The ecology of cancer differentiation therapy I: non-spatial models

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A promising, yet still under development a roach to cancer treatment is based on the idea of differentiation therapy (DTH). Most tumours are characterised by poorly differentiated cell populations exhibiting a marked loss of traits associated to communication and tissue homeostasis. DTH has been suggested as an alternative (or complement) to cytotoxic-based a roaches, and has proven successful in some specific types of cancer such as acute promyelocytic leukemia (APL). While novel drugs favouring the activation of differentiation therapies are being tested, several open problems emerge in relation to its efectiveness on solid tumors. Here we present a mathematical a roach to DTH based on a well-known ecological model used to describe habitat loss in a logistic-growing population experiencing death. This model seems to account for some of the observed clinical and in vitro outcomes of DTH while it provides relevant insight into potential treatment scenarios. Furthermore, the same ecological a roach is tested in a hierarchical model that accounts for cancer stem cells, proving that DTH might be an effective o ortunity to tackle all the self-renewing cellular compartments in a tumor. We show that the lessons learnt from metapopulation ecology can help guide future developments and potential difficulties of DTH.

I. INTRODUCTION

Cancer is a set of complex diseases, and the success of tumor progression (and the eventual death of its recipient organism) requires a number of changes to make cells capable of overcoming selection barriers. These changes provide the source of proliferative power that makes tumors able to expand and evolve (Weinberg 2015). One particularly remarkable feature of cancer cells is the loss of molecular markers associated to the differentiated state. As the tumor evolves, some cancer cells a ear to be in a de-differentiated state closer to early developmental stages, similar to that of normal stem cells, with increased potential for self-renewal and plasticity (Magee et al 2012). To some extent, cancer is a disease of multicellularity: the cooperative order required to maintain organism's coherence is broken in favor of unicellular-like traits (Aktipis et al 2015, Davies et al 2011).

The standard treatment of tumors has been grounded in the use of either specific cytotoxic drugs or radiotherapy, or a combination of both. The success of this a roach has been discussed and even questioned over the last decades (Gatenby 2009). Treatments involving a general mechanism of cell damage associated to toxicity are often inefficient and can trigger evolutionary pressures that select aggressive and resistant clones (Pe er et al. 2011). As a consequence, cytotoxic therapies can create undesirable side effects such as the development of metastasis. To a large extent, despite the undeniable success in our increasing understanding of the underlying molecular basis, cancer remains incurable. Because of these limitations, novel a roximations have been proposed mainly from evolutionary and mathematical biology. They are based on the view of cancer as an ecological and evolutionary problem (Merlo et al 2006; Korolev et al 2014). In particular, ecological principles can guide alternative insights to cancer development and treatment (Basanta and Anderson 2013).

One specially promising alternative to conventional cytotoxic agents is the use of so called *differentiation therapy*. Here the a roach, early suggested more than 50 years ago (Pierce and Wallace, 1971; Pierce 1983) is inspired in the observation that one hallmark of cancer is the loss or blocking of differentiation that leads to cells with increased potential for self-renewal and plasticity. Differentiation therapy (DTH) involves the use of diverse molecular agents able to induce differentiation in cancer cells. Since differentiated cell types are a terminal branch of development, the goal is to facilitate this process and remove cancer cells from the proliferative compartment. A growing family of DTH agents include neural growth factors, all trans retinoic acid, arsenic trioxide, butyric acid or cAMP, which have been shown some degree of differentiation-inducing capability both in vitro and/or in vivo. The success of DTH is well illustrated by the best known case study, namely its use in Acute Promyelocytic Leukemia (APL) by means of a combined cytotoxic therapy with all-trans retinoic acid (RA) (Huang et al., 1988).

