

Perspective

Modeling tumors as complex ecosystems

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SUMMARY

Many cancers resist therapeutic intervention. This is fundamentally related to intratumor heterogeneity: multiple cell populations, each with different phenotypic signatures, coexist within a tumor and its metastases. Like species in an ecosystem, cancer populations are intertwined in a complex network of ecological interactions. Most mathematical models of tumor ecology, however, cannot account for such phenotypic diversity or predict its consequences. Here, we propose that the generalized Lotka-Volterra model (GLV), a standard tool to describe species-rich ecological communities, provides a suitable framework to model the ecology of heterogeneous tumors. We develop a GLV model of tumor growth and discuss how its emerging properties provide a new understanding of the disease. We discuss potential extensions of the model and their application to phenotypic plasticity, cancer-immune interactions, and metastatic growth. Our work outlines a set of questions and a road map for further research in cancer ecology.

INTRODUCTION

Over the past few decades, a convergence of clinical, experimental, and theoretical cancer research has illuminated the intricate nature of cancer as an ecological, evolutionary, and developmental phenomenon.^{1–5} This conceptual framework has provided oncologists with a well-established set of methods and tools from these disciplines, advancing our comprehension of cancer progression and treatment strategies.

The way cancer populations avoid different selection barriers (from physical constraints on the tissue level to immune-related attacks) can be understood as a combination of ecological and evolutionary processes. Much has been written about the latter: well-defined evolutionary events usually punctuate the path toward a malignant tumor. However, the ways these events unfold in time are mediated by ecological change. Once a given barrier is surpassed, new ecological interactions are set in motion and population dynamics determines the outcome of the new context. Ecology is, therefore, at the heart of the many scales relevant to tumorigenesis and cancer treatment, from the growth dynamics of novel phenotypes to the emergence of angiogenic or metastatic properties (Figure 1).^{3,6–9} This cancer ecology framework has even prompted recent advances in cancer therapy, including the understanding of competitive release and its role in adaptive therapy¹⁰ and the unraveling of the complex web of interactions between tumors and the immune system.¹¹

Mathematical models of cancer ecology provide us with an explanatory framework that offers both qualitative understanding of the underlying mechanisms as well as potential predictive power.²¹ By exposing the logic of cancer population dynamics, models can help explain how and why therapies succeed or fail. These models have been traditionally built as coarse-grained descriptions of cell populations, often reducing them to more or less homogeneous compartments. Their simplicity allows for a full understanding of their implications, providing a descriptive link between the ecological rules at play and the growth of the tumor.^{3,16,22–24} (Figure 1D). In some cases, the tumor is represented as a single population of cancer cells.¹⁶ Later extensions incorporated the interactions between the cancer population and a second compartment, from healthy tissue to the immune system. These two-dimensional models have successfully illuminated crucial aspects of the nonlinearities involved.^{23,25–27} However, the improvement in our understanding of the richness of tumor diversity has led to the realization that cancer population dynamics makes sense under a community ecology picture.²⁸ Intratumor heterogeneity pervades cancerous genomes, phenotypic properties, and cellular types. This multiscale diversity dictates that tumors are in fact complex adaptive ecosystems built of many interacting populations (see Box 1, the study by Dujon et al., Lee et al., Mathur et al., and West et al.^{4,29–31}). Furthermore, despite the traditional dominance of competition as a driver of cancer dynamics, evidence accumulates indicating that ecological interactions between cancer cells are not only competitive but cooperation or commensalism could also be at play.^{29,32–34} More importantly, the combination of dedicated experimental efforts and improved mathematical models has revealed a multiscale picture of cancer where novel phenomena emerge as we move across scales (Figure 1).

Mathematical oncology has made great progress over the last decades, where a whole array of theoretical approaches has been developed.^{3,57–60} Along with population dynamics in space and time, approaches applying evolutionary game theory have also been helpful in understanding the emergence and interplay of different cancer phenotypes.^{61–67} These frameworks have provided accurate descriptions

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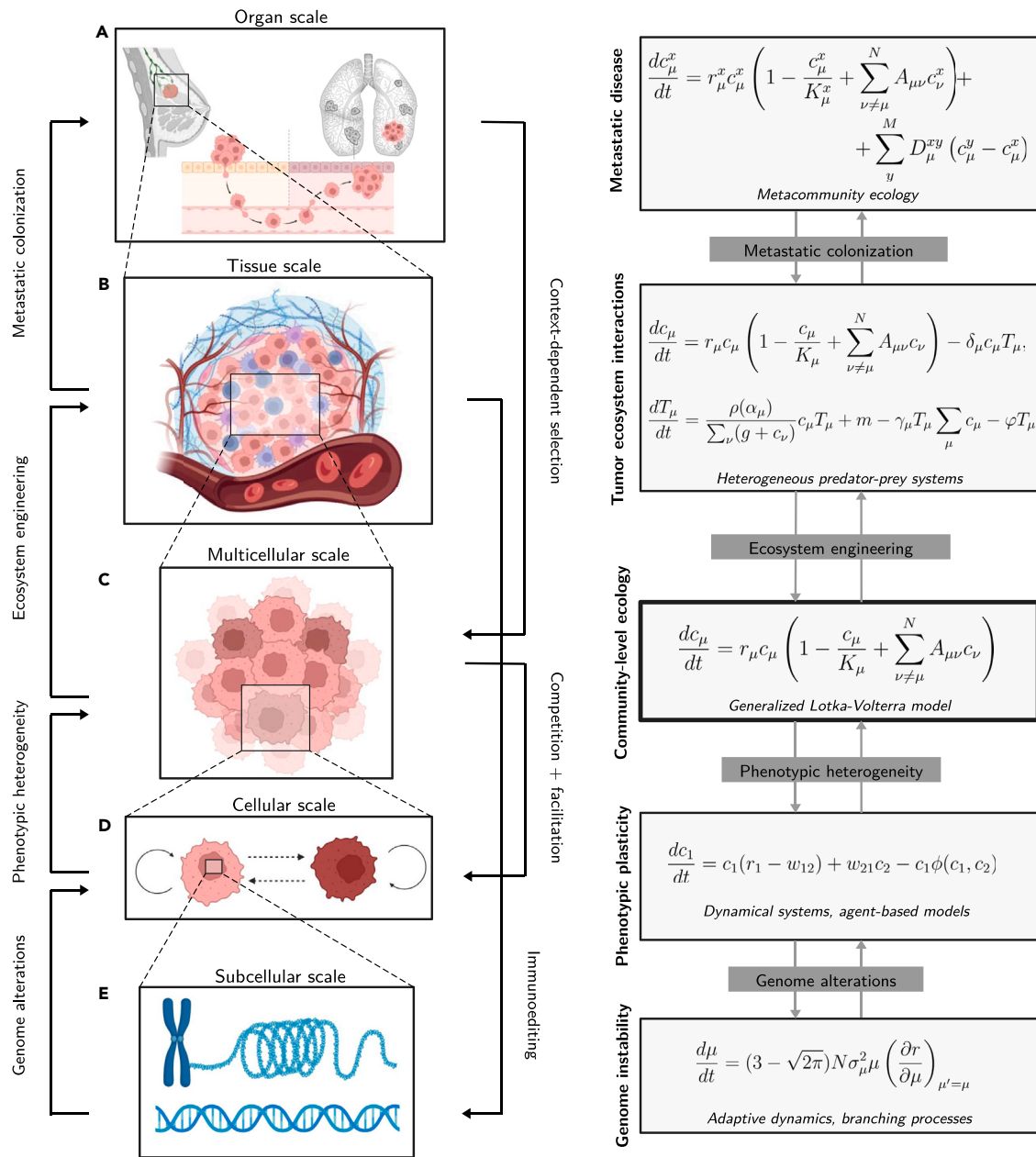


Figure 1. Multiscale complexity, emerging feedbacks, and mathematical models of cancer ecology

Multiple scales of complexity participate in the progression toward malignancy, each establishing a set of ecological processes over which evolution operates. We define the layer at play, examples of feedbacks between layers, and potential mathematical models able to describe their dynamics.

(A) Metastatic colonization at the organ scale.^{12,13}

(B) Ecosystem-level interactions with other cell types (in blue) at the tissue scale.^{14,15}

(C) Intratumor community ecology at the multicellular scale.

