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Testing Multi-Task Cancer Evolution: How Do We Test Ecological Hypotheses in Cancer?

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Recently several authors described a family of models, according to which different cancer types and subtypes fall within a space of selective trade-offs between archetypes that maximize the performance of different tasks: cell division, biomass and energy production, lipogenesis, immune interaction, and invasion and tissue remodeling. On this picture, inter- and intratumor heterogeneity can be explained in part as a product of these selective trade-offs in different cancers, at different stages of cancer progression. The aim of this Perspective is to critically assess this approach. I use this case study to consider more generally both the advantages of using ecological models in the context of cancer, and the challenges facing testing of such models.

Keywords: multi-task, evolution, cancer, ecology, testing, genomics

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INTRODUCTION

Cancer evolves; that is, populations of cancer cells change over time in distribution of genotypic and phenotypic features, and relative survival is due in part to interactions with the surrounding environment. This idea is not new, and has indeed led to an active research program (Nowell, 1976; Merlo et al., 2006; Greaves and Maley, 2012). If cancers evolve, then investigating the *ecologies* of cancers, and selective trade-offs at work in these different local microenvironments, will be centrally important to explaining how and why cancers progress slowly or quickly, respond to treatment, or fail to do so.

What, however, does it mean to explain or describe cancer's "ecologies" or "ecological dynamics"? While several scientists have proposed general theoretical frameworks and mathematical models for predicting and explaining cancer's evolutionary dynamics (Michor et al., 2004; Frank, 2007; Wodarz and Komarova, 2014), relatively few have drawn upon ecological theory (F. Adler and Gordon, 2019). However, Maley et al. (2017) describe what they call the "Evo-" and "Eco-Index" of cancers – that is, a taxonomy of various features that enable various patterns of evolutionary and ecological change in cancers over time. Thus, for instance, a major component of the "Evo-index" of a tumor is *extent of heterogeneity*, which enables a population of cancer cells to respond to selection. The "Eco-Index," in contrast, consists in a "profile" of "hazards" and "resources" (what can kill a cell, or resources required for cell maintenance and growth), which might be expected to select for the particular life history strategies (Aktipis et al., 2013). High levels of hazard or fluctuating resources might tend to yield rapid reproduction and little investment in maintenance and survival. Low hazards and a steady supply of resources, in contrast, might predict an expansion of the carrying capacity of the habitat, and competition for limiting resources.

International sequencing efforts have now provided data that allows cancer researchers to test some of these hypotheses (Hutter and Zenklusen, 2018). These sequencing efforts demonstrated that cancers are enormously heterogeneous. Cancers arising in different cell types, tissues, or organs vary in the extent and type of mutations most common. This "inter-tumor" heterogeneity is often contrasted with "intra-tumor" heterogeneity: the extent of genetic variation within a single population of cancer cells. In order to optimize treatment, we need to better understand why variation arises between cancers, and among cell lineages in a tumor, both in space, and over time.

Hausser and Alon (2020) apply multitask evolution to genomic data, in service of identifying the specific trade-offs at work in different cancers, and among cell lineages (Hausser et al., 2019, p. 2). They predicted that, given trade-offs among various tasks of cancer cells in a tumor, both space, and over time, selection among these trade-offs could also yield "archetypal" genomic profiles. For instance, early on in the development of a tumor, one might expect genetic profiles associated with rapid growth, whereas later on, there may be genetic profiles associated with immune resistance, or capacity for invasion and metastasis.

To identify the trade-offs at work in cancer progression, they use a Pareto-optimal modeling strategy, drawing upon gene expression profile data (transcriptomic data) from TCGA and METABRIC databases. Using PCA (principal component analysis), they reduced the number of dimensions in the data, identifying the most common variants across tumors. They then subject this reduced dataset to ParTI (Pareto task inference). ParTI has been used to illustrate the role of selective trade-offs between tasks in a variety of other systems. The "Pareto front" represents gene expression profiles for which performance cannot be improved without decreasing performance in another task: gene expression profiles along a Pareto front are "Pareto optimal." When there are three or more tasks, one can generate a polyhedron, where the vertices represent the "archetypes" – or, "specialists" at specific tasks.

They showed that different cancers seem to have distinctive optima, or gene expression profiles associated with trade-offs among different tasks. For instance, in glioma, the trade-offs were between cell division, invasion and tissue remodeling, and immune interaction, with a cluster close to the cell division archetype. In contrast, in liver cancer, the trade-offs appear to be between biomass and energy production, cell division, and invasion and metastasis, with a cluster closer to biomass and energy production. Moreover, they found that, depending upon stage or grade, different cancers within a type (e.g., breast cancers) seemed to display gene expression of higher frequency coinciding with one or another Pareto optimum, suggesting that selective trade-offs likely change from early stage tumors to invasive metastatic disease. Such selective trade-offs might be driving change in the distribution of tasks in cell populations in a tumor over time, and thus, changes in the distribution of gene expression profiles. Such information could, they argue, be linked with clinical data, and drug sensitivity data, in service of more effective therapy.

There were some limitations to their analysis, however. They "could not reliably detect polyhedra for seven out of 15 cancer types; these seven cancer types showed gene expression that fell in a cloud without detectable vertices." That is, fully half of the cancer types they analyzed did not fall within the archetype framework. As they note, future research could determine what might explain lack of fit, where one option is simply that "trade-off theory is not applicable such as a lack of strong selection," or, perhaps, "too many tasks (many archetypes) that cannot be resolved given the noise." (Hausser and Alon, 2020, 250) Below, this example will be considered as a case study for generating important insights about what we ought to look for when testing hypotheses about cancer's eco-evolutionary dynamics.