A few numbers reveal some features of the impact of DTH. Again within the context of APL, before the use of DTH, cytotoxic-based therapies increased the likelihood of remission from 50 to 80 % but with only a third of long-term survival. The combination with RA changed drastically the situation, with 90 % remission

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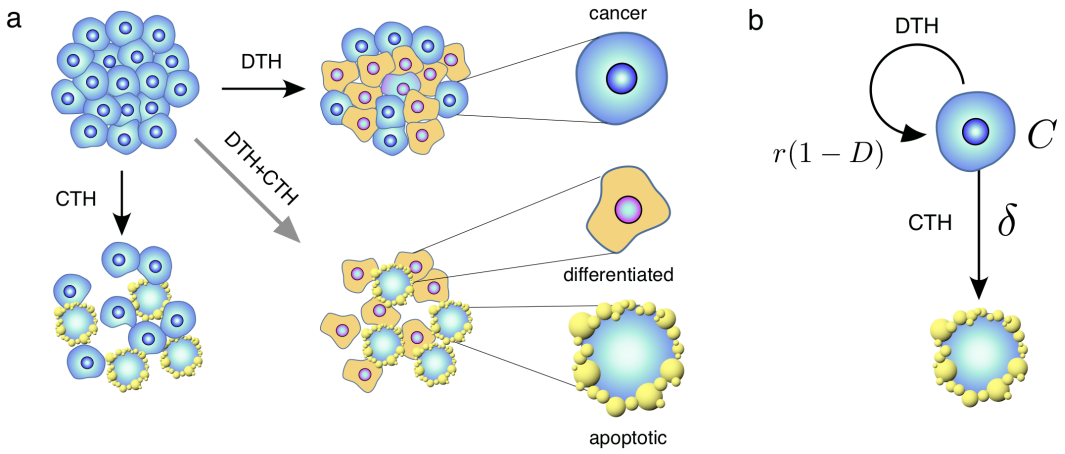

FIG. 1: A metapopulation model of tumor differentiation therapy. In tackling alternative treatments to cancer progression, DTH exploits the potential of blocking tumor growth by activating differentiation pathways than might have been blocked along the evolution of the cancer cell population. An example is provided by APL: the synergistic effect of targeting both differentiation and apoptosis pathways can eradicate the disease (figure **(a)**). In **(b)**, a minimal a roach based on the metapopulation ecology of habitat-loss is capable of reproducing the results of **(a)** while presenting further insight into the possible dynamics of the therapeutic a roach.

and a 75 % cure (see Dela Cruz and Matushansky 2012 and references therein). Interestingly, when DTH alone is used, despite cell differentiation perfectly well identified (it can actually be massive) only combination with standard drugs seems to be really successful. How can a model account for these results?

Over the last years, DTH agents have been also used for treating solid tumors. In contrast with the APL case study, the therapeutic effect of the differentiation-inducing agents on solid tumors is not strong when compared with that of conventional chemotherapeutic agents. However, because most of the differentiation-inducing agents can potentiate the effect of conventional chemotherapy or radiation therapy, combination therapy might be used as a second- or third-line therapy in patients with advanced cancer. Are the solid nature of the tumors, their genetic complexity or their hierarchical architecture leading factors for this limited success? Here too, a theoretical model can be helpful in interpreting the observations and provide valuable insight. The analysis presented below is based in an ecological a roach to tumor dynamics inspired in well-established results from habitat loss and fragmentation in metapopulations (Mollanen and Hanski 1998 Hanski 1999).

II. METAPOPULATION MODEL OF TUMOR DIFFERENTIATION THERAPY

The simplest form of our mathematical a roach taken here is based on the assumption that two different therapies act together on the growth of a cancer cell population. The cancer cell population grows in a logistic manner while being inhibited in two different ways. The first corresponds to standard therapies, based. on cancer-targeted cytotoxic drugs.In this first scenario, a population of cancer cells C expands at some rate r within an environment (that includes the host tissue) while experiences a death rate caused by the drug. The model reads:

$$\frac{dC}{dt} = rC\left(1 - \frac{C}{K}\right) - \delta C \tag{1}$$

where for simplicity the carrying capacity will be normalised to one ($K = 1$) and thus C can be understood in terms of the fraction occupied by the tumor. The last term in the rhs indicates the linear decay caused by the drug. The parameter δ would here weight This is equivalent to the well-known Levins model, where growth and decay would be related to colonization and extinction (Levins 1969). The analysis of this system reveals that two equilibrium states C^* are possible: extinction $C^* = 0$ and $C_1^* = 1-\delta/r$. Tumor growth will occur when $r > \delta$, i. e. if growth overcomes the negative impact of treatment.

