The complexity of cancer ecosystems

J.E. Keymer & P.A. Marquet, IEB and PUC de Chile

1 Abstract

The tumorigenic process shares many similarities with the evolution of ecosystems. Different processes promote heterogeneity in the population of neoplastic cells, this in turn is manifested in differential rates of proliferation and the emergence of selection, whereby tumor cells with the highest survival and proliferative advantage are selected for in the face of environmental filters. This model of clonal selection, is of wide acceptance and represents core knowledge regarding cancer progression and tumor evolution. However, according to it, tumor evolution is associated to a series of clonal expansion, linked to driver mutations that confer fitness gains such that one clone competitively exclude less fit ones. The end result of this process will be the eventual domination by one clone (clonal homogenization). However, heterogeneity is the rule. The issue we address in this contribution is what prevents clonal homogenization and what is the impact of this upon metastatic progression. We do that by developing two separate ecological models to understand neoplastic progression and invasion of secondary organs (metastasis) respectively. In particular, we propose that after its initial appearance, populations of malignant cells can further fine-tune their local fitness by internal Darwinian selection creating new malignant strategies which are more efficient at exploiting the growth opportunities within the local tissue. This initiates an evolutionary progression of clone replacements. After a period of such microscopic directional evolution, the local ecology of the tissue undergoes a transition into a neutral ecology. Such ecology then generates malignant clones with a range of proliferation strategies (neoplastic biodiversity) which then venture into the circulatory system reaching out secondary organs. Subsequently, at a secondary organ, the malignant cell remain in a latent state until opportunities for invasion show up due to the disappearance of resident normal cell linages that prevented their invasion. A process akin to invasion in metacommunities.

2 Resumen

El proceso de crecimiento tumoral comparte muchas similitudes con la evolución dentro de ecosistemas. Distintos procesos promueven la emergencia de heterogeneidad en la población de células neoplasicas, esto a su vez se manifiesta en tasas diferenciales de proliferación celular y la emergencia de selección, tal que las células tumorales con la mayor sobrevivencia y ventaja proliferativa son seleccionadas. Este modelo de selección clonal es ampliamente aceptado. Sin embargo, de acuerdo a él, la evolución del tumor se asociaría a una serie de expansiones clonales asociadas a mutaciones tipo "driver" que confieren ganancias en adecuación tal que un clon excluiría a los menos competitivos. Este proceso terminaría con la eventual dominación por un único clon (homogeneización clonal). Sin embargo la heterogeneidad es la regla. El problema que nos ocupa en este trabajo dice relación con entender qué es lo que previene la homogeneización clonal y cúal es el impacto de este proceso sobre la progresión metastática. Para hacer esto desarrollamos dos modelos para entender la progresión neoplásica y la invasión de otros órganos secundarios (metástasis) respectivamente. En lo particular, proponemos que las poblaciones de células malignas, en el órgano primario, atraviesan por un proceso de selección clonal que genera clones con potencial de crecimiento e invasión cada vez mayor y que este proceso termina con una ecología neutral. Los clones que caracterizan este ecosistema neutral poseen un rango de estrategias proliferativas (biodiversidad neoplásica) algunos de los cuales se dispersan y llegan a otros órganos. Una vez en el órgano secundario, las células malignas esperan en un estado de latencia, la emergencia de una oportunidad que les permita invadir, lo que asociamos a la desaparición de ciertos linajes que previenen la invasión. Un proceso similar a la invasión en metacomunidades.

3 Introduction

Complexity science is increasingly gaining importance in biomedicine [1] as a result of the realization that the human body, as any other living system, is inherently complex and that to fix its malfunction requires an interdisciplinary approach. This trend is particularly apparent in cancer research, where new perspectives coming from fields such as physics [2–5], ecology [6–9] and evolution [10–13] are becoming popular to deal with the challenges that the complexity of cancer poses. The complexity of neoplastic disease progression is manifested somehow in the hallmarks of cancer [14]; six biological capabilities acquired during the multistep development of tumors (sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis) that, as we will discuss more in detail, manifest in the emergence of a complex cellular ecosystem. The existence of these hallmarks, however, does not imply that all cancers are equal, for another quintessential characteristic of cancer is heterogeneity. This is manifested in changes in the identity of genes that drive the development of tumorigenesis across different cancers, in the diver-

sity of clones that coexist within tumors and through out cancer progression within each cancer type, and in the range of potential non-exclusive processes that underlie this diversity, including genomic instabilities, drift, selection, stochasticity in gene expression, and non-genetic causes [15–18]. Further, understanding the functional roles associated to this diversity, which is sustained and sustains a complex web of intracellular and extracellular networks known as the "tumor ecosystem" [19], may be a key to harness cancer progression and its robustness [20].