(D) Phenotypic growth and plasticity at the cellular scale.^{16–18}

(E) Genetic, epigenetic, and chromosomal alterations at the subcellular scale.^{19,20} While mathematical models in (D, E) are well established (see references in Section I; Box 2), we lack a general framework that can account for the heterogeneity and high dimensionality of the interaction networks involved in (A–C). Toward this goal, establishing the GLV model as the foundational model of heterogeneous tumors (C, bold rectangle, see Section II) can open the door toward understanding cancer dynamics at higher scales (A, B, see Sections III.B–C).¹⁴

of oncogenesis at the lower scales of complexity (Figure 1). At the level of the cancer genome, evolutionary footprints⁴⁵ have been described with adaptive dynamics^{19,68} (depicted in Figure 1E) and branching process models.²⁰ Moving one scale above (Figure 1D), genome alterations drive the emergence of different cell phenotypes, and population dynamics have been used to define qualitative and quantitative models of

Box 1. Tumor ecosystems as complex adaptive systems

The ecological nature of cancer cell populations shares a number of universal properties with other complex adaptive systems (CASs), and with ecosystems in particular. As far-from-equilibrium, dissipative structures, they exhibit nonlinear dynamical properties that pervade their stability but are also responsible for the structure of the phase space of potential dynamical transients. They are in fact CASs.^{35–37} Crucial features that characterize them as CASs would include.

- (1) Diversity: as it occurs with species diversity in natural ecosystems, intratumor phenotypic diversity is known to play a key role in maintaining robust behavior.³⁸ While in the former, biodiversity acts as a firewall to invader species and is a surrogate of a healthy state, in cancer, we understand heterogeneity (tumor diversity) as a source of adaptation³⁹ and resistance to therapy.^{40,41} Yet, as in bacteria, what defines a *cancer species*, and how many of them can be found inside a tumor, is a much more nuanced question.^{42–44} In this context, the emergence of new mutations⁴⁵ and the phenotypic plasticity driven by epigenetic alterations⁴⁶ can rapidly modulate the species composition of tumors, resulting in an increased adaptive potential.
- (2) Non-linearity: as complex ecosystems, tumors exhibit non-linear properties due to the nature of many-species interactions. Such nonlinear behavior is often characterized by the presence of bifurcation points in parameter space. These special parameter combinations define the boundaries between different attractor states, i.e., states (here defined in terms of population abundances) toward which a system tends to evolve over time. Beyond stability, the intrinsically non-linear nature of tumor dynamics implies that unstable and transient dynamics can also play a fundamental role in the oncogenic process, as seen in the abrupt transition from long dormancy periods toward rapid growth.^{47,48}
- (3) Self-organization: tumors have the capacity to self-organize in space and time,⁴⁹ forming patterns and structures without external control. Also postulated as a mechanism of gene regulation in cancer cells,^{50,51} self-organization arises from the interactions among individual components (genes or cells), leading to emergent properties at higher levels of organization. These patterns emerge through a combination of both negative (competitive) and positive (cooperative) interactions.

All these concepts have been part of the early development of theoretical ecology⁵² and provide the basis to formulate mathematical models that reveal the presence of several key phenomena. These include the stability properties of attractor states and their robustness against perturbations, but also the out-of-equilibrium trajectories between states^{53,54} and long transients^{55,56} and the presence of breakpoints, i.e., parameter values that define sharp changes in the dynamics. Formulating a mathematical description of tumors as CASs, where their cellular heterogeneity is explicitly accounted for, can allow us to understand the mechanisms behind cancer adaptation and drug resistance.

cell-cell interactions¹⁶ also in the presence of the immune system,²⁶ healthy tissue,²⁷ or a phenotypic switching population^{17,69} (Figure 1D, see Box 2). With the rapid development of omics data and improvements in single-cell level analysis, the distance between theory and experimental and clinical information has been rapidly shrinking (see Box 3).

However, how do we model tumors knowing there are many cancer phenotypes as well as other cell types in place? There is no current consensus on a mathematical framework that upscales simple models toward describing the species-rich cancer ecosystem (Figures 1A–1C). Following its widely accepted application on ecological and microbial systems,^{77,78,80,93} we propose that the high-dimensional model defined by the so-called generalized Lotka-Volterra (GLV) interactions is a powerful candidate to understand and predict the complexity of tumors as ecological communities.¹⁴

In this paper, we present the emerging properties of the GLV model and their implications in tumor population dynamics. We first describe the model itself and its application in cancer ecology. In particular, the model captures four different regimes, each characterized by different phenotypic dynamics toward a set of community states. To wrap up, we outline potential mechanisms by which a tumor can transition from one regime into another and how spatial constraints can be implemented in the model. Second, we propose three additional extensions of the species-rich GLV cancer model that account for high-dimensional phenotypic plasticity, cancer-immune interactions, and the metastatic process.

Inspired by the pioneering work of Robert Gatenby on the application of ecological models to cancer research, *Population ecology issues in tumor growth*¹⁶ (Figure 1D), our work can be read as an updated proposal of *Community ecology issues in tumor growth* that takes into account our current understanding of cancer complexity (Figures 1A–1C).

THE MATHEMATICS OF HETEROGENEOUS TUMORS

Due to their diverse phenotypic makeup, heterogeneous tumors can display intricate dynamic patterns over both space and time. This phenomenon has been a focal point in ecology, with a long-standing tradition addressing this challenge.⁹⁴ Particularly, the use of multispecies models based on mass-reaction kinetics, as encapsulated by the GLV equations, has been prevalent.^{77,95–97} These mathematical frameworks have been instrumental in comprehending the dynamics of real ecosystems, aiding in the elucidation of underlying organizational principles. They have played a pivotal role in making sense of counter-intuitive findings, such as the relationship between diversity and connectivity,⁷⁹ and in understanding how ecosystem resilience and species composition evolve with gradual changes in environmental variables.⁹⁸

Yet, tumors hold particular properties not seen in natural ecosystems. Due to pervasive genome instability (Figure 1E),⁴⁵ ecological and evolutionary timescales in cancers become intertwined, with the emergence of new mutations and phenotypes directly modulating the ecological dynamics of growing tumors^{2,5} and maintaining them permanently out of equilibrium (see Box 1). Moreover, the frontiers defining what makes a *cancer species* are not necessarily sharp, with heterogeneity at the genomic and phenotypic levels pervading the whole cellular ecosystem. In this context, lessons learned from microbial ecology might prove particularly useful.^{42–44} Acknowledging these differences, can we write a GLV model for cancer? How does it inform us of novel dynamical properties not expected from few-species models?

Box 2. Few-species models of cancer growth

The general equations introduced by the GLV model (1) contain all the classical low-dimensional examples of ecological dynamics in cancer, including the effects of spatial constraints on a single population or the cooperation and competition between two cell lines.¹⁶ Because of its pervasiveness in tumors⁷⁰ and its relation to drug-sensitive and drug-resistant scenarios and adaptive therapy,¹⁰ the two-species competition system provides an interesting insight into the dynamics of the higher-dimensional GLV model.

For $S = 1$, using $A_{11} = -1$, we obtain the logistic equation (which is one of the possible candidates for cancer growth, see the study by Jansson and Révész, Bajzer et al., and De Pillis^{71–73}), whereas for $S = 2$, using the matrix,

$$\mathcal{A} = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix}$$

and assuming $A_{ij} < 0$, we obtain the standard Lotka-Volterra two-species competition, which could represent the competition between cancer and healthy cells.^{74,75} One particularly simple case is provided by the symmetric scenario, where $r_i = r$ and self-regulation occurs with strength $A_{11} = A_{22} = -1$ and $A_{12} = A_{21} = \beta < 0$. For this particular case, the model already exhibits four equilibrium (fixed) points obtained from the condition $\phi_i(N_1^*, N_2^*) = 0$. These points define four possible attractor states $S^* = (N_1^*, N_2^*)$, namely: $S_0^* = (0, 0)$ (extinction), $S_1^* = \{1, 0\}$ and $S_2^* = \{0, 1\}$ (exclusion points), and S_3^* coexistence state where both species are present at $N_i^* = 1/(1 + \beta)$. If we analyze the stability of these points, it is found that, for $\beta < -1$, the only possible stable solutions are the exclusion points S_1^*, S_2^* : competition is so strong that the population that starts at higher abundance will outcompete the other. The coexistence alternative is obtained when $\beta > -1$. In that case, it can be shown that the system exhibits stable coexistence and the exclusion points are unstable. For $\beta > 1$, we have outgrowth (and the system diverges). Other kinds of pairwise clonal interactions in cancer can be defined, including commensalism and even parasitism. Their relevance for quantitative clinical studies and their connection with different mathematical approximations are summarized in the study by Lee et al.²⁹ As a final remark, it is interesting to observe that the two-species case harbors the competitive exclusion property of the species-rich GLV model, but might not capture other relevant phenomena. In species-rich tumors, the heterogeneity of cell-cell interactions could imply the presence of so-called *emergent coexistence*, a phenomenon observed in bacterial communities by which strongly competing species can nevertheless coexist when in the presence of the whole community.⁷⁶ If this was so, it would provide another example of how low-dimensional models, albeit insightful, might not be enough to explain the resilience and plasticity of the tumor ecosystem.