How can differentiation treatment be introduced in this a roach? The impact of DTH is dynamically very different. As a fraction of cancer cells gets differentiated, they have an impact in population dynamics as they contribute to the overall population and thus limit the potential carrying capacity. If D weights the effectiveness of the DTH the simplest extension of the previous model incorporates the amount of

$$\frac{dC}{dt} = rC(1 - D - C) - \delta C \tag{2}$$

The ecological equivalent here is the extended Levins model incorporating habitat loss (Bascompte and Solé, 1996, Figure 1b). In habitat loss models, the D term is

associated to the amount of habitat that has been degraded thus being unavailable to colonisation. In figure 1c the basic description of the model is graphically displayed (see below). The interpretation within the context of DTH is easy: the fraction of cancer cells that have become differentiated correct the maximum achievable. The non-trivial fixed point is now:

$$C_1^*(D,\delta) = 1 - D - \frac{\delta}{r} \tag{3}$$

In this case, cancer decay will be expected provided that differentiation (and thus the efficiency of DTH) is larger than a critical value:

$$D > D_c = 1 - \frac{\delta}{r} \tag{4}$$

One particular relevant and non-obvious result from this result is that even if there's a arently room for further growth, the dynamics of the system reveals a transition from cancer growth to cancer decay. Once the critical point D_c is reached, tumor dynamics faces extinction.

In figure 2a we show a diagram for D against δ space where the critical line $D = D_c$ has been used to separate the two phases associated to cancer progression and cancer decay. The lower axis indicates the efficiency of single cytotoxic therapy in the absence of DTH. A threshold is found for $\delta_c = r$ as defined from model (1). By adding the second axis (differentiation) we can see that lower levels of chemotherapy are required to achieve tumor decay. This is at the core of our explanation for the success of DTH: the combination of both treatments can successfully achieve remission when the right combination of chemotherapy and differentiation is used. Since toxicity can be reduced provided that D is large enough, the diagram su orts the observed success and long-term remission in APL. On the other hand, the levels of differentiation that are required for small δ can be very large (perhaps unrealistically large). An important point needs to be made here: could DTH only also achieve remission? The model in this case reads:

$$\frac{dC}{dt} = rC(1 - D - C) \tag{5}$$

which can be shown to behave always in the same way: a logistic growth towards an intermediate level $C^* = 1 - D$ with no threshold value. This implies, and seems consistent with clinical evidence, that only-DTH will fail to succeed given the lack of a remission threshold.

In order to understand how the combined therapy model works and what are the differences between the two therapies in terms of their dynamical impact, let us consider an early growth scenario where $C \ll 1 - D$. The model described by equation (2) now reads

$$\left(\frac{dC}{dt}\right)_{C \ll 1-D} \sim [r(1 - D) - \delta]C \tag{6}$$

with exponential growth solution, i. e. starting from an initial population $C(0)$,