There is limited knowledge on the structure of the tumor ecosystem and the kind of interactions that different neoplastic clones can sustain, both among themselves and with recruited normal cells [21, 22]. Available evidence suggests, however, that at least competition, commensalism and cooperation are important [3, 7, 23]. Similarly, the dispersal of cells from the primary tumor during metastatic progression also represents a research challenge. We know that those migrant cells that can survive in the circulation and adapt to the new environment of a distant organ are the ones that will prevail and proliferate but it looks like describing metastasis as a simple one-way migration of cells from the primary tumor to the target organ may not do justice to the complexity of the phenomenon and may miss important mechanisms that can be therapeutic targets [24]. Thus to achieve understanding of the complexity of tumor ecosystems and the suite of adaptive strategies that cancerous cells can exhibit in different host environments is of paramount importance for todays cancer research [25] and may be key for the development of effective therapeutic interventions.

The tumorigenic process shares many similarities with the evolution of ecosystems; there are factors within tumors and in the surrounding healthy tissue that promote the emergence of heterogeneity in the population of neoplastic cells, this in turn is manifested in differential rates of proliferation and the emergence of selection, whereby tumor cells with the highest survival and proliferative advantage are selected for in the face of environmental filters, which could be a therapeutic treatment or associated with the process of cancer progression itself, such as hypoxia that occurs as a consequence of growing further and further apart from servicing blood vessels [26, 27]. This model of clonal selection, first proposed by Peter Nowell in a seminal contribution [17], has become a well established core knowledge of cancer progression and tumor evolution. However, according to it, tumor evolution is associated to a series of clonal expansion, linked to driver mutations that confer fitness gains such that one clone competitively exclude less fit ones much alike periodic selection in stressed bacteria [28]. The end result of this process will be the eventual domination by one clone (clonal homogenization). However, heterogeneity is the rule [21]. The issue then is what prevents clonal homogenization and what is the impact of this upon metastatic progression. In a recent review [18] has pointed out that tumor homogenization could be constrained by driver mutations having a small fitness effects, by spatial variability and by microenvironmental variability, which may tend to equalize fitness and promote coexistence of clones.

In this chapter we develop two separate ecological models to understand neoplastic

progression and invasion of secondary organs (metastasis) respectively. We aim at generating a simple mathematical framework that will increase our understanding of the linkages between tumor progression and subsequent metastasis. To achieve this we strongly argue for an ecology of cancer ecosystems bringing together ecological approaches to oncology. In particular, we propose that within the tissue located in the primary organ, after its initial appearance, populations of malignant cells can further fine-tune their local fitness by internal Darwinian selection [13, 16, 17] creating new malignant strategies which are more efficient at exploiting the growth opportunities within the local tissue. This initiates an evolutionary progression of clone replacements. After a period of such microscopic directional evolution, the local ecology of the tissue undergoes a transition into a neutral ecology [29]. Such ecology then generates malignant clones with a range of proliferation strategies (neoplastic biodiversity) which then venture into the circulatory system reaching out secondary organs. Subsequently, at a secondary organ, a transition in tissue status from resistant to permissive ecologies could characterize the latent *versus* metastatic transition.

Before delving into our model for the emergence of clonal selection and diversity in tumor ecosystems we need to make some consideration regarding our view of multicellular organisms and in particular, to introduce a conceptual view of organisms as cellular ecosystems.

4 Metazoa as coherent multicellular ecosystems

Life cycles span a continuum of cellular ecosystems exhibiting multiple levels of integration, cooperation, degrees of physical attachment, as well as other adaptations for viscous selective assortment. Along this continuum we find several life history strategies ranging from: quorum sensing bacteria like *Vibrio harveyi* that exhibit high degree of functional coherence; loose aggregates of cells with little degree of differentiation, coordination and integration such as the case of *Trichoplax ahaerens*; or like *Dictyostelium discoideum*, which behaves as a population of single-celled amebas as well as a multicellular slug and fruiting body. Higher order metazoa are highly integrated and aggregated life cycles that lie at the complex end of the continuum of integration levels and therefore posses highly structured regulatory systems. These regulatory structures exist at multiple scales within the individual host and have been structured by thousands of years of evolution. Such macroevolutionary process has produced a large degree of modularity, with bodies being organized into organs and organs into tissues and where numerous cell types are continuously being produced and destroyed allowing for the dynamic emergence of a multicellular individual. The evolutionary trajectory of metazoa, however, endowed each cell with a hidden repertoire of modular ancient regulatory structures. This repertoire or toolkit corresponds to pre-existing adaptations, of an earlier layer of genes that controlled loose-knit colonies of only partially differentiated cells, similar to tumors, and characteristic of

proto-metazoan or transitional forms between unicellular and multicellular organisms. These hidden modules (*i.e.* Metazoa 1.0s *toolkits*) can overrun the current modes of operation upon environmental insult [3]. Metazoa organisms are monopolies of niche construction [30] on which cells transiently generate an autopoietic machine [31] operating far from equilibrium [32]. In homage to Davis and Lineweaver [3], we label this machine as if running a "Metazoa 2.0" as its *operating system*.