The GLV model of cancer growth

The GLV model is a benchmark description for the dynamics of ecological communities of many interacting species.^{77,99,100} We propose here that each cancerous population, defined by a set of signatures yielding a functional phenotypic behavior μ ,^{14,31,33,39} needs to be understood as an individual species with abundance c_μ growing while interacting with the other cellular populations c_ν .⁸² Depending on the dynamics under study, here c_μ could be restricted to populations with equivalent mutational or antigenic features (so-called genetic clones³⁹), or even include additional layers of the non-cancerous tissue such as the stroma¹⁰¹ or the immune system.¹⁴

In some instances, accumulated genetic diversity can imply that the frontiers separating cancer populations can be much less defined than those of ecological species, and tumors might be better described as a *quasispecies*.^{27,45,102} Conversely, when viewed from a phenotypic lens, tumors can be characterized by a few well-defined populations.^{82,101–103} In this context, decades of efforts in microbial ecology provide the necessary toolset to understand how genomic information^{42,44} as well as ecological function and niche occupation^{43,44} establish phenotypic constraints that define a cancer population (see Box 1 in the study by Capp et al.⁸² for an extensive discussion on delimiting cancer phenotypes). Once a *cancer species* is defined, an inherently novel property of the cancer GLV model is that the number of cancer species N can not only shrink due to extinctions but also increase when mutations generate new functional phenotypes in the tumor^{19,68} (see section “*oncogenic transitions across the four regimes*”). A minimal expression for the abundance dynamics of a phenotype μ in the presence of $N(t)$ other phenotypes can be written as

$$\frac{dc_\mu}{dt} = r_\mu c_\mu \left(1 - \frac{c_\mu}{K_\mu} + \sum_{\nu \neq \mu}^{N(t)} A_{\mu\nu} c_\nu \right) \quad (\text{Equation 1})$$

Here, r_μ and K_μ represent the replication rate and carrying capacity of the phenotypic species μ . Together, they characterize the adaptation of the cellular population to its niche, here determined by the constraints imposed by the tumor microenvironment and the evolutionary innovations to circumvent these barriers.^{4,68,104,105} Consistent with the view of sigmoid growth saturating at high abundances,^{106,107} the simplest assumption is to assume that the intrinsic growth of each cellular population follows a logistic growth curve.¹⁰⁷ Given the dynamics of each of the tumoral populations, the GLV provides a framework to analyze the dynamics of the whole tumor bulk, $dV/dt = \sum_{\mu} (dc_\mu/dt)$. This is partic-

ularly important because other growth curves departing from the logistic model might better fit temporal data of tumor volumes, with the Gompertz law and sublinear allometric scaling being prominent examples (see e.g., the study by Rodriguez-Brenes et al. and Ghaffari Laleh et al.^{107,108} for in-depth reviews on the topic). Knowing if the microscopic dynamics of each population and their interactions upscale toward generating such nontrivial macroscopic patterns remains an open question that could be directly explored with the GLV cancer model.

Box 3. From qualitative to quantitative GLV cancer models

The main limitation toward applying the GLV framework to predict clinical and experimental tumor dynamics stems from the massive number of parameters at play. In a tumor composed by e.g., $N = 6$ interacting phenotypes, one would already need to infer $N(1 + N) = 42$ parameters to calibrate the model and estimate the trajectories of each cell population, plus an added set of 42 more parameters if a therapy was to be administered that could change the ecology of the targeted tumor.

In natural ecosystems, where the number of species can be orders of magnitude larger and data are harder to access, species-rich models have faced this issue by assuming that parameters can be sorted from random distributions where we only have minimal information of their statistics.^{77–79} Albeit this might only provide an intermediate picture of the real dynamics, the approach seems to be able to predict certain properties and patterns of species-rich coexistence.^{80,81}

Beyond assuming random community matrices, what are the possibilities that a GLV cancer model can be parameterized with available data? Although initial endeavors are underway to measure the interaction strengths encoded in \mathcal{A} within tumors, accurately mapping intercellular effects *in vivo* remains a formidable challenge.^{29,82–85} As extensively reviewed in the study by Lee et al. and Li et al.,^{29,83} recent experimental and technological advances are opening the door to estimating clonal interaction strengths—the elements of \mathcal{A} . This can be done by estimating relative population abundances and their evolution in time, changes in growth rates, or tracing cellular lineages.⁸⁶ It is likely that deep sequencing technologies will soon allow for the accurate quantification of how cancer cell populations grow or decay in the presence of one another, which can provide estimates for how they interact. Even if estimating the complete parameter space of *in vivo* tumors still seems unlikely, these methodological advances will soon provide first estimates for the overall statistics of \mathcal{A} in growing tumors.

Accumulated knowledge on the crosstalk between theory and field data in community ecology can also provide information on how to look at tumor cell data.^{87–89} A prototypical example here concerns so-called *species abundance distributions*, a measure describing the distribution of abundant and rare species in ecological communities, typically characterized by a fat tail distribution of many rare and few abundant species.^{88,90,91} Comparing phenotypic abundance data to the predictions of the model depending on the underlying interactions provides a promising step to better understand the ecology of heterogeneous tumors.^{29,82,92}

Departures from logistic growth dynamics are particularly relevant in the context of tumor robustness, as e.g., sublinear growth rates across phenotypes could lead to alternative scenarios of increased community stability.^{109–111}

Beyond population-level growth, the last term of the GLV model explicitly accounts for interactions between cellular species (Figure 2A). The simplest possible description is that each cancer population interacts with itself via the self-regulation imposed by logistic growth but also interacts with the rest of the tumor through a complex network of inter-species bilinear growth effects encoded in the so-called community matrix \mathcal{A} , defined as:

$$\mathcal{A} = \begin{pmatrix} -1/K_1 & A_{12} & \cdots & A_{1S} \\ A_{21} & -1/K_2 & \cdots & A_{2S} \\ \vdots & \vdots & \ddots & \vdots \\ A_{S1} & A_{S2} & \cdots & -1/K_S \end{pmatrix}.$$

The $A_{\nu\mu}$ element of community matrix encodes the possible effects of a species c_ν on the growth rate of c_μ . Note here that the diagonal elements, which are written outside the sum in Equation 1, are in fact the intrinsic self-regulation terms for each population, so that $A_{11} = -1/K_1$ and so on. This model contains several limiting cases that describe standard, low-dimensional models of cancer growth (see Box 2). Beyond the well-accepted view of cancer clones competing for resources and space ($A_{\mu\nu} < 0$),^{29,68,112} recent research highlights that tumors also harbor cooperative interactions ($A_{\mu\nu} > 0$), resulting from the secretion of shared growth factors and inflammatory signaling,^{14,29,32,113} as well as commensalism, where other populations freely benefit from an angiogenic, invasive, or metastatic phenotype ($A_{\mu\nu} > 0, A_{\nu\mu} = 0$) (Figure 2A).^{29,114} Although initial endeavors are underway to measure the interaction strengths encoded in \mathcal{A} within tumors,²⁹ accurately mapping intercellular effects *in vivo* remains a formidable challenge (see Box 3). As in natural ecosystems, the main reason is that the number of species S and the complexity of their interactions make it extremely hard to empirically obtain the hundreds or thousands of free parameters in Equation 1.

High-dimensional models of species-rich ecosystems have proposed to overcome this barrier by assuming that interactions are in fact so complex that species-specific parameters cease to matter and one can ask whether generic patterns emerge.⁷⁸ Since the early work of Robert May, this has been studied by modeling the elements of $A_{\mu\nu}$ as randomly distributed variables with certain statistics,⁷⁹ a method that has brought fundamental insight into the functioning and stability of complex ecosystems (see e.g., the study by Barbier et al. and Serván et al.^{78,100}; Box 3). Despite the fact that important ingredients might be lost when assuming interaction strengths are random variables, the method provides a surprisingly clear intuition of the dynamical properties of Equation 1.

