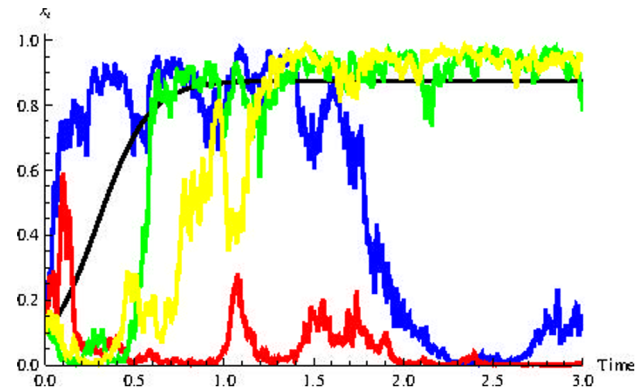


Figure 5. Some possible trajectories for the population dynamics with strong noise. The rugged curves show four realizations of stochastic process (13) with $\sigma=6.0$. The black curve shows the deterministic case, $\sigma=0$. Some cases demonstrate the possibility of spontaneous remission.
doi:10.1371/journal.pone.0069131.g005

$$\dot{\xi} = -\frac{1}{\tau}\xi + \frac{1}{\tau}\zeta(t) \tag{22}$$

where $h(x) \equiv \chi - \mu x + \alpha x(1-x)$, $g_1(x) \equiv 1$ and $g_2(x) \equiv x(1-x)$ and $\eta(t)$ and $\zeta(t)$ are white noises with the following properties

$$\langle \zeta(t) \rangle = \langle \eta(t) \rangle = 0 \tag{23}$$

$$\langle \zeta(t)\zeta(t') \rangle = 2\sigma\delta(t-t') \tag{24}$$

$$\langle \eta(t)\eta(t') \rangle = 2\Gamma\delta(t-t') \tag{25}$$

$$\langle \zeta(t)\eta(t') \rangle = \langle \eta(t)\zeta(t') \rangle = 2\lambda\sqrt{\sigma\Gamma}\delta(t-t'), \tag{26}$$

where σ and Γ are the noise intensity of $\zeta(t)$ and $\eta(t)$ respectively, and λ is the correlation between noises. Equation (22) represents the Ornstein-Uhlenbeck process that displays exponential correlation function described in equation (27) below with correlation time τ . This stochastic process is called “colored noise”.

The two dimensional Markovian process defined by equations (21)–(26) is stochastically equivalent to the one-dimensional non-Markovian process described by (21), (24) and (25), with Gaussian colored noise $\xi(t)$ [52]:

$$\langle \xi(t) \rangle = 0, \quad \langle \xi(t)\xi(t') \rangle = \frac{\sigma}{\tau} \exp\left(-\frac{1}{\tau}|t-t'|\right). \tag{27}$$

We are considering the possibility of a colored noise in χ (for correlation time $\tau > 0$). Thus we intend to capture the effects of noise in the plasticity more realistically.

Following [66], the stationary probability distribution is given by

$$P_{st}(x) = N \frac{C(\tau, x)}{\sqrt{B(x)}} \exp\left[\int^x \frac{h(x')C(\tau, x')}{B(x')} dx'\right] \tag{28}$$

where N is a normalization constant and $B(x)$ and $C(\tau, x)$ are given by

$$B(x) = \Gamma[g_1(x)]^2 + 2\lambda\sqrt{\Gamma\sigma}g_1(x)g_2(x) + \sigma[g_2(x)]^2$$

and

$$C(\tau, x) = 1 - \tau \left(h'(x) - \frac{g_1'(x)}{g_1(x)} h(x) \right).$$

In figure (7) we show the stationary probability distribution with $\lambda=0.9$, $\tau=0$, $\sigma=1 \times 10^{-9}$, $\Gamma=5$ (blue), $\Gamma=10$ (red, dotted) and $\Gamma=15$ (black, dashed). Now we see that even for very small σ (the background noise intensity due to χ), extinction of CSCs is possible for sufficiently high Γ (the noise due to α), which does not occur when χ is deterministic. For $\tau \neq 0$ this statement becomes more evident, as shown in figure (8) where we used the same parameter values of previous figure with $\Gamma=10$ except that $\tau=0.1$ for blue thick curve and $\tau=0$ for red dotted curve. The conclusion is that the induction of fluctuations in the population of progenitor cells (represented by the background noise due to χ) can promote CSC extinction.