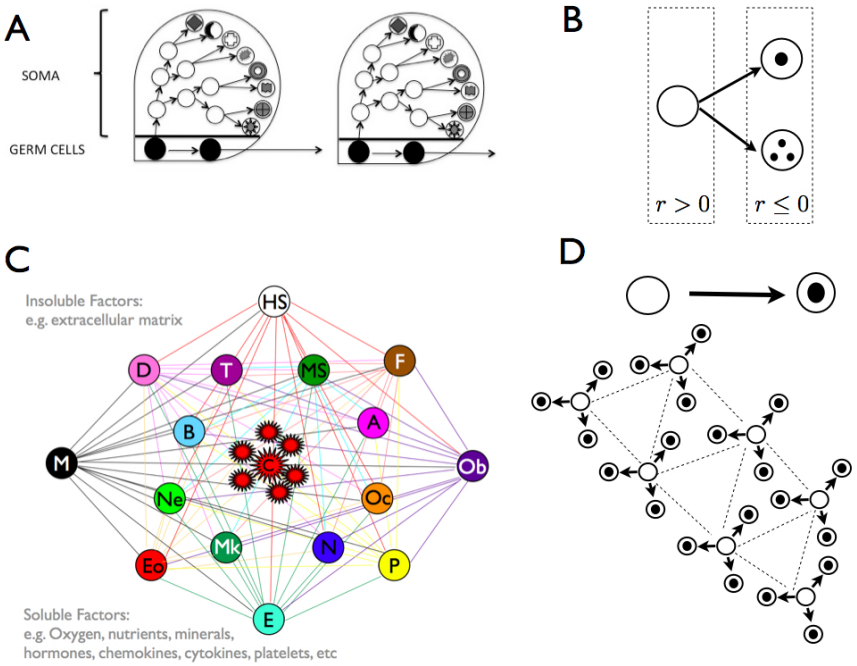

Figure 1: Metazoa as cellular ecosystems and the organ's tissues as a lattice. (A) At different time scales tissues are generated from somatic stem cell lines (white circles). Filled circles represent the germ line, and white circles filled with symbols represent several terminal somatic cell lines. Reproduced from [33]; (B) Stem cell populations are capable of longterm proliferation and persistence while local populations of differentiated cells represent sink populations, whose persistence depends upon the continuous recruitment from stem cell differentiation. (C) A network of ecological interactions. Adapted from [8]; (D) Stem cell (white circles) differentiate into specific somatic cell type populations (patterned white circle), they do it in specific locations that are the basic units of tissue physiology. We represent such spatial landscape as the organ lattice $\mathcal{L} = \mathcal{L}_{\text{SC}} \cup \mathcal{L}_{\text{Diff}}$: a network of stem cell niches (white circles, sub-lattice $\mathcal{L}_{\text{SC}}$) connected by dispersal (dashed edges) to other stem niches and by differentiation-migration (black arrows) to specific somatic niches (patterned white circles, sub-lattice $\mathcal{L}_{\text{Diff}}$).

Organ's tissues as cellular networks building networks of patches

Coherent supra cellular structures such as tissues and organs from metazoa form a body (see Figure 1A) which is for the reproduction of the germinal line through a monopoly of niche construction [30] enforced by control systems which are nested and modular. At temporal scales larger than the lifespan of the host, only the germinal line has reproductive potential while bodies are transient structures. As ecosystems, bodies are also modular systems where proliferation, differentiation, cell migration, and cell attachment are highly structured by a combination of global and local control factors. Persistent somatic stem cell lines (open white circles in Fig. 1A,B) supply all differentiated cell types (patterned white circles in Fig. 1A,B) by differentiation, migration (black headed arrow) and recruitment.

Inspired by the work of Pienta and collaborators [8], we describe an organ (such as the bone marrow for example) as an ecological community of different cells types interacting in a complex network embedded together within a landscape of extracellular components. In Figure 1C we depict such scenario as an interaction graph. In this graph, each node (colored circles) represent a cell of a given cell type (species) such as: hematopoietic stem cells (HS), mesenchymal stem cells (MS), endothelial cells (E), pericytes (P), fibroblasts (F), macrophages (M), T lymphocytes (T), B lymphocytes (B), dendritic cells (D), and other cell types interacting in several manners (colored edges) while co-constructing the organ (bone marrow) in a coherent fashion. Each of these types in the network, has cell populations in precisely regulated anatomic locations around stem cell micro environments known as stem cell niches (SCN, [34]) forming a landscape ecology determined by the histology of the tissue. Local stem cell populations inhabit such locations and from these stem cell micro-patches, differentiated cells migrate to replenish nearby locations hosting sink-populations of terminally differentiated cells. In Figure 1B we represent such differentiation and dispersal process where a persistent ($r > 0$) stem cell population at a given location, supply with new cells a nearby sink population ($r \leq 0$) of differentiated cells. Such landscape can be abstracted as a lattice $\mathcal{L}$ consisting of discrete locations (Figure 1D), referred here as ecological micro-scale patches, which have the potential to host local populations of a given cell type. This *lattice organ* is composed of a sub-lattice $\mathcal{L}_{\text{SC}}$ of SCNs and a sub-lattice $\mathcal{L}_{\text{Diff}}$ of patches with the potential of hosting local populations of terminally differentiated cells.