What are the outcomes of explicitly accounting for the complex ecological nature of cancer? A key feature of the GLV model is that four different dynamical regimes emerge depending on the statistics of the interaction strengths^{54,77,78,99,115} (Figure 2B). In particular, the dynamics of the system depend on the mean interaction strength, depicting the degree of cellular competition, i.e.,

$$\mu_A = \langle A_{\mu\nu} \rangle = \frac{1}{S(S-1)} \sum_{\mu \neq \nu} A_{\mu\nu} \tag{Equation 2}$$

and the heterogeneity of interaction strengths, encapsulated in their standard deviation, i.e.,

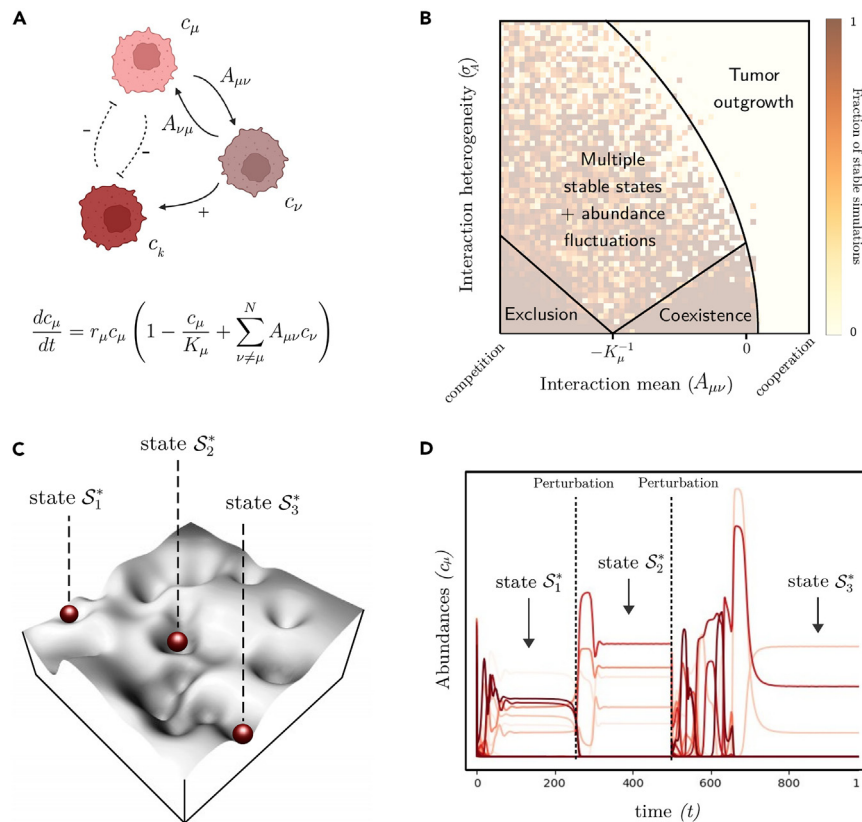


Figure 2. Tumors as species-rich ecological communities

(A) Many phenotypic populations $\{c_\mu\}$ coexist within a tumor and interact under multiple ecological processes encoded in $\{A_{\mu\nu}\}$. The GLV model (lower formula) is a suitable model to describe such high-dimensional tumor communities. A crucial concept in this modeling approach is the presence of distinct dynamical regimes (B), each emerging for given mean interaction strength $\langle A_{\mu\nu} \rangle$ and interaction heterogeneity σ_A values. The model harbors both a regime of unique stable coexistence as well as a particularly relevant regime of community multistability, where multiple attractor states can coexist, as represented in (C) with the minima of the landscape associated to multiple stable states. In (D), we simulate the trajectories of 50 interacting populations in this multistability regime and apply two perturbations that decrease the abundance of all populations at random (dashed lines). Even if each perturbation strictly reduces the number of present cells (e.g., a treatment shock), community dynamics can lead to shifts as well as complex dynamical trajectories from a heterogeneous tumor community S_1 toward communities with higher abundances S_2 and S_3 .

$$\sigma_A = \sqrt{\langle A_{\mu\nu}^2 \rangle - \mu_A^2} \quad (\text{Equation 3})$$

where $\langle \cdot \rangle$ represents the average across all non-diagonal entries of the matrix \mathcal{A} . These two statistical average values allow to define a partition of the (μ_A, σ_A) plane into a set of four distinct regimes. A fundamental implication of this species-rich result for cancer is that not only the strength and sign of interactions, as studied in simple models (see Box 2), but also their heterogeneity determine the properties of the ecosystem. Each of the four regimes is characterized by transient dynamics toward different types of attractor states.¹¹⁶ In the following paragraph, we describe how these dynamics can have direct implications for our understanding of cancer.

Four dynamical regimes in the GLV model

Four distinct dynamical regimes can be discerned within the GLV model, as depicted in Figure 2B.^{54,77} These regimes encompass (1) stable species coexistence, (2) competitive exclusion, where a single population dominates over the community, (3) unbounded growth of all populations, and (4) a more intricate regime marked by fluctuations, complex transient dynamics, and multistability. Each regime illuminates a distinct aspect of the cancer development process: depending on the mean and heterogeneity of the interaction matrix of the cancer community, a tumor would deploy one of the following four dynamical properties (Figure 2B).

Phenotypic coexistence and intratumor heterogeneity

If interspecies competition is homogeneous and weaker than carrying-capacity regulation, i.e., $\langle |A_{ij}| \rangle < 1/K_\mu$, the tumor will fall inside the coexistence regime, where a large fraction of cancerous phenotypes will be able to grow and survive together. This can characterize an early

regime of tumor growth, where low physical or nutrient constraints (and hence low competitive pressure) allow many phenotypes to coexist.^{117–119}

The fact that many cancer species can coexist without a single dominant phenotype populating the tumor finds its mirror into the problem of ecological biodiversity. Understanding how ecological communities can maintain a high number of coexisting species has troubled ecologists for decades.^{120–122} From theoretical predictions, one would expect that strong competitors exclude each other,¹²³ that multiple consumers require as many different resources to survive,¹²⁴ or that species-rich communities become unfeasible at high diversity.^{79,125} This paradox is also relevant—and almost equivalent—in cancer research.^{118,126} The GLV framework provides an explanatory regime in which many phenotypic and mutational profiles can coexist inside a tumor,^{39,127,128} while we would expect selection to allow for only a few.¹²⁹

Moreover, the distributions of population abundances in this regime can be explicitly predicted^{54,77} and are particularly wide, indicating that some species—and hence cancer populations—can be very abundant while others remain rare.¹³⁰ In some instances, cancer growth and emerging clonal distributions have been proposed to follow neutral dynamics, where clonal abundance can be predicted from mutation arrival history.⁹² Yet competition is expected to disrupt neutrality in many other cases.^{29,68,112,131} The GLV model hence brings forward an explicit framework to predict, given an estimate of clonal abundances, the underlying competitive interactions at play.

Competitive exclusion and therapy resistance

In other scenarios, strong environmental pressures can impose strong competition driven by large fitness differences. If competition overcomes self-regulation, the cancer ecosystem might fall into the regime of *competitive exclusion*. In it, communities are dominated by a single, strongly competing phenotype (Figure 2B) that would eventually grow toward populating the tumor. This regime is particularly relevant to treatment design, as shown in earlier studies describing drug-sensitive-drug-resistant interactions under therapy.^{132,133} The framework of adaptive therapy (AT), for instance, has shown how maximum dosage treatment can eradicate drug-sensitive populations and provide a competitive advantage to the drug-resistant phenotype to govern.^{16,24,134} Based on a low-dimensional approximation of the ecological framework proposed here (Box 2), AT instead aims at adapting drug dosage and timing to maintain the tumor within the controlled coexistence regime (Figure 2B). Given that multiple phenotypes might be grouped into the sensitive compartment, we hypothesize that the multi-species GLV model better predicts the conditions by which a mixture of sensitive populations can keep resistant phenotypes at bay.¹³⁵

Tumor outgrowth

A third regime of the GLV model considers *tumor outgrowth*: under heterogeneous interactions involving weak competition but also a certain degree of cooperation, multiple phenotypes will grow indefinitely, as empirically observed in the study by Chapman et al.³³ This can happen if the mean of interaction strengths is positive, meaning the tumor is mostly built upon cooperative interactions—an unlikely scenario (Figure 2B, bottom right). Interestingly, the same regime can also emerge if interactions are on average competitive, but their heterogeneity (σ_A) is high enough, meaning that a small fraction of strongly cooperating species are in place (Figure 2B).^{33,113} This can also imply that K_μ , the carrying capacity of each phenotype mirroring its adaptation to the tumor microenvironment, is no longer a hard limit. Facilitative interactions, such as coexistence with an angiogenic phenotype that increases blood supplies, can allow phenotypic growth beyond the constraints imposed by the tissue.^{68,114,136} Consistent with empirical findings,³³ the GLV model then provides an explanation for how heterogeneity might be intrinsically linked to the emergence of cooperation leading to tumor outgrowth.^{64,113}

Fluctuations and shifts between multiple cancerous states

Internal dynamics and interaction strengths across cancerous phenotypes are likely to be highly heterogeneous.^{39,137} Moreover, competition is also expected to be strong in advanced stages of resource-limited tumors: persistent acidification of the environment, reduced resources, or increased crowding likely induces negative $A_{\mu\mu}$ values.¹³⁸

In this context of competition (negative μ_A) and heterogeneity (high σ_A), the GLV model opens the possibility for a new paradigm in cancer ecology. In the model, heterogeneity can drive the system toward a complex and plastic regime of complex phenotypic fluctuations and shifts between multiple community states^{53,77,115} (Figure 2B). Such regime has recently been hypothesized to explain complex dynamics in experimental microbial communities.^{80,139,140} What are the implications of these emerging dynamics for cancer research?