Some remarks on the interpretation of σ , Γ and λ .

Before we continue the discussion about the effects of background noise, we will make some considerations about the interpretation that we assign to the parameters σ , Γ and λ .

About σ : Given equation (9), we can interpret the system formed by CSCs as an isolated system that exchanges “particles” (P cells) with the external environment and “feels” the disturbances of the medium through the parameter χ , the window of communication with the outside. The intensity of these external disturbances is represented by parameter σ , and $\xi(t)$ can therefore be interpreted as an external noise, external to the system formed by CSCs. When the body of the tumor is subjected to the effects of clinical treatments such as radiotherapy, chemotherapy or thermotherapy [67], the increase in the intensity of this parameter can be considerable.

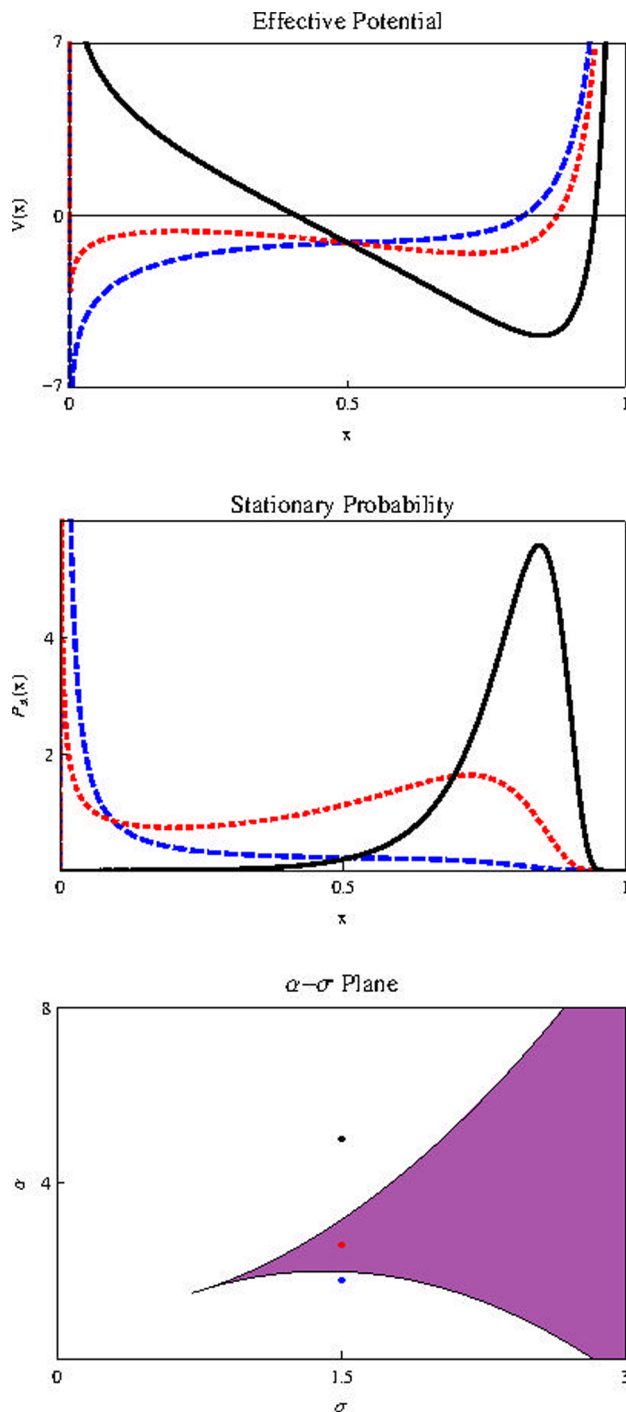


Figure 6. Effect of α on $V(x)$ (on the top) and $P_{st}(x)$ (in the middle) and the α - σ plane at bottom (α on the vertical axis and σ on the horizontal axis). The parameters are: $\sigma=1.5$ in all figures. Blue-dashed: $\alpha=2.2$. Red-dotted: $\alpha=2.6$ and Black-thick: $\alpha=5$. doi:10.1371/journal.pone.0069131.g006