5 Neoplastic progression and the adaptive phases of cancer

The control of proliferation within microscopic patches

Tissue architecture is represented here by a lattice of local patches of opportunity (local niches) for clonal expansion at given anatomical locations $x \in \mathcal{L}$. We can think of the dynamics of cell densities within a single patch. The local environment is limited from the

top-down by physical factors such as insoluble factors patterning the extra-cellular matrix and pressure from the nearby tissue. Thus, the patch has its maximum carrying capacity (in terms of local cell density of a given type). A patch is also regulated *bottom-up* by the host by providing local soluble factors which act as nutrients. We imagine a local population of cells with density $\phi \in [0,1]$ following density dependent growth,

$$\frac{1}{1-\phi}\frac{1}{\phi}\frac{d}{dt}\phi = r(\vec{s},\vec{\omega}) \tag{1}$$

and where $r(\vec{s},\vec{\omega})$ is the local per-capita per-niche population growth rate. The growth rate depends on the cell proliferation strategy $\vec{s} = (\beta,\delta)$ and the control field from the host $\vec{\omega} = (\omega_+,\omega_-)$ operating in the local tissue. Thus we define,

$$r(\vec{s},\vec{\omega}) \equiv \vec{s}\cdot\vec{\omega} = \beta\omega_+ + \delta\omega_- \tag{2}$$

to represent local growth (here $\omega_+ \in [0,1]$ and $\omega_- \in [-1,0]$). Notice that growth is regulated by both, a cell's strategy $\vec{s}$ as well as by the location dependent factor $\vec{\omega}$ representing the host's tissue renewal processes operating as complex spatial fields.

For simplicity let's imagine a location $x \in \mathcal{L}_{\text{Diff}}$ within some terminally differentiated somatic tissue such that $\omega_+ = \omega$ ($0 \leq \omega \leq 1$) and $\omega_- = -1$. In such location x, the rate of cell death is δ and it sets up the lifespan δ^{-1} for a cell of a specific somatic type. Host's homeostasis and self regulation regenerates levels of habitat quality ω in the location at a net rate $F = \lambda(1-\omega)$, where λ is the overall rate at which the components of habitat quality (i.e. nutrients, oxygen) are provided,and working against a local habitat degradation rate $C = \epsilon\phi\omega\beta$ (where ϵ takes care of units). With such representation of a cell population and its local ecology of habitat renewal we get,

$$\frac{d}{dt}\phi = (\beta\omega - \delta)\phi(1-\phi) \tag{3}$$

$$\frac{d}{dt}\omega = \lambda(1-\omega) - \epsilon\phi\omega\beta \tag{4}$$

which corresponds to the system studied by Keymer and collaborators [29, 35]. For terminally differentiated cell populations, proliferation rates ($\beta\omega$) have to be small compared to apoptotic processes (δ) such that long-term persistence is not possible in the system described by eqs. 3-4. Regeneration of such local terminally differentiated populations is only by differentiation and migration from a near-by SCNs. In this manner, terminally differentiated cell populations are controlled so they cannot persist in the long-run. Thus, all somatic terminally differentiated populations are represented by the "extinction" solution $(\hat{\omega}_0,\hat{\phi}_0) = (1,0)$ of equations 3-4 which corresponds to the "normal" phase of healthy tissue.

Normalizing the timescale by the scale of the maximum cell proliferation rate (β^{-1}), we can represent a cell proliferation strategy $\vec{s}$ by the scalar $\omega^* \equiv \delta/\beta$ which corresponds

to a dimensionless niche utilization parameter space (ecological aspect space). With these rescaled parameters, the system is,

$$\frac{d}{d\tau}\phi = (\omega - \omega^*)\phi(1-\phi) \quad (5)$$

$$\frac{d}{d\tau}\omega = \frac{\lambda}{\beta}(1-\omega) - \epsilon\phi\omega. \quad (6)$$