$$C(t) \approx C(0)e^{[r(1-D)-\delta]t} \tag{7}$$

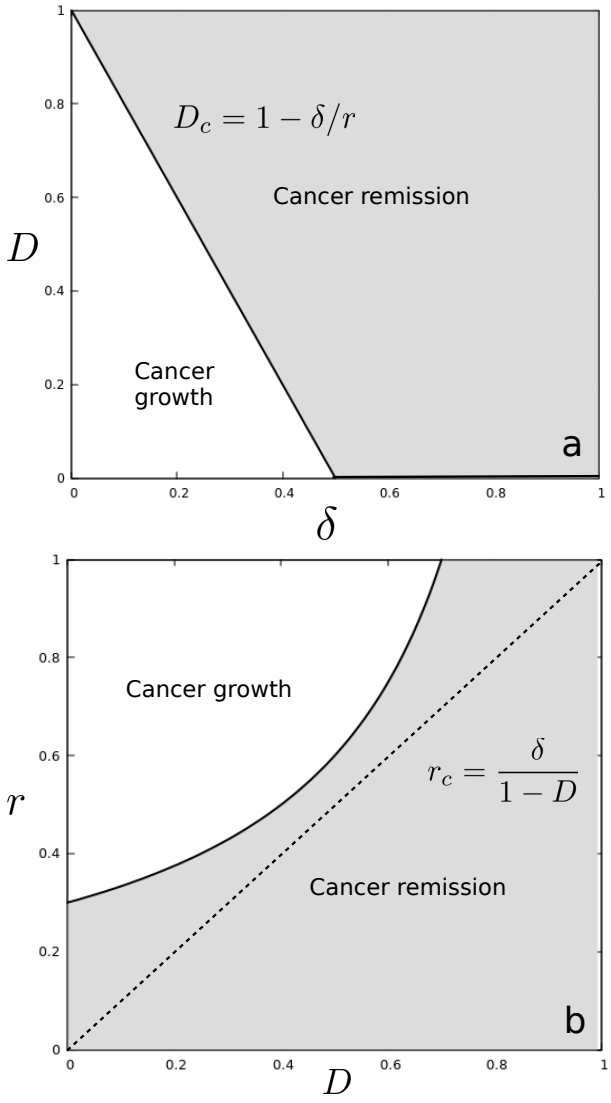

FIG. 2: Phase space of cytotoxic-differentiation combination therapies. In **(a)**, the use of DTH can induce cancer remission even for death rates smaller than the tumor cells replication rate. In **(b)**, the nonlinear effect of DTH is pictured. For $C << 1 - D$, the replication rate necessary for cancer outgrowth r_c grows linearly with δ (dashed line), while increasing D imposes a stronger condition (curved black line).

which gives cancer expansion only if the growth rate of the cancer cells is larger than a threshold value r_c, namely

$$r > r_c = \frac{\delta}{1 - D} \tag{8}$$

We can a reciate here the enormous difference between the impact of cytotoxic therapy (acting linearly) and DTH (acting in a nonlinear fashion). In figure 2b we summarize these results by displaying cancer growth rates against the efficiency of DTH. The curve separating the two phases is now described by the previous $r_c(D)$ equation. Values below the curve are associated to cancer remission. Growth will occur in the u er part (white

area) but the values of the growth rate allowing that to occur rapidly increase with D. In the absence of differentiation, the tumor will grow if $r > \delta$, but increasing D values push this threshold in such a way that higher replication will be needed, which might be impossible to achieve, thus leading to cancer decline. A quick comparison with standard epidemiology models shows that this corresponds to epidemics su ression through vaccination:as more individuals are vaccinated and thus moved out from the pool of potentially infected individuals, the pathogen requires an increase in infectivity that might not be achievable.

Several interesting points arise from describing cancer differentiation under the perspective of habitat-loss ecological models. First of all, the existence of a differentiation threshold for tumor arrest indicates the possibility of differentiation therapy driving an all-or-none response similar to that seen in APL treatment outcomes (Huang et al. 1988). However, this threshold generates from considering a single population under differentiation, so that its significance is probably restricted to genetically simple and homogeneous cancers (de Thé 2017). Further modeling needs to take tissue complexity into account.