About Γ : The direct contact of CSCs with their immediate microenvironment (their niche) is what enables exchange of nutrients and complex biochemical interactions that allow for cell life. Variability in this context represented by Γ , can be interpreted as an internal noise (internal noise here is not related in any way to the internal demographic noise as modeled by master equations). This internal noise affects the cell proliferation rate α .

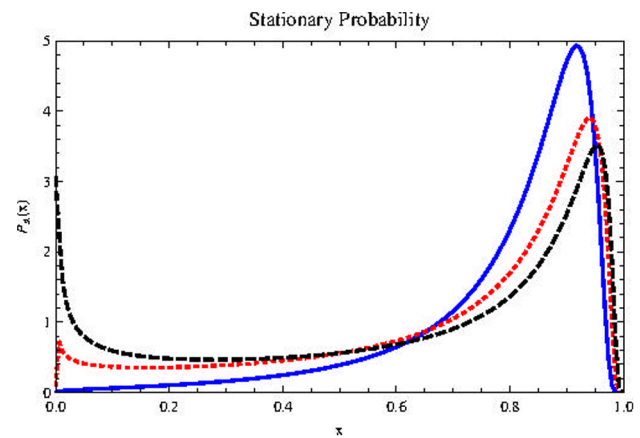


Figure 7. Stationary probability distribution for different values of Γ . $P_{st}(x)$ with parameters $\lambda=0.9$, $\tau=0$, $\sigma=1 \times 10^{-9}$, $\Gamma=5$ (blue), $\Gamma=10$ (red dotted) and $\Gamma=15$ (black, dashed). Horizontal axis represents population size x . Fluctuations in the progenitor population P can stimulate CSCs extinction. doi:10.1371/journal.pone.0069131.g007

About λ : A very important aspect about cancer, as mentioned in the introduction, is that tumors contain heterogeneous populations of cells, which may contribute differently in extent and mechanism to the progression of malignancy [68]. Tumor heterogeneity is possibly one of the most significant factors that most treatment methods fail to address sufficiently. While a particular drug may exhibit initial success, the eventual relapse into tumor growth is due in many cases to subpopulations of cancer cells that are either not affected by the drug mechanism, possess or acquire a greater drug resistance, or have a localized condition in their microenvironment that enables them to evade or withstand the treatment. These various subpopulations may include cancer stem cells, mutated clonal variants, and tumor-associated stromal cells, in addition to cells experiencing a spatially different condition such as hypoxia within a diffusion-limited tumor region.

This important aspect is related to different forms in which the various sub-populations respond to various types of internal and external stimuli. Thus, we argue that the correlation coefficient λ

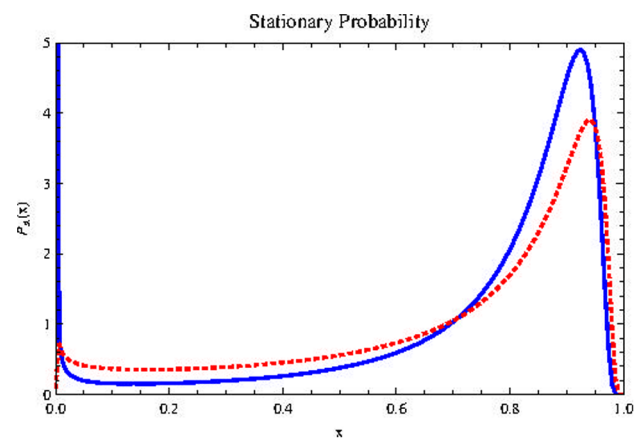


Figure 8. Dependence of P_{st} with τ . $P_{st}(x)$ with parameters $\lambda=0.9$, $\tau=0$ (red curve), $\tau=0.1$ (blue curve), $\sigma=1 \times 10^{-9}$, $\Gamma=10$. Horizontal axis represents population size x . High values of τ facilitates CSCs extinction. doi:10.1371/journal.pone.0069131.g008