The emergence of Neoplastic progression

Here, the *extinction* solution $(\hat{\omega}_0, \hat{\phi}_0) = (1, 0)$ of equations 5-6 corresponding to the healthy state is stable for proliferation strategies satisfying $\omega^* \geq 1$ (see left panel in Figure 2). We denote these collection of healthy strategies $\Omega_0 = \{\omega^* : \omega^* \geq 1\}$. However, due to genomic instabilities one cell can mutate and change its strategy to a new one in the strategy space defined $\Omega_{\neq 0} = \{\omega^* : 0 \leq \omega^* < 1\}$ leading to the stability of the *bottom up* $(\hat{\omega}_{1/2}, \hat{\phi}_{1/2})$ and *top-down* $(\hat{\omega}_1, \hat{\phi}_1)$ solutions of equations 5-6 (see [29]. If this happens we have the emergence of neoplastic progression, which starts with a cell changing its healthy strategy $\omega_r^* \in \Omega_0$ into a malignant one $\omega_\mu^* \in \Omega_{\neq 0}$. Genetic instability, environmental insults as well as genetic predisposition and non-genetic factors [18] can trigger such change but the origin of the first malignant cell population is not at focus here. What it is, is what follows once this mutant malignant clone has appeared within a tissue.

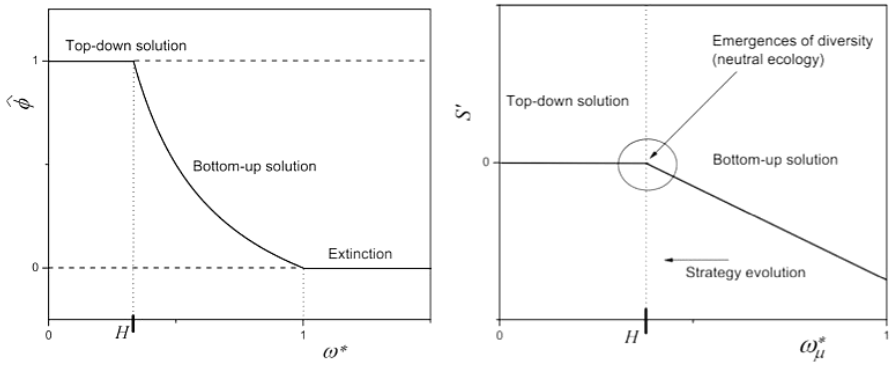

Figure 2: Solutions and fitness landscape for the adaptive dynamics of eqs. 5-6. Left is the stable solution $\hat{\phi}$ as a function of parameter ω^*. Right, is the fitness gradient S' for the range of cell proliferation strategy parameter. The value H identify the transition between the periodic selection and the neutral regime. Adapted from [29].

The aftermath of cell's disobedience

The neoplastic progression starts when a somatic cell stops listening to the social contract ruling its host and instead opts for the non-trivial solutions ($\hat{\phi} > 0$) of equations 5-6. Once a malignant cell line exists, it starts evolving its strategy ω^* by internal darwinian mechanism outlined by [17]. Here there is directional selection towards more efficient types with more aggressive growth rates and smaller values of ω^* than their ancestor linages. Ecological replacements ensure low biodiversity of clones exhibiting unregulated growth rates and causing a persistent accumulation of biomass (pressure) which create the tissue anomalies characteristic of hyperplasia. The topology of the fitness landscape characterizing the adaptive dynamics [29], induces a succession of evolutionary replacements $\omega_r^* \to \omega_\mu^*$ driven by driver mutations that confer fitness advantages, increasing the growth rate or fitness of the mutant in the environmental condition set by the resident. This is manifested in increasingly larger invasion exponents calculated as

$$S \equiv S_{\omega_r^*}(\omega_\mu^*) \equiv \frac{1}{\phi_r}\frac{d}{d\tau}\phi_\mu = (\omega_r^* - \omega_\mu^*)(1 - \hat{\phi}_r) \tag{7}$$

that dictate that a malignant clone will take over the patch from the healthy resident and the fate of that mutant clone once a new one arises. At each replacement event $\omega_r^* \to \omega_\mu^*$, the mutant becomes a resident and due to its smaller value $\omega^* \in \Omega_{\neq 0}$ it will establish itself. As shown in the right panel of Figure 2, we can see that the fitness gradient S' rules the adaptive dynamics so that that every new mutant who's strategy is to the left (smaller in value) of the resident clone will invade the patch. Under this regime, malignant clones evolve towards smaller values of ω^* thus becoming incresingly aggresive in terms of growth advantage.

The development of heterogeneous tumors

The serial replacement of clones proceeds until a critical value $H = \lambda/(\lambda + \epsilon\beta)$ is reached; a point where the ecology of the tissue transitions into a neutral regime, that is the fitness landscape becomes flat. At this critical value of a cell strategy $\omega^* = H$, an heterogenous neoplasia begins to develop as the local ecology saturates and biodiversity emerges [29] and thus the tumor ecosystem begins to accumulates biodiversity and developing heterogeneity. The emergence of invasive neoplasia, corresponds to the emergence of neutrality in the local ecology of the tissue. At this point in neoplastic progression the malignant population has a strategy $\omega^* \leq H$ and therefore has no competitive advantage towards any other mutant on the left of H (with small enough ω^*). Here multiple clones coexists in a neutral ecology consisting of a diverse cellular metacommunity of cell proliferation strategies $\omega_{r_1}^*, \ldots, \omega_{r_N}^*$.