Opposite to the notion of homeostatic stability of a single precancerous state, here heterogeneity drives the system to a much more nuanced scenario. In it, evolutionary changes^{39,92} or persistent phenotypic switching⁴⁶ would drive the system toward a metastable regime, in which the whole tumor community can not only transition through a set of multiple cancerous states^{115,141} but also persist in out-of-equilibrium dynamics^{54,142} (Figures 2C and 2D). In ecology, this is linked to the concept of ecological succession, by which ecosystems can follow directional—albeit not always predictable¹⁴³—transitions from one ecosystem state to the next^{141,144} (Figure 2D). Together with recent evidence of ecological interactions modulating the prevalence of drug resistance,¹⁴⁵ this regime opens the possibility that nontrivial out-of-equilibrium phenomena previously observed in ecosystems, such as persistent fluctuations¹⁴⁶ and long dynamical transients,⁵⁵ also play a key role in oncogenesis.

In cancer, recent research highlights the possibility that tumor ecosystems explore recurrent and potentially stepwise predictable trajectories in their composition and malignancy.⁵ In this context, the GLV model can provide a first mathematical framework explaining how successive oncogenetic stages and the complex trajectories between them emerge in heterogeneous cancers. A powerful framework could result from connecting cancer models with the structural stability approach,¹⁴⁷ which has successfully explained switching patterns in microbiome dynamics.¹⁴⁰

Beyond explaining the non-trivial natural histories of tumors,^{5,148} the possibility of multistationarity in cancer also holds key implications for therapy. In this regime, the extinction of a targeted population under treatment could induce secondary extinctions and invasions,¹⁴⁹ yielding a complex transient regime followed by a shift toward a different phenotypic community (Figure 2D). In ecology, this is characteristic to the notion of *communities as superorganisms*, where the survival of each species is strongly intertwined to the presence or absence of other species.¹⁵⁰ If tumors behave as GLV superorganisms, this would mean that a whole new ecological mechanism of community-level plasticity is at play without the need for mutational or epigenetic alterations. Abrupt transitions from one phenotypic composition to another imply that not single phenotypes²⁴ but entirely new resistant communities could emerge after a failed treatment attempt.

Overall, the possibility that heterogeneity drives tumors toward a non-trivial regime involving whole-community shifts urgently asks for a more dynamical understanding of cancer and its complexity if we are to design successful therapeutic strategies.¹⁵¹

Oncogenic transitions across the four regimes

The GLV framework discussed earlier uncovers that, for a given set of phenotypes N , characterized by r_μ and K_μ , and interactions characterized by (μ_A, σ_A) , the tumor community will display dynamics and attractor states of one of the four regimes (Figure 2B). Yet, tumors are inherently unstable dynamical systems, and multiple mechanisms can alter the set of parameters. A change in the parameters, in turn, implies that the tumor will shift toward a novel dynamical regime. Here, we outline mechanisms driving such changes, namely evolutionary, microenvironmental, and therapeutic, and link them with observations of oncogenic transitions.

As discussed earlier, a main property of tumors as CASs is that evolutionary dynamics occur at a similar scale of the ecological interactions of Equation 1. As opposed to many ecological systems, where mutations are rare when compared to their time to fixation,¹⁵² some tumors might be close to viral quasispecies, meaning the emergence of new mutants has the same timescale of their interactions.^{27,153,154} The first consequence is that, if mutations translate into novel phenotypes with acquired ecological functions, the number of species N can increase in time. Here, the theory of ecological invasions provides a direct toolset to understand the conditions by which new phenotypes can succeed at invading the tumor.^{155,156}

Moreover, a new phenotype can modulate the statistics of \mathcal{A} in a way that changes the dynamics of the tumor.¹¹² For example, an angiogenic phenotype can emerge, positively impacting resident species and driving a transition toward tumor outgrowth.^{32,157} Also, a strong competitor (e.g., a rapidly replicating mutant) can drive the system to the competitive exclusion regime.¹³³ The GLV then provides an explanation of the transition from apparent dormancy toward tumor outgrowth.¹⁵⁸ This transition would result from a new phenotypic population displacing community interactions \mathcal{A} toward crossing the coexistence-to-outgrowth threshold, through e.g., immune evasion¹⁵⁹ or a shared invasive phenotype³³ (Figure 2B).

Beyond evolutionary dynamics, parameter changes can also come from external alterations of the microenvironment such as therapeutic interventions,¹⁶⁰ dietary changes,¹⁶¹ or acidity changes (see e.g., the study by Dujon et al. and Pienta et al.^{4,104} for a discussion). As discussed earlier, a powerful example here is provided by AT: excessive drug dosage can drive a tumor away from a regime of multiphenotype coexistence and toward so-called *competitive release*, where drug-resistant cells become free of competitors and can populate the relapsing tumor.^{10,24} All in all, the GLV cancer model establishes a framework by which we can understand how tumor ecology, invasion of novel phenotypes, and alterations driven by therapy shape cancer dynamics.

A note on the spatial ecology of tumors

A key missing ingredient in the GLV formulation of the tumor ecology is the role of space.¹⁶² In solid tumors, clinical, experimental, and mathematical efforts have shown that spatial constraints can modulate cellular growth and death due to nutrient availability,^{163,164} the infiltration of immune cells into the tumor,^{165,166} or the overall emergence and heterogeneity of novel rogue phenotypes.^{127,167–171}

Yet, as discussed further in the open questions section, explicitly including space in a GLV-like formulation remains an ongoing research task. This necessary bridge between community and *spatial ecology*,^{172,173} however, might come at the cost of losing some of the fundamental insights that the analytical formulation of the GLV model has provided.^{54,77,99} In that view, implicit extensions of the model that can act as proxies for spatial processes can prove as a powerful intermediate step. Examples of these include the classical inclusion of carrying capacities mirroring spatial and nutrient limitations,^{16,68,107} the use of saturating functions to depict decreased immune penetration of larger tumors,^{26,174} incorporating fractal growth exponents emerging from surface replication,^{107,175,176} or the application of metapopulation and metacommunity frameworks to describe cell dispersal and heterogeneity.^{127,177} These implicit descriptions of spatial processes within a GLV cancer framework are described throughout this work and in the open questions section.

ONCOLOGICAL EXTENSIONS OF THE GLV MODEL

High-dimensional phenotypic plasticity

The parallel between species-rich communities and heterogeneous tumors suggests new and unexpected cancer properties. Yet, there are characteristics of tumor cells and their plastic genome that cannot be described by classical ecological dynamics. For example, accumulated evidence indicates that rogue cells do not necessarily express a stable phenotype (as animal or plant species do), but are much more plastic and can stochastically switch into others.^{46,178,179} A relevant example here is the recent observation of a complex architecture of four well-defined switching phenotypes in glioblastoma.¹⁸⁰ How can we mathematically characterize such a system, and what are the implications for therapy?