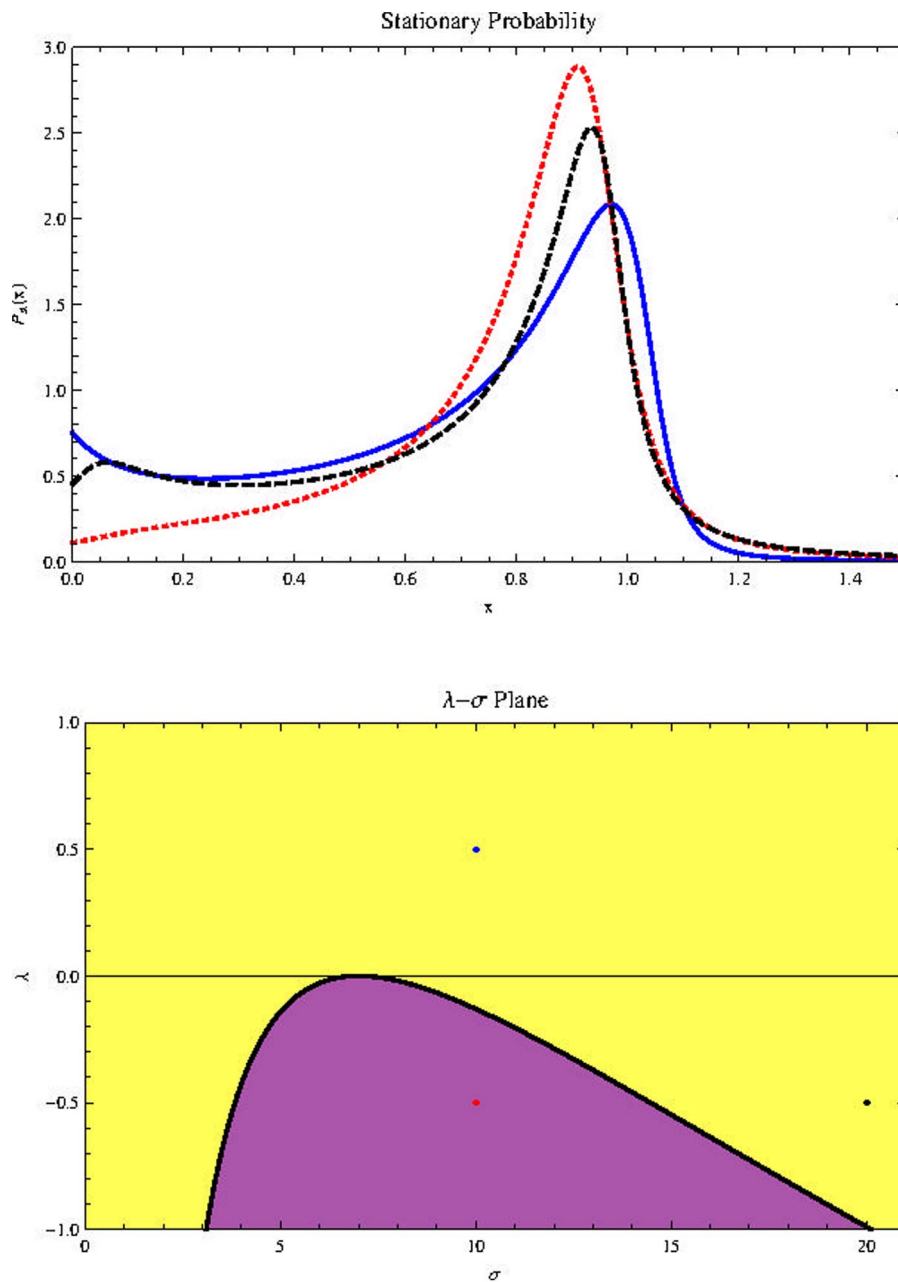


Figure 9. Effect of λ on $P_{st}(x)$ (top) with parameters $\sigma=10$, $\lambda=0.5$ (Blue, thick line), $\sigma=10$, $\lambda=-0.5$ (Red, dotted line), $\sigma=20$, $\lambda=-0.5$ (Black, dashed line), $\tau=0$, $\Gamma=10^{-1}$, $\mu=1$, $\alpha=8$, $\chi=0.00045$. Horizontal axis represents population size x . Bottom: λ - σ plane with σ in the horizontal axis.
doi:10.1371/journal.pone.0069131.g009