Additionally, the model indicates that DTH is only effective when combined with cytotoxic therapies directly targeting the cellular death rate δ (Figure 1a). This could explain why arsenic, that triggers p53-driven senescence a art from differentiation (Ablain et al. 2014), is functional as a single-agent therapy, while retinoic acid and other differentiation drugs that do not target cell death specifically require combined cytotoxic therapy to success (Dos Santos et al. 2013). The model reflects that early tumor growth is also an interesting scenario for differentiation a roaches. Interestingly, the effect of DTH on a tumor clearance threshold is nonlinear and of greater efficiency compared to that of cytotoxic agents. This introduces the notion that tumor stage might be a significant parameter when predicting sensitivity to DTH.

The previous model ignores several features of cancer populations, including heterogeneity in mutational landscape (Gerlinger et al., 2012) and differentiation degree (Magee et al., 2012). However, it is worth noticing that previous work using a multispecies approach to a diverse community reveals very similar results when habitat loss is considered under colonization-extinction trade-offs (Solé et al 2004). Another important factor is the potential role of spatial degrees of freedom: DTH is not yet completely understood in solid tumors (Cruz and Matushansky, 2012). These problems will be considered elsewhere, since in this paper we want to keep our model a roach as close as possible to the standard toy models of habitat loss. One important extension that keeps the simple a roach is to consider non-homogeneous tissues where stem cells play a leading role.

III. DIFFERENTIATION THERAPY IN HIERARCHICAL TISSUES

A wide set of cancers types are hierarchically organized, with a population of *cancer stem cells* driving tumor growth and plasticity (Meacham and Morrison, 2013). Besides the relevance of this in radio- and chemotherapy resistance (see e.g. Dean, Fojo and Bates, 2005), we are interested in understanding if the hierarchical architecture specific to a stem cell compartment is related with the fact that most solid and genetically complex tumors do not show valuable responses to differentiation therapy (Cruz and Matushansky 2012, de Thé 2018).

A wide range of mathematical models have been powerful in highlighting the sometimes undercover role of cancer stem cells (see e.g. Michor 2008 and references therein). We here consider a minimal view of the accepted modeling of tissue architecture as a set of hierarchically organized cancer subpopulations (Michor et al. 2005, Dingli et al. 2007, Solé et al 2008, Figure 3). To understand the role of habitat loss through DTH in such a hierarchical structure, we start with only two populations of seeding cells S and dying cells C

$$\frac{dS}{dt} = r_s S(1 - D - S - C) - \mu S \tag{9}$$

$$\frac{dC}{dt} = r_c C(1 - D - S - C) + \mu S - \delta C \tag{10}$$

The only considerations here are that a population of stem cells S replicates, sensible to loss of reproductive resources and overall tumor population, at rate $r_S(1 - D - C - S)$, and differentiates into general cancer cells at rate μ. Such cancer cells are still able to replicate at a lower rate $r_c < r_S$ and die at rate δ. This minimal construction is descriptive of a more general framework that usually takes into account several differentiation stages (Molina-Peña and Álvarez 2012, Werner et al. 2016).

It is relevant here to mention the conceptual differences between D, the density of differentiated habitat no longer colonizable by self-renewing cells, and μ, the rate at which CSCs divide into progenitor cancer cells. Learnings from APL show us that specific drugs, such as RA or Arsenic, might drive complete differentiation of large tumor masses (de Thé 2018). On the other hand, we know that drugs such as imatinib actually reduce the rate or speed of progenitor cell production μ in BCR-ABL mutated leukemias such as CML (Michor et al 2005). We will later discuss the possible outcomes and therapeutic effects of the complementary roles of D and μ.

Two obvious attractors of the system are the cancer-free scenario, $A_0 = (0, 0)$ and the single population without seeding, $A_1 = (0, 1 - D - \delta/r_c)$, that we have already studied in the previous section. In particular, we know that this attractor collapses as the density of differentiated habitat surpasses a given threshold $D_c = 1 - \delta/r_c$. However, clinical and experimental insights from the last