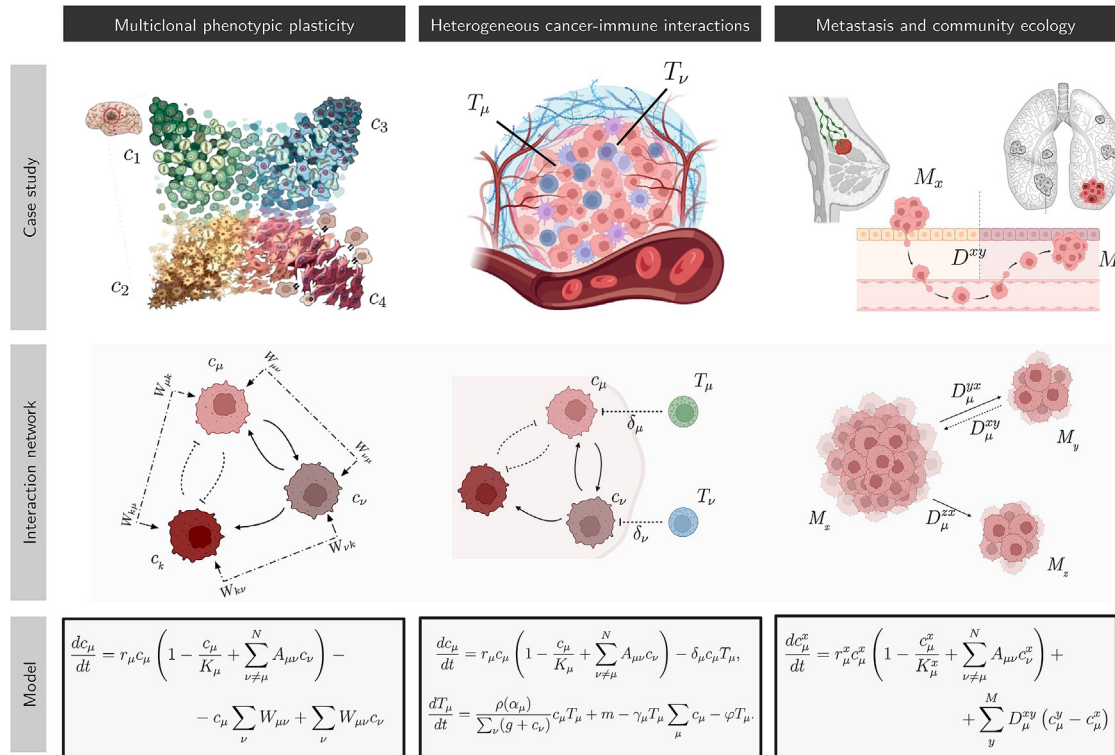


Figure 3. Oncological extensions of the GLV cancer model

The species-rich nature of tumor communities holds implications in other areas of cancer research, as exemplified here with three case studies. First column: ecological interactions between cellular phenotypes are sometimes intertwined with stochastic phenotypic plasticity, as it occurs with glioblastomas, where genetic analysis revealed four transitioning phenotypes.¹⁸⁰ These transitions can be described by a matrix of rate flows between population compartments indicated by the terms $W_{\mu\nu}$. Second column: interactions between cancer and the immune system are inherently high dimensional, and complex patterns of cancer-immune interactions appear to be a common feature. Multiple cancer clones $\{c_\mu\}$ interact with corresponding T cells $\{T_\mu\}$, where each T cell species can only recognize and attack one immunogenic antigen. Third column: the problem of metastasis can be modeled as a metacommunity with multiple patches $\{M_i\}$ connected by cell dispersal $\{D_{\mu}^{ij}\}$, yielding emerging properties of the tumor-nodes system.

Inspired by minimal models of bacterial plasticity,¹⁸¹ now cells in each population c_μ switch at rate $W_{\nu\mu}$ toward the phenotypic population c_ν , whereas cells in this second population c_ν switch at a different rate $W_{\mu\nu}$ towards the first phenotype c_μ (Figure 3A). The diagonal elements of the W matrix are zeros, as self-switching does not exist, and off-diagonal terms are not necessarily symmetric.⁴⁶ The previous dynamical equation for the interaction and growth of tumor populations now reads:

$$\frac{dc_\mu}{dt} = r_\mu c_\mu \left(1 - \frac{c_\mu}{K_\mu} + \sum_{\nu \neq \mu}^N A_{\mu\nu} c_\nu \right) - c_\mu \sum_{\nu} W_{\mu\nu} + \sum_{\nu} W_{\nu\mu} c_\nu \quad (\text{Equation 4})$$

A first approach to understand the added complexity is to consider minimal scenarios with two phenotypes at play, such as the study of epithelial-mesenchymal plasticity and its implications in metastatic spreading¹⁸² or the analysis of a drug-sensitive-drug-resistant switch.^{183,184} Recent studies modeling tumor phenotypic plasticity have already applied the low-dimensional version of the ecological formalism proposed here (see Box 2; the study by Agudé-Gorgorió et al. and Gunnarsson et al.^{17,69}). Such low-dimensional models involving a two-phenotype switch following Equation 4 predict that therapy can only succeed if it targets the switching matrix W .¹⁸⁵ Treatment aiming at cell division or death alone will fail if phenotypic switching is at work, as this will maintain the heterogeneous community in place.^{17,69} As seen for bet-hedging strategies in bacteria¹⁸¹ and closely connected to game theory models,^{65,69,93} phenotypic switching models predictably explain how plasticity emerges as a community-level resistance strategy.

What happens when more than two populations can actively switch phenotypes?^{180,186} A recent work proposes to model phenotypic plasticity in glioblastomas following a simplified version of the GLV formalism.^{69,180} In particular, the species-rich model predicts not only the necessary targeting of switching rates but also a threshold number of drug-sensitive phenotypes below which the tumor can escape treatment.^{69,184}

Even if preliminary results already indicate the potential of phenotypic plasticity as a resistance mechanism, the complete picture painted by Equation 4 is yet to be fully understood. When both ecological interactions (A) and stochastic switching (W) are taken into account,

phenotypic switching between populations might prompt resistance as well as community-level shifts toward alternative tumor states.^{180,186} Theoretical analysis of the full system (3) should search for potential weak spots to this otherwise robust and plastic system: treatments for phenotypically plastic tumors are likely to fail unless such emerging complexity is fully accounted for.

Heterogeneity in cancer-immune interactions

Uncovering the ecological interactions between cancer cells and the immune system has prompted revolutionary changes in cancer therapeutics. The immune system, in fact, is itself an ecosystem of cellular species interacting in complex ways to mediate the immune response.¹⁸⁷ In cancer, different immune cells participate in tumor cell recognition and destruction,^{22,188} but also in pro-tumor inflammatory responses.⁸

One of the most relevant components for cancer treatment is adaptive T cells and their complex recognize-and-kill cascade (Figure 3B).¹⁸⁸ Early ecological models proposed that cancer T cell interactions behave as a predator-prey system with added competitive components.^{22,26} Also fundamental to this process is the discovery that cancerous mutations can alter surface antigens and activate T cell recognition.¹⁸⁹ This poses a selective barrier: tumors that escape the immune system are more likely to avoid early deletion.^{159,190}

Accumulated evidence indicates that one escape mechanism is rooted in tumor heterogeneity: it is not only the number of neoantigenic mutations but also their variety that dictates the failure of the immune response.^{191,192} Here, we propose extending the GLV cancer model to account for immune attack. One possible starting point is the two-dimensional cancer-immune model where both predation and competition are in place,^{25,26} described by the dynamical equations,

$$\frac{dc}{dt} = rc \left(1 - \frac{c}{K}\right) - \delta(\alpha)cT \quad (\text{Equation 5})$$

$$\frac{dT}{dt} = \frac{\rho(\alpha)}{g+c}cT + m - \gamma cT - \phi T \quad (\text{Equation 6})$$

where the last term in \dot{c} describes a death rate mediated by immune attack ($\delta(\alpha)$) proportional to the neoantigen load of the tumor α and its so-called neoantigen fitness.^{15,193,194} T cells proliferate at rate ρ when in contact with cancer cells, again proportionally to α . Proliferation via contact recognition saturates following a Michaelis-Menten function: larger tumors will be harder to penetrate and circulate by the immune system.^{26,174} The Michaelis constant g indicates the tumor size at which T cell proliferation is half of its maximum predicted rate. The influx constant m indicates the rate at which T cells arrive to the tumor bulk,^{22,26} γ is the death rate of T cells mediated by the presence of the tumor,¹⁷⁴ and ϕ accounts for the natural decay rate of T cells.

A key feature of the model stems from the fact that two interaction schemes are in place: T cells can recognize and predate tumor cells, increasing their proliferation through a clonal selection process.^{11,195,196} Yet, T cells also die under competition with cancer cells due to glucose limitations and a degraded tumor microenvironment.^{26,196} This multilayered two-species model can already give rise to a rich landscape of different dynamics seen *in vivo*, such as immune control keeping tumors in a dormant state¹⁹⁷ or immunostimulation of tumor growth²⁶ (see the study by Eftimie et al. and d'Onofrio et al.^{22,198} for an extended analysis). Moreover, accumulated efforts have analyzed how different versions of the model, also considering sensitive and resistant cancer populations, succeed at describing experimental data of lymphomas²⁶ and colorectal carcinomas¹³³ in mice.