between the noise acts as a measure of this heterogeneity between the two populations we are considering. Since each noise is related primarily to a specific cell type, we have that parameter λ “measured” different responses of these cells to these stimuli. If the different subpopulations behave more or less in the same manner when subjected to various stimuli (low heterogeneity), λ tends to approach 1. If the behaviors are independent, $\lambda \approx 0$. If the responses to the stimuli tend to be opposite (great heterogeneity), λ tends to approach -1 .

Figure (9) (Top) shows the possible effect of changes in λ in stationary probability distribution for the parameters values shown in the description. The results for $\tau \neq 0$ are analogous. Below is the

λ - σ diagram. In the yellow region the stationary probability distribution is bimodal. We see that negative values of λ favor the survival of cancer stem cells. This result is no surprise, since it is known that the heterogeneity of the tumor provides the phenotypic variation required for natural selection to act to increase the robustness (a property that allows a system to maintain its function despite internal and external perturbations) of the tumor [10].

Possible effect of conventional treatments

The proposed model in this paper is idealized and highly simplified. In addition, it does not rely on biological data for some

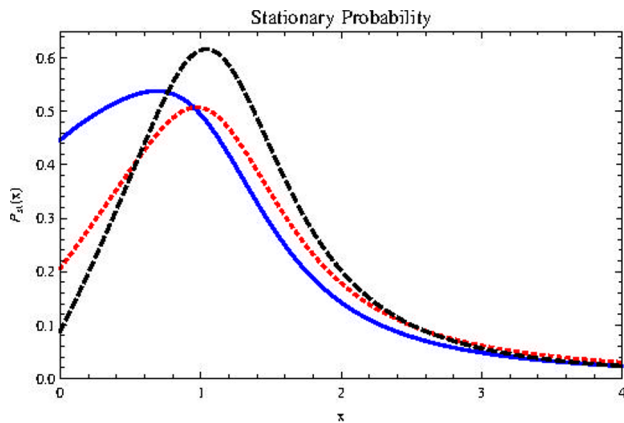


Figure 10. Effect of τ on $P_{st}(x)$ with parameters $\tau=0.0$ (Blue, thick line), $\tau=0.05$ (Red, dotted line), $\tau=0.1$ (Black, dashed line), $\Gamma=10$, $\sigma=10$, $\lambda=-0.5$, $\mu=1$, $\alpha=8$, $\chi=0.0$. Horizontal axis represents population size x . doi:10.1371/journal.pone.0069131.g010

values of the k parameters. Therefore, the conclusions we can get from it in this section are merely theoretical speculations. Having said this, let's try to estimate the effects that conventional treatments may have on the CSC population.

In the proposed model we imagine that such treatments work directly on progenitor cells, since such treatments are designed to act mainly in cells that reproduce faster [69]. Thus, the effect on CSCs is indirect via background noise in a manner that is analogous to what was discussed above. Now we have the possibility of noise intensity σ being much larger. Treatments act to eliminate progenitor cells and the tendency, therefore, is for parameter χ to approach zero. Since this is the parameter that connects the “underlying world” of cancer stem cells to the world of progenitor cells, we could imagine that the contact between the worlds is lost. This is no problem, however, because now we think of the background noise as an additive noise that arises as a result of external perturbations to the CSCs. Thus, we can consider equation (21) with $\chi=0$ and think about the noise $\xi(t)$ as is commonly understood when you introduce an additive noise in the equations “phenomenologically” or “by hand”.