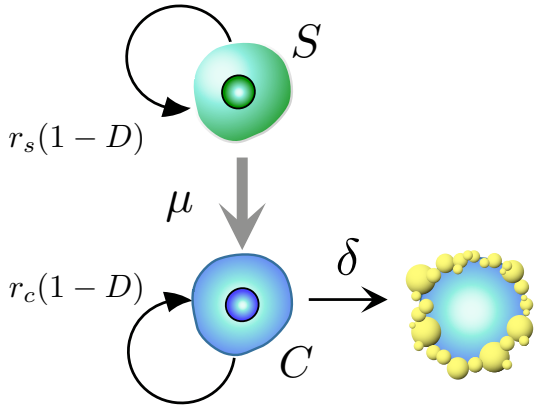

FIG. 3: Tissue architecture and the ecology of tumor differentiation therapy. The minimal hierarchycal model involves a cancer stem cell compartment S that replicates under the constraints of a differentiated environment while seeds a progenitor cancer population C. This population replicates at a lower rate r_c while dying at rate δ.

decades point out that a cancer stem cell compartment might coexist under dynamic equilibrium in small numbers with the rest of the tumor subpopulations (Bonnet et al 1997, Reya et al 2001, Meacham and Morrison 2013). Consistently, our model admits a single coexistence attractor for S, C

$$S^* = (1-k)\left(1 - D - \frac{\mu}{r_s}\right) \tag{11}$$

$$C^* = k\left(1 - D - \frac{\mu}{r_s}\right) \tag{12}$$

It is easily seen that the attractor describes a total population of $(1 - D - \mu/r_S)$, divided into stem and normal cancer cells by a factor

$$k = \frac{1}{1 + \frac{\delta}{\mu} - \frac{r_c}{r_s}} \tag{13}$$

We know that, prior to treatment, the proportion of cancer stem cells to general malignant cells in a tumor remains a roximately constant and very small (Werner et al. 2016). Under this statement, a condition for k can be found, namely

$$\frac{S^*}{C^*} = \frac{1-k}{k} \ll 1 \tag{14}$$

leading to the inequality

$$\frac{\delta}{r_c} > \frac{\mu}{r_s} \tag{15}$$

which predicts that stem cells must be better replicators in order to survive and maintain the observed equilibrium, consistent with the cancer stem cell hypothesis (Magee et al. 2012). This imposes a critical limit for the rate of stem-to-progenitor turnover

$$\mu < \frac{\delta r_s}{r_c} \tag{16}$$

beyond which we would not observe tumors with a seeding cell compartment at equilibrium with the rest of subclonal populations.

At this point we might ask if there are conditions, even for a low turnover rate μ, under which differentiation can eliminate the coexistence equilibrium defined by (11) and (12)? This ha ens for

$$D_s = 1 - \frac{\mu}{r_s}. \tag{17}$$

In other words, the differentiation threshold condition matches the one found for the homogeneous population. If the proportion of destroyed habitat, through differentiated non-replicative cells, increases beyond a certain level, the cancer attractor becomes null.

However, an interesting point reflects the special role of stem-driven hierarchy in robustness to DTH. The threshold to cancer extinction depends now only on the parameters associated to stem cell dynamics. Furthermore, from equation (14) it is easy to prove that

$$D_s = 1 - \frac{\mu}{r_s} > D_c = 1 - \frac{\delta}{r_c} \tag{18}$$

which indicates that the system with hierarchy will collapse at higher differentiation levels than that of the single self-renewing population. The transitions governed by DTH are better observed through the nullclines $\varphi_1(c)$ and $\varphi_2(c)$ of system (11,12) from $dS/dt = dC/dt = 0$, namely

$$\varphi_1(c) = 1 - D - \frac{\mu}{r_s} - c \tag{19}$$

$$\varphi_2(c) = \frac{c(1 - D - (\delta/r_c) - c)}{c - (\mu/r_c)} \tag{20}$$

By finding the intersections of φ_2 with φ_1 and $S = 0$ the fixed points, their existence and stability can be determined. The bifurcation diagrams associated to each population as a function of D are shown in Figure 4.