However, recent evidence indicates that ecological interactions between cancer cells and the immune system are also pervaded by heterogeneity (Figure 1B). In the context of lymphocytic interactions, the success of cancer immunotherapy is strongly related to how homogeneous the tumor neoantigen load is.^{15,191}

The GLV model provides a methodological way to account for neoantigen heterogeneity in cancer. If each cancer population c_μ is now defined by its mutational subclonal profile, yielding a specific neoantigenic component α_μ , and T_μ is each T cell population recognizing the most immunogenic neoantigen in c_μ , the dynamics of the system can be reduced to (see the study by Gatenbee et al. and Agudé-Gorrión and Solé^{14,15}):

$$\frac{dc_\mu}{dt} = r_\mu c_\mu \left(1 - \frac{c_\mu}{K_\mu} + \sum_{\nu \neq \mu}^N A_{\mu\nu} c_\nu\right) - \delta(\alpha_\mu)c_\mu T_\mu, \quad (\text{Equation 7})$$

$$\frac{dT_\mu}{dt} = \frac{\rho(\alpha_\mu)}{\sum_\nu (g+c_\nu)} c_\mu T_\mu + m - \gamma_\mu T_\mu \sum_\mu c_\mu - \phi T_\mu. \quad (\text{Equation 8})$$

Now tumor populations interact through the GLV model with an additional predatory component (Figure 3B). Recent studies modeling heterogeneity in cancer T cell interactions focused on the first equation, by which one can rewrite the original cancer GLV model with an additional immune-mediated death term without explicitly describing T cell dynamics.^{14,15} This approach already provides insights into immunotherapy responses in melanoma¹⁵ and immunoediting in colon cancers.¹⁴

Yet, certain aspects of the cancer T cell interaction indicate that we might benefit from extending the GLV model by explicitly accounting for the T cell compartment. If immune populations were included in the GLV model with a single equation for both cancer and T cells, we would only be able to capture one of the two main interactions at play. As described earlier, immune cells not only compete under a bilinear mass action function with cancer cells (the $-c_\mu T_\mu$ terms in both equations), but T cells also predate on cancer cells following a saturating

function.^{26,196} This implies that the cancer T cell model benefits from an explicit multilayer description that can capture both competition and predation.^{196,199}

More importantly, explicitly capturing the dynamics of the two compartments separately allows us to model a key asymmetry that only emerges in the species-rich formulation. Cancer populations c_μ are preyed by the immune compartment that can recognize them, resulting in a term $-\delta(\alpha_\mu)c_\mu T_\mu$.¹⁹² Conversely, T cells die in the presence of whatever cancer populations are in place, $\sum_\mu c_\mu T_\mu$. This implies there is an underlying *divide and win* mechanism in place: each T cell clone recognizes one cancer clone, while all cancer clones can kill T cells and also cooperate to avoid immune infiltration of the tumor.¹⁵ Is there a limit beyond which the *divide and win* strategy succeeds? Can it explain why immunotherapy is so dependent on neoantigen load and immunogenicity?

Early models of HIV progression uncovered a similar problem: there is a critical viral diversity beyond which the immune system can no longer control viral growth.²⁰⁰ Similarly, a recent study of the cancer GLV model with immune death uncovers a *neoantigen heterogeneity threshold*¹⁵: if the number of different neoantigenic clones overcomes a critical value, the tumor will become too heterogeneous to be effectively targeted by the immune system.^{191,192} When applied to clinical data of melanoma treated with CTLA-4 immunotherapy, the model consistently predicts that patients with lower neoantigen heterogeneity values respond better to immune blockade treatment.¹⁵

Finally, the whole network of cancer-immune interactions spans well beyond the predator role of T cells. T cells themselves can also hold tumor-promoting phenotypes, yielding non-trivial scenarios where tumor cells become engineers of their own microenvironment.^{8,14} Similarly, the role of macrophages in cancer is inherently multimodal: type-1 macrophages interact in a cooperative anti-inflammatory cascade with tumor cells, while type-2 macrophages can eradicate rogue cells.⁸ Beyond immune cells, stromal recruitment is another of the many layers that participate in dynamics of the tumor ecosystem²⁰¹ (Figure 1B). Cancer vaccines, which modulate the landscape of immune recognition of neoantigens, could also be introduced.²⁰² As done for neoantigen heterogeneity biomarkers in melanoma,¹⁵ including these additional layers in the complex ecology of Equations 6 and 7 could bring new insights into the tumor ecosystem network and how to best modulate it to treat cancer with immunotherapies.

Metastasis and metacommunity ecology

Advanced-stage metastatic disease accounts for the majority of cancer-related deaths.¹³⁵ On top of the aforementioned cellular heterogeneity, seeding between the primary tumor and multiple metastases colonizing different organs imply an ever more complex disease that is inherently difficult to understand and treat²⁰³ (Figure 1A). In this direction, theoretical ecology has shed light into different aspects of the process.^{12,203,204} Recent research has unveiled the topology of the tumor-metastases seeding network across 28 cancer tissue types.²⁰⁴ Moreover, an eco-evolutionary modeling study predicts how phenotypic differences between the primary tumor and its metastatic nodes can inform of the seeding mechanisms in ovarian, colorectal, and breast cancer samples.²⁰⁵

Ecologically, the complexity of the problem is that we no longer have a community adapted to a given niche (the microenvironment of the host organ, Figure 1B), but rather a set of heterogeneous tumor communities connected by cell migration^{135,206} and adapted to alternative microenvironments.¹⁵⁸

Since the 1990s, ecologists know that a *metapopulation*—a population distributed along spatial patches connected by dispersal—can display dynamics not found in single-patch systems.²⁰⁷ While stochastic birth-death processes can drive single populations to extinction, migration between patches allows the metapopulation to thrive, yielding a so-called *rescue effect*. Early work already indicated that metapopulation dynamics could be at play in heterogeneous tumors and provide an explanation (based on spatial ecology) for the coexistence of diverse clonal cancer cell populations.¹²⁷ In the context of metastatic disease, this emerging property could explain how migration from the primary tumor or seeding between metastatic nodes^{135,206} could allow weaker or targeted metastases to survive under therapy.

What happens when host-level disease is not a single ecological community (Figure 1C) but many communities connected by migration (Figure 1A)? Will the metastases replicate the phenotypic composition—and hence the treatment sensitivity—of the main tumor, or can theory help explain if each metastasis forms a community of its own? We propose here that the complexity of the metastatic process can be fundamentally captured by the theory of metacommunity ecology (Figure 3C). Metacommunity ecology is an extension of metapopulation ecology that studies a network of geographic patches connected by species migration, where each patch is itself a community of interacting species.¹³ The GLV system is extended to a network of M communities (the primary tumor and metastatic nodes), where the abundance of phenotype μ on node x , c_μ^x , depends on its GLV dynamics but also on the dispersal from and toward the rest of the nodes (Figure 3B)²⁰⁸:

$$\frac{dc_\mu^x}{dt} = r_\mu^x c_\mu^x \left(1 - \frac{c_\mu^x}{K_\mu^x} + \sum_{v \neq \mu} A_{\mu v} c_v^x \right) + \sum_y D_\mu^{xy} (c_\mu^y - c_\mu^x), \quad (\text{Equation 9})$$

where D_μ^{xy} captures the migration of μ -cells between the nodes x and y . The migration matrix might not necessarily be symmetric ($D_\mu^{xy} \neq D_\mu^{yx}$) and is written here as such only for simplicity. Current research allows us to accurately capture the properties of this matrix D , which represents how the tumor seeds different metastatic nodes across tumor types.^{204,205} This provides a glimpse into this key property of the metacommunity. Here, we highlight three recent results on species-rich metacommunity ecology that could provide novel predictive tools to understand metastatic cancers once D can be estimated.

First, and inspired by island biogeography,⁹⁹ the GLV model with cellular seeding from a large phenotypic pool could be seen to describe a single metastatic community seeded by the main tumor. The model allows us to establish a link between the phenotypic composition of the

metastases and the primary tumor. More importantly, it hints at how both are impacted by species interactions and the tissue microenvironment at each site.^{99,204}

However, measuring the interactions and environmental impacts *in vivo* is a very difficult task. Recent results show that species distribution patterns (how different phenotypes are distributed along metastatic sites) can predict certain properties of the niche differences and the community interactions at play.²⁰⁸ Applying these results to cancer data could help unravel if the phenotypic composition of different metastases^{205,209} can inform the microenvironmental differences at play. This could help design combination therapies able to target the heterogeneous adaptation strategies that have emerged at each site.