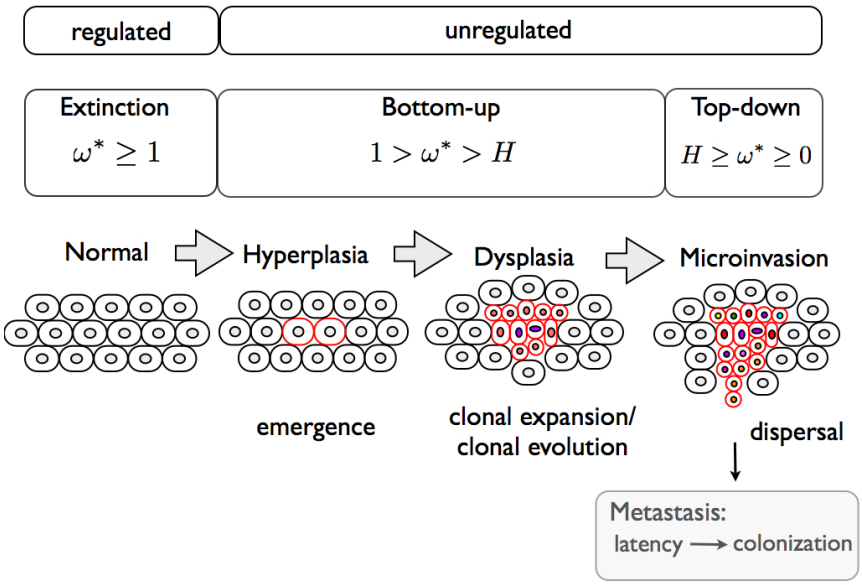

Figure 3: The progression of Neoplasia and the emergence of biodiversity

Biodiversity emerging as the onset of neoplasia

The adaptive dynamics studied by [29] can be made to correspond to the continuum of tissue phenotypes characterizing neoplastic progression: (0) normal tissue, (1) hyperplasia (precursor to neoplasia), (2) dysplasia (intra-epithelial neoplasia), (3) micro invasive (invasive neoplasia), (4) metastasis. We can think these phenotypes as caused by cell proliferation strategies which are distributed along an ecological aspect-space defining a cell's capacity to exploit system disobedience. In Figure 3, we map the neoplastic progression to the three possible regimes of the adaptive dynamics:

- *extinction regime*, where a population of healthy cells running "Metazoa 2.0" is maintained by the supply of differentiated cells from SCNs dispersing into local niches hosting differentiated sink-populations (where $r \leq 0$). Here the extinction solution $\hat{\omega} = 1$ and $\hat{\phi} = 0$ represents the state of the tissue

- *bottom-up regime*, where an unregulated population of differentiated cells is growing at rate $r > 0$ by avoiding the control mechanisms of the host. These cells, running some broken version of a "Metazoa 1.0" toolkit start generating new variants. Thus, they malignant biomass begins to evolve a better proliferation strategy ω^*. New more efficient clones take over and expand the malignant biomass. Clonal replace-

ments continues until the evolving value of proliferation strategy reaches a critical value $\omega = H$.

- *top-down regime* is when the local ecology has become neutral due to saturation. An invasive neoplasia consists of a community of multiple neutral strategies. Such neutral ecology produces a diverse spectrum of aggresive malignant cell types which go around trying to disperse to a differnt community or secondary organ, and initiating metastasis progression.

In a linear and order sequence the affected tissue progresses from the bottom-up regime towards the top-down regime where it will produce malignant cells that disperse into other organs. The issue then is Would these cells invade this new communities of cells and colonize the secondary organ or not?

6 Metastasis, dispersal and invasion of secondary cell communities

So far we developed a simple model to understand neoplastic progression but does not include metastasis. Neoplasias, however, produce invasive malignant cell populations that will reach far away organs where after some time in dormancy (latency) these cancer cells invade and colonize the secondary organ [36]. Metastasis is the final stage of neoplastic progression and associated to the spread, and colonization of a distant organ by cell originated from a primary tumor. This process can be conceptualized as an invasive ecology problem [8]. In what follows we describe a simple model, originally used in metapopulation dynamics, to understand this process.

The conditions that allow for the colonization and invasion of a secondary organ is the critical question underlying metastasis formation. This process is complex as cells arriving in secondary organs can be hidden in small numbers without invading the tissue suggesting that successful invasions by metastatic propagules could be facilitated or prevented by the ecological status of the cell community at the secondary organ. This can be shown by developing models of organogenesis based on schemes of cell community assembly using metapopulation models. By extending on the work of Chen and collaborators [9], We suggest that changes in the patterns of species packing could determine the susceptibility to invasions by metastatic cells.