Therefore, even in the presence of a strong population of progenitor cells still able to replicate, the total elimination of a tumor will depend on the characteristics of the stem cell compartment, which poses a stronger threshold to the amount of differentiated tissue necessary for treatment effectivity. Even a minimal hierarchical model indicates the central role of stem cells in maintaining a tumor under loss of overall self-renewal capacity through differentiation. This is consistent with the notion that any therapy for hierarchically organized cancers must eradicate the cancer stem cell population (Dingli and Michor 2006).

Beyond the specific effects of complete cellular differentiation on hierarchical tumors, it is interesting to study

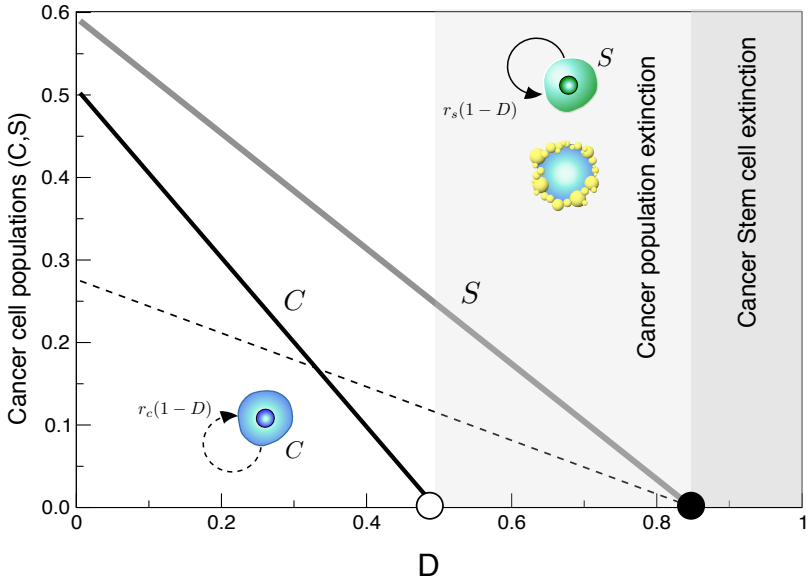

FIG. 4: Effects of differentiation therapy on the attractors of a hierarchical tissue. The single population attractor decays linearly as the amount of differentiated habitat increases (bold line), until it collapses at $D_c = 1 - \delta/r_c$ (empty dot). The coexistence attractor (gray and dashed lines) also decays as differentiation increases. However, this decay is slower, and the hierarchical tumor remains in place until a higher amount of habitat has been differentiated (filled dot). This is indicative of the fundamental role of cancer stem cells in resistance to differentiation therapy.

possible other a roaches to combination therapies. On the one hand, it is obvious that strong therapeutic a roaches able to reduce reproduction rates of tumor cells r_s, r_c can drive the system to the cancer-free scenario. Several a roaches could fit in this, such as EGFR inhibitors (Woodburn 1999) or ABL tyrosine kinase inhibitors in CML (Michor et al 2005), but it is clear nowadays that cancer stem cells are particularly resistant and might evade targeting by entering quiescent states (Foo et al 2009, Meacham and Morrison 2013).

Since common chemotherapeutic a roaches with strong effects on δ might not suffice when a seeding population is at place, the model indicates that therapies targeting the rate of stem-to-progenitor differentiation, μ, could be a key complement to drugs able to fully differentiate all populations. This kind of a roaches have been studied in CML, where imatinib can reduce the speed at which progenitor cells are produced from their ancestors (Michor et al 2005, Foo et al 2009). However, both in the original a roaches and in our model, reducing μ in a stem population able to avoid lasting effects on r_s only confers further stability to the CSC compartment.

Finally, increasing μ seems to point towards effective combination therapy. By means of destabilizing the cancer stem cell compartment by excessive differentiating divisions the higher threshold D_s could be reduced to that of D_c. A similar a roach has been proposed in another mathematical setting (Molina-Peña and Álvarez 2012). However, increasing μ in an experimental setting is probably related to a general increase of the rates at which malignant cells replicate or cycle, meaning further knowledge on specific CSC differentiation pathways needs to follow before attacking this a roach.