Third, recent results have elucidated how the rescue effect upscales when multiple interacting populations are at play. The model shows that species migrations could allow the metacommunity to survive even further than its metapopulations due to emerging interspecies cooperation.²¹⁰ When translated to oncology, multicellular rescue effects between metastatic compartments could provide insights into how and why heterogeneous metastatic disease is so difficult to treat. Again, species-rich ecology needs to be considered if we are to design successful therapies for advanced cancers.

OPEN QUESTIONS IN CANCER COMMUNITY ECOLOGY

The GLV cancer model provides an advanced toolset to predict the conditions that dictate multispecies coexistence, disease outgrowth, and competitive release after treatment. The model also harbors a non-trivial regime where heterogeneous interactions can drive the tumor ecosystem toward complex dynamical transients and shifts between multiple cancer states. If cancer does behave as a GLV community, these salient features could provide a fundamentally novel view on cancer as a plastic and persistently changing complex ecosystem. In this perspective, we propose that modeling tumors as species-rich GLV communities opens the following novel research avenues and questions in mathematical oncology.

- (1) The diversity-stability debate in ecology plays a key role when modeling pervasive tumor heterogeneity. Given that cancer populations might grow following sublinear dynamics, can this explain and predict the degree of heterogeneity a tumor can support?
- (2) Species-rich models, as opposed to simpler population dynamics, predict the emergence of multiple stable states separated by nonlinear trajectories. Given that cancers are complex ecosystems of many interacting species, could nonlinear transitions between multiple cancerous states provide an additional mechanism for tumor resilience?
- (3) Tumor phenotypes might be much more plastic than ecological species. How does this additional layer of complexity impact our ability to treat cancer?
- (4) Tumor-immune competition is strongly governed by the neoantigen heterogeneity of the cancer bulk. Can there be predictable thresholds, beyond which the predatory role of T cells is impaired by excessive antigenic diversity?
- (5) Metastases progress by establishing novel cancer communities in different microenvironments. Can the metacommunity ecology of connected ecosystems explain the heterogeneity and resilience of the tumor-metastases system?

Despite our work being focused on the aforementioned topics, the GLV formalism offers additional paths for further exploration in mathematical oncology. Future work could extend our discussion by exploring the impacts on tumor heterogeneity, the role of space and time, the implications of critical points, or the origins of plasticity and robustness. Some of these open questions not discussed earlier are:

- (6) The models presented here share a deterministic character, but stochastic dynamics can be implemented by generalizing the previous equations.²¹¹ One way is to write down the GLV competition scenario as follows^{77,142}:

$$\frac{dN_i}{dt} = N_i \left(r_i + \sum_{j=1}^S A_{ij} N_j \right) + \lambda_i + \omega_i \sqrt{N_i(t)} \eta_i(t). \quad (\text{Equation 10})$$

where the last term on the right-hand side introduces stochasticity as demographic noise,²¹² where $\eta_i(t)$ represents white noise that depends on a constant ω_i particular to each population, and an abundance term $\sqrt{N_i}$ that reflects the scaling of noise due to population size.¹⁴² The term λ_i stands for immigration, in an ecological context, from a geographical species pool, but could also be used to introduce mutational events. A relevant result in this context is that, when species diversity increases, competitive communities have a landscape pervaded by marginal attractor states leading to complex fluctuations^{142,213} (see also the study by Solé et al.²¹⁴). Could cancer cell populations evolve toward these marginal states?

- (7) The attractor landscape that we have presented here can be challenged by the presence of long transient phenomena.²¹⁵ It has been known for a long time that the convergence to a given attractor state can be strongly affected by the nature of the nonlinearities, stochastic fluctuations, as well as spatial degrees of freedom.^{216,217} The role played by space and long transients has been shown to provide opportunities of ecosystem management.²¹⁸ Could these phenomena play a role in heterogeneous tumors?
- (8) Spatial interactions have been shown to introduce novel properties in the dynamics of complex ecosystems. A whole research area within theoretical ecology is devoted to *spatial ecology*.^{172,173} The presence of spatially explicit metapopulations provides a dramatic example of how space modifies the expectations from well-mixed (mean field) approximations. An example is competitive

exclusion: competition becomes local under the presence of space, and global coexistence is possible.²¹⁹ Similarly, the locally constrained nature of interactions among cancer cell phenotypes explains the coexistence of diversity in tumors^{127,168} and increases waiting times for neoplasms to develop.¹⁷⁰ An extension of the GLV framework with spatial degrees of freedom would provide valuable insights into the conditions for persistent heterogeneity and how it relates to the resilience of tumors to perturbations.

- (9) As it occurs in ecological systems, models of cancer progression often display tipping points separating tumor growth from extinction (or different regimes of growth). What can be learned from the study of tipping points and catastrophic shifts as a way to approach cancer therapies? It has been suggested that we can actually use shifts to “turn ecology against cancer.”²²⁰ Indeed, the potential success of some cancer treatments might be grounded in the possibility of crossing bifurcation points leading to non-viable (or stagnation) states.^{23,27} What is the effect of considering a multispecies scenario? What are the conditions under which a rich cancer cell population will cross a tipping point after a given therapeutic approach?
- (10) Ecological communities are often seen as the result of an assembly process leading to a directional sequence of transitions. This so-called *ecological succession* refers to a process where a set of populations undergoes a series of changes that follow predictable paths after an initial colonization event in a given habitat, which could be an abandoned field. As discussed in the study by Kareva,²²¹ this has a clear parallel in cancer, where this initial event would correspond to the establishment of a primary tumor or secondary metastatic tumor. The use of the GLV formalism would be very helpful to address this problem against available single-cell data on growing tumors. Some useful metrics have already been proposed to quantify the directionality (the arrow of time) of complex multispecies communities.¹⁴¹
- (11) The interactions between growing tumors and the host microbiome might play a fundamental role in oncogenesis,²²² and evidence indicates a potentially oncogenic and cooperative role between rogue cells and bacteria at some stages of tumor progression.²²³ Given the current state of rapid advances in microbial community ecology^{224,225} and the successful application of GLV frameworks in modeling microbial dynamics,⁸⁰ our work could be extended to include cancer-microbiome interactions²²⁶ as well as the potential metabolic networks underlying them.²²⁷ Results could allow us to understand under which conditions a healthy or disrupted microbiome can foster or prevent the progression of malignant cells.
- (12) Over the last decade, a successful approach to ecosystem complexity has emerged from the analysis of synthetic ecologies obtained from sampling actual communities and growing them in cell cultures.^{80,228} By studying the dynamics of these *in vitro* ecologies, it has been possible to validate several general principles of community ecology using a combination of experiments and GLV models. These experiments have confirmed the mathematical approximations made by canonical models of tipping points, cooperation, or extinction dynamics. Could we consider building synthetic cancer communities to perform similar experiments in the test tube? The emerging science of microbiomes²²⁹ (where the GLV approach has been widely adopted) and the possibilities of metagenomic characterization of their complexity could inspire an analogous research within tumor dynamics.

DISCUSSION

Ecological interactions shape all stages and scales of tumor progression. Beyond the usual focus on the cancer cell, evidence indicates that tumors are built upon a rich and heterogeneous set of populations interacting under ecological mechanisms. In this context, current one- or few-species ecological models of tumor growth cannot capture the complex dynamics of cancer progression.

We propose to upscale current ecological models of tumor growth by applying the mathematical theory of species-rich ecological communities. Our central hypothesis is that the GLV model and its variations provide a candidate framework to describe cancer dynamics, and that its emerging properties shed new light into different regimes of tumor progression.

Several limitations of this study need to be surpassed toward the goal of quantifying a GLV cancer model beyond the qualitative insight provided here. As discussed throughout this work, we can highlight three as the ones we consider most urgent to tackle. First, estimating the parameters of the GLV cancer model or, as proposed by the random interactions literature, at least its statistical properties remains an incredibly complex task. Second, delimiting what makes a *cancer species* in the view of the genetic, epigenetic, phenotypic, and immunogenic diversity of tumor cells will require additional knowledge across these fields and a bridge with the methods of microbiology. Third, applications of the GLV cancer framework will need to assess which of the many dynamical ingredients described earlier should be included in the model, so that it captures the key processes under study.

All in all, the present work provides a necessary bridge between theoretical community ecology and cancer research. Applying the GLV framework to quantitative tumor systems will bring novel understanding and, more importantly, a more nuanced framework to design therapies targeting ecosystem-level properties of cancer.

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AUTHOR CONTRIBUTIONS

G.A.-G. proposed the original ideas and wrote the first draft. R.S. wrote the open questions section. All three authors discussed and improved together all content, figures, and the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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