To motivate our model we will focus in a particular tissue the bone marrow. Like in many tissues, in the bone marrow, differentiation from stem cells occurs in patches know as Hematopoietic Stem Cell (HSC) niches. At these locations, persistent populations of HSC can be found. Since there are multiple of these locations within the tissue, at a large enough spatial scale (a landscape metapopulation scale), following Chen and collaborators [9], we can represent the tissue by a patch occupancy model of a HSC metapopulation.

In this view, several locations (stem cell niche patches) can be empty or occupied by a local population of HSC at any given moment. Thus, we can use the following model [37],

$$dp/dt = fp(1-p) - mp, \tag{8}$$

to represent the proportion of occupied patches the metapopulation of HSC holds in the organ. A particular strategy characterizing the metapopulation is given by the pair of colonization and extinction rates (f and m respectively). A persistent HSC metapopulation in endured as long as its reproductive number (R) satisfy $R = f/m > 1$.

The question we will now try to address is Under which conditions would this system be invaded by a malignant cell? In the metapopulation scenario of Chen and collaborators [9], the invasion of a secondary organ (i.e. the bone marrow) can be understood by applying the corresponding two-species (cancer clone vs. HSC) model representing a competitive hierarchy between a superior competitor (HSCs, type 1) and an inferior one (cancer clones, type 2) but which nonetheless has a better colonization strength ($f_2 > f_1$). Under a constant extinction rate m we represent such system by,

$$\frac{d}{dt}p_1 = f_1 p_1(1-p_1) - mp_1 \tag{9}$$

$$\frac{d}{dt}p_2 = f_2 p_2(1-p_1-p_2) - (f_1 p_1 + m)p_2. \tag{10}$$

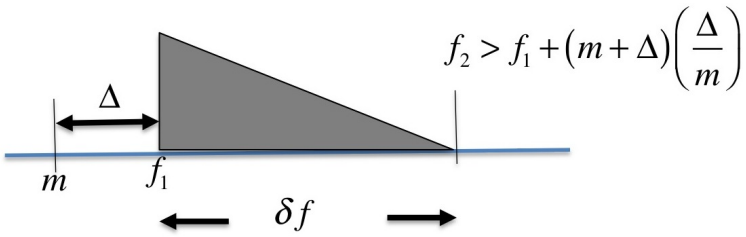

Figure 4: The limiting similarity and packing in secondary organs (see text for details). Fig. Adapted from [38]

As noticed by [9], the consequences of this trade-off (Figure 4) is associated with the emergence of a "competitive shadow" (depicted in black), which imposes a limit to how similar the two species can be in aspect space. For the sake of simplicity let us consider the mortality constant case where the HSCs that are the top competitor which have the lowest colonization rate f_1. At equilibrium, it is clear that $f_1 > m$ is needed for the viability of the HSCs. Note then that now the cancer cells are represented as another value $f_2 > f_1$, since they are better colonizers but poorer competitors for the niche-lattice (representing the 2-cell-type model of the organ—bone marrow). A cancer strategies with a parameter

value f_2 lying within a zone of aspect space shadowed by strategy f_1 cannot invade. Thus for cancer colonization we have $\delta f \equiv f_2 - f_1 = (m + \Delta)(\Delta/m)$, where $\Delta = f_1 - m$ and we have,

$$f_2 > f_1 + \delta f \tag{11}$$

A cancer cell can only coexist (invade the organ) if its fecundity is greater than that of the HSC by amount δf. Notice that the long-term occupancy of HSC-niches by HSCs (vertical hight) determines the size of the shadow and this is an organ property, not a cancer cell property. If another sub-type of HSCs is created which would have a lower fecundity it would achieve a lower site-occupancy and therefore it will cast a smaller shadow.

An organogenesis model of a diverse bone marrow

Inspired by the diversity that has been described in adult tissue SCs [39], we imagine the same principle as discussed above (between cancer and one type of HSC) but now we apply a multi-cell type model of the organ (bone marrow) where HSCs are not only a single type with a specific colonization capability $R = f/m$ but rather a diverse collection of values $R_i = f_i/m$ forming an organ community with the same competitive trade-off.

A simple model for organogenesis can be simulated by using a community assembly model consisting of serial introductions of different cells types with random values for their relevant parameters (see refs [40] and [41]). Taken the constant mortality case, we get that our bone-marrow-organ-lattice would look now like a multi-type competitively hierarchical community of different stem cells,

$$\frac{1}{p_i}\frac{d}{dt}p = f_i\left(1 - \sum_{j\leq i} p_j\right) - \sum_{j<i} f_j p_j - m. \tag{12}$$

The important point is that organogenesis is the process by which an equilibrium community is achieved. And this involves the assembly of different SCs that fill up physical space (patches/stem cell niches) as well as aspect space while being serially introduced. These serial introductions of types (see [40]) acts here as a model for bone marrow organogenesis. In this view, as organs (communities) assemble, shadows in aspect space emerge. These shadows protect the local organ from cancer invasion. Even though there might be dormant cancer cells waking up everywhere, since the community is packed with cell types whose aspect space is covered with their competitive shadows, the invaders (the dormant cancer cells) cannot invade.