IV. DISCUSSION

In this paper we have shown that the dynamics of differentiation therapy can be modelled by means of a metapopulation a roach. This is done by including habitat loss as a surrogate of differentiated patches, while an independent extinction term incorporates cytotoxic therapy. Early models of ecological decline due to habitat loss show that a well-defined threshold exist: once a given critical loss is present, no viable populations are allowed, despite that some amount of habitat is still present (Levins 1969, Bascompte and Solé 1996). Within the cancer context, when a critical amount of cancer cells have been differentiated, remission results from the same kind of critical point, provided that standard cytotoxic therapy is also present. In order to test the generality of the a roximation, both an homogeneous metapopulation model and an extension considering the specificity of a cancer stem cell compartment have been explored. The models consistently match several qualitative observations concerning the impact of DTH.

On the one hand, a roaching differentiation as an ecological process for a simple population can predict interesting dynamics in genetically simple cancers such as APL where DTH has been successful. Our model predicts a well defined threshold for differentiation, beyond which a malignant population is not able to progress even

in cases where replication rates overcome death. The fact that this threshold is dependent on cytotoxic therapy is consistent with studies on DTH for leukemia, where arsenic, that triggers p-53 driven senescence as well as differentiation, is effective as a single-agent therapy, while other agents might require combined cytotoxicity. Further learnings from the single population model indicate that DTH becomes much more effective than chemotherapy for small, growing tumors away from the carrying capacity of their tissue. This result opens novel questions on the role of DTH as an early therapeutic scheme.

An extension of the ecological model introduces a minimal architecture to understand the possible role of a cancer stem cell compartment in sensitivity to DTH. The introduction of a hierarchical tissue predicts a coexistence equilibrium between stem and non-stem cancer cells, consistent with that observed in many cancer types (Bonnet et al 1997, Reya et al 2001). Furthermore, this tumor equilibrium perishes under similar threshold conditions as for a single population. Suprisingly, this new DTH threshold condition does not depend on the replicative potential of the non-stem population, but only on the stem cell compartment. This implies that the condition is harder to attain, as cancer stem cells have higher self-renewal potential than other malignant cell compartments. All in all, even a minimal hierarchical model indicates that the cancer stem cell compartment needs to be taken into account when trying to understand the complications of DTH in solid tumors.

Several shortcomings, potential extensions and implications of this work can be outlined. First of all, the model involves the most minimal set of rules and assumptions, sacrificing the details of the population description in favor of an ecological picture that can be intuitively interpreted. Real tumours include several layers of complexity, from cell-cell physical interactions to hierarchical developmental paths tied to stem cells (Meacham and Morrison 2013). Moreover, models of habitat loss including noise reveal the importance of considering several sources of disturbance, from demographic stochasticity to large catastrophes (Casafrandi and Gatto 2002). We keep the description at the population level and only in the hierarchical model interactions take into account the architecture related to the cancer stem cell hypothesis. Further exploration would require considering, for example, the heterogeneous spatial organization of cancer populations associated to cell-cell interactions and the corresponding models of heterogeneous tumor growth (Sottoriva et al 2010). However, despite the need for such a more realistic models does not invalidate the key findings of our study. In fact, a similar criticism could be raised in relation to the simplicity of habitat loss models derived from Levins equation. Despite the lack of realism, the simplest models (also ignoring the details of species-specific metabolic or physiologic features) have been extremely valuable in understanding the problem as well as how to prevent its consequences (Lande 1988, Hanski 2011). In the next paper, we will explore the role played by heterogeneity in two different contexts, namely the presence of differentiation-degree heterogeneity in a "liquid" tumor where no spatial correlations are at work and secondly the impact of spatial dynamics, in order to analyse the potential effects and shortcomings of DTH in solid tumors.

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