For large values of σ , the parameter of greater relevance is τ . Figure (10) shows the effect on the stationary probability distribution: Positive values, even small ones, help cancer stem cells considerably not going extinct. The most important, however, is another fact, which is explicitly shown in this figure: The main consequence of exploring the possibility of an intense additive noise is that the population of cancer stem cells may be considerably greater than the maximum population of the deterministic model $C_\infty = \mathcal{Q}_{C^*}$. This means that the effects of conventional treatments that act primarily in the fast cycling cells, here represented by progenitor cells, can be extremely exciting for CSC proliferation. *Cancer stem cells enjoy noise.*

Discussion

The importance of cellular plasticity in the conclusions we have drawn so far, is evident. In [32] the authors point out potential conceptual difficulties associated with the phenotypic switching hypothesis. They argue that if cancer cells can turn into cancer stem cells, then the very notion of CSC becomes blurred, since in this way the cancer cells could dedifferentiate at any time and acquire the potential immortality of CSCs. In the authors words,

“the distinction between phenotypic switching and the original conventional model, run the risk of becoming purely semantic.” From a clinical perspective, this means that the existence or not of the CSCs is irrelevant, since we must try to kill all tumor cells and not just focus on tumor initiating cells. However, the fact that we have to kill the greatest possible amount of tumor cells does not mean that we have to try to do it in the same way for all of them. In [70], a near-twofold reduction in the density of brain tumors in mice was observed when authors combined standard anticancer drugs with the selective killing of CSCs, if compared with standard agents alone. With regard to the phenotypic switching property, selectively killing a population of CSCs can make room for progenitor cells to dedifferentiate and occupy this vacant niche space. Trying to limit “stemness” instead, by changing conditions of the niche that supports the life of CSCs, may be a more promising therapeutic strategy. This idea is in line with what is thought to be necessary for major mass extinctions [71].

Until now the properties of cancer stem cells were tested only in transplantation assays and their very existence have been questioned several times [6–8]. In [72], the authors use a lineage tracing technique that allows permanent, *in vivo* fluorescent marking of stem cells and their progeny, trying to put an end to the controversy of the existence of cancer stem cells in solid tumors. They unraveled the *in vivo* mode of tumor growth in its native environment and found that the majority of labeled tumor cells in benign skin tumors have only limited proliferative potential, whereas a fraction has the capacity to persist in the long term, giving rise to progeny that occupies a significant part of the tumor. Progression to cancer in benign skin tumors was associated with expansion of the CSC population and a decrease in the production of non-stem cells. This suggests that tumor evolution enriches the CSC population. Designing therapies that prevent increases in stemness may be a means to restrict tumor progression into cancer.

Conclusion

We propose a model to describe the population dynamics of cancer cells, using the theory of cancer stem cells (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 $\sim 1\%$ of the cancer cell population. More recent experiments, however, suggest that the CSC population need not be small. Taking into account the cellular plasticity property, which permits more mature cells to dedifferentiate into cells with characteristics of stem cells, we show 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. We assume that these conditions can be described by the inclusion of noise in the rate of tumor growth or in the rate at which the plasticity phenomenon occurs.

In the model where we take into account only the noise in the rate of CSC proliferation, we conclude that there is the possibility of the stationary probability distribution being bimodal. In the model that also incorporates noise in parameter χ associated to the cellular plasticity phenomenon, the possibility of extinction arises and the fraction of CSCs in the tumor can assume quite high values, exceeding the threshold C_∞ . The “color” of this noise stimulates the CSC population. The correlation coefficient between noises is interpreted as a measure of heterogeneity between progenitor cells and cancer stem cells, since different cells respond to stimuli in different ways. This heterogeneity also excites the CSC population.

In future work we plan to extend the model to include spatial distribution. We will also investigate the possibility of a model based on a master equation to investigate the effects of demographic stochasticity.

Supporting Information

Appendix S1 Appendix to a possible explanation for the variable frequencies of cancer stem cells in tumors. (PDF)

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Author Contributions

Conceived and designed the experiments: RVS LMS. Analyzed the data: RVS. Wrote the paper: RVS LMS.

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