Invasion and extinction cascades

If any of the cell-types in the assembled organ goes extinct, it will trigger a domino effect since its shadow will go away with it and then a hole in aspect space is created. As these holes develop, the protected polymorphism of cell types making the organ looses

protection from invasion by the same cancer cells which where not able to invade before. If such scenario is true there are immediate consequence for cancer metastasis. The organ side is important. Sometimes recurrence of a tumor that was cured can be due to changes in the native cells of an organ. If changes due to host aging or other stresses change the patterns of ecosystem packing in host organs they could become vulnerable to invasion by awakening dormant cancer cells already present on the organ which nevertheless have always the same intrinsic properties. As organs change their composition in terms of cell strategy parameters (aging), otherwise healthy organs could become vulnerable to metastatic invasion due to intrinsic changes on their constituent cells rather than changes in the cancer cells themselves.

7 Final remarks

In this contribution we have presented our views on the phenomenon known as cancer. We see it as an ecological and evolutionary process that can be understood using simple models of ecological interaction and evolution. In particular, we have shown that the model introduced by us to account for the emergence of diversity in microbial ecosystems [29] can be applied to understand the emergence of diversity in tumor ecosystems and in particular the existence of two adaptive regimes; one of competitive replacement or clonal selection, and one of neutral coexistence. This result helps to reconcile the existence of tumors with different amounts of heterogeneity and suggest that clonal diversity should increase through time. Interestingly, in a recent study of Barret´s esophagus, a premalignant condition in which the lining of the esophagus is damaged due to chronic stomach acid exposure, Carlo Maley and collaborators [42] showed that clonal diversity increases through time, as the disease progresses and asserts that "*Progression to cancer through accumulation of clonal diversity, on which natural selection acts, may be a fundamental principle of neoplasia with important clinical implications*." We could not agree more. However, how much time is required to attain diversity may differ among tumor ecosystems. In [43, 44] it is reported on the early emergence of diversity in colorectal cancer progression. It would be particularly illuminating to compare the trajectories of clonal diversification in different types of tumors to get a better understanding on how variable is clonal succession in tumor ecosystems.

Ours is not the only model that attempts to understand clonal evolution and interaction. Among the first models to explicitly cue in on the interaction between clones in a tumor is the model of cellular competition by [45] on clones found in Ehrlich ascites carcinoma. Their model, and subsequent elaborations upon it [46] are purely ecological and do not includes evolution or progression, but they highlight the importance of competition among clones. An interesting step forward is [47] who models the interaction dynamics of normal and cancer cell populations to derive the conditions under which a cancer cell population would invade, and concludes "*the importance of increased efficiency in substrate*

absorption as a mechanism enabling tumor cells to (a) proliferate despite inefficient energy production and (b) compete successfully for resources with the numerically superior host cells. As with many biological invasions observed in nature, success of the invaders can be enhanced by disruption of the local ecology..." Although the model by Gatenby does not include evolution, it does point out to a plausible mechanism by which the progression of cancer could get started, emphasizing the importance of the up regulation of glycolysis observed in cancer cells (or Warburg's effect) and the increase in acidity that this ensues, as fundamental for cancer invasion. In subsequent models Gatenby have included evolution explicitly by using game theoretical arguments to understand the emergence of the glycolytic phenotype [48, 49] but do not explicitly reproduce cancer progression and the coexistence of multiple clones in the tumor ecosystem. We see our model as similar, though more general and less mechanistic, that the one introduced by [49]. Both models point out that ecological theory and evolutionary dynamics may hold the clue to crack open the tumor ecosystem and advance in both treatment and understanding of cancer complexity.

Space is recognized as an important factor in ecological dynamics and in explaining coexistence in interacting populations (e.g. [50, 51]). In cancer research, the existence of spatial heterogeneity in tumor ecosystems has long been recognized (e.g. [6, 52, 53]) but only recently became under mathematical analysis, after the seminal work by [6] on the role of spatial heterogeneity in maintaining clonal diversity. Stochastic spatial models have shown that space may affect both cancer initiation and progression [54] as well as the emergence of diversity [55]. The latter work in particular use ecological and life history theory to assess the role of competition-colonization tradeoffs, typically associated to the spatial dynamics of species invasion and persistence to model tumor ecosystems. In particular, the authors aim at testing the notion that clonal diversity may result from the existence of different and spatially predictable selection regimes that select for different phenotypes; an invasive one at the front of the tumor and a maintenance one associated to promote tumor infrastructure inside the tumor. Their model support the existence of spatially variable selection regimes that promote the existence of different phenotypes, we argue that this may be one of the process involved in the competitive replacement that we observe in our model, but it cannot account for the coexistence of clonal diversity, which in our case is associated with the emergence of neutrality.

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