CANCER GENOMIC DATA AS A SOURCE OF BIAS

Hausser et al., generated their archetypes by drawing upon TCGA and METABRIC data, reducing the dimensions of the data using PCA (principal component analysis). It's worth briefly considering how these data were generated, to consider whether either the data themselves, or the reduction in of dimensions of the data (or both), might bias the results they found.

The TCGA "pipeline" had several stages. First, tumor samples and healthy cells are taken from each patient, typically at first diagnosis – i.e., early stage cancers. Though, how early this may have been in the progression of disease likely varied significantly across cancers – for instance, pancreatic cancers tend to be diagnosed later than prostate or breast cancers. Second, at least during the first 5 years during which TCGA was conducted, whole exome sequencing was not an option. So, initially, the second stage of the pipeline involved targeted sequencing of genes known (already) to be tumor drivers: genes, mutation to which were already known to be common in cancers of this or that type (Hutter and Zenklusen, 2018). The third stage involved comparing frequency of different mutations within cancers of a particular type or subtype. During the last half decade of sequencing efforts, whole exome sequencing and "mutation calling" algorithms, systematically generated data on which mutations were common or rare in different cancer types. These algorithms were designed to exclude certain genes not known or believed to be relevant to cancer phenotype, and thus *weighted some genes as likely more significant than others*, based on functions known or likely typically associated with the cancer phenotype – e.g., if a gene was associated with mitosis, etc.

In other words, the driver mutations identified by TCGA as more or less common in cancers of this or that type were identified by algorithms designed to detect mutations to genes known to be associated "hallmark" functions of cancer cells (e.g., TP53, APC, etc.) (Hanahan and Weinberg, 2011). Genes typically thought to have no role in "hallmark" features of cancer cells were (by and large) ruled out as "noise." Thus, one concern that any analysis of cancer genomic data may have when using such data to test hypotheses about selective trade-offs is that cancer genomic data (at least that data published in the consensus genome papers) were already filtered by algorithms designed to identify mutations to genes associated with the "hallmarks" of cancer. Thus, it is no surprise that data drawn from TCGA

would generate "archetypes," or show relatively high frequency of mutation and/or gene expression for these five major tasks. Hausser and Alon's (2020) discovery that glioma and bladder tumors, for instance, fit a polyhedron model, with axes that are represent trade-offs among gene expression for specialization in cell division or immune interaction, in other words, may in part be not entirely unexpected. Further, their analysis reduced the dimensions of the data, and averaged gene expression patterns within any given cancer type or subtype – such a process may have led to loss of important information, such as about unique gene expression profiles distinctive to particular cancers, or subpopulations of cells within cancers. This could well explain the lack of fit with the models, for a proportion of the cancers studied.

STANDARDS OF EVIDENCE IN TESTING ECOLOGICAL MODELS IN CANCER

A second general concern one might have has to do with standards of evidence for testing hypotheses about trade-offs. In a classic discussion, Stearns (1989) gives a brief overview of what information is required to test hypotheses about life history trade-offs in whole organism biology:

That trade-offs can be measured and analyzed at the level of the genotype, the phenotype and what lies between (intermediate structure) . . . *It is not a question of either genetic correlations or phenotypic correlations or physiological trade-offs but of how such measurements combine to deliver information about potential evolutionary responses*. A study conducted at just one of these levels is likely to be of as little use as the information on the nature of the elephant delivered by one blind man holding its tail ... Knowledge of all three of these levels is necessary to understand how a trade-off works (Stearns, 1989, p. 259).

Stearns gives several examples of tests of hypotheses about life-history trade-offs – for instance, trading off between growth and reproduction. In all these models, there is a quantitative measure of the traits in question in a given population, their effects on fitness, and in some cases, experimental manipulation of the population to test these hypotheses.

According to Stearns, for a genuine test of an ecological hypothesis about trade-offs, it is important to give quantitative measures of how trade-offs between phenotypic traits negatively covary. Moreover, in principle, one should also establish that there was sufficient variation within the initial population for both traits to be subject to selection. If manipulation of the traits is possible, experimental manipulations should be conducted to test hypotheses about these proposed trade-offs. Ideally one must give ecological information about how and why traits are likely to trade off, and not only demonstrate how they negatively covary. Testing requires some quantitative measure of fitness, a function that describes how fitness depends on variable phenotypes (and trade-offs among them), and a set of alternative phenotypic profiles that describes options for manipulating the variables at work in these fitness trade-offs. How does Hausser et al.'s theoretical framework perform in this regard?

They do cite indirect evidence that there are plausibly selective trade-offs likely at work in cancer. Some resources, such as ATP, are needed for both growth and metastasis, and are limited in supply (Broxterman et al., 1988), metabolic constraints were also reported (Jerby et al., 2012), harsh conditions cause cancer cells to become quiescent (Gade et al., 2017), and proliferation is stimulated more favorable microenvironments (Wang et al., 2017a,b). Hausser et al., cite several papers that they claim support the general view that cancer cells face fitness trade-offs (Hatzikirou et al., 2012; Aktipis et al., 2013; Gillies et al., 2018; Gallaher et al., 2019).

However, a closer look at these papers indicates that they show not that cancer cells do as a matter of fact face trade-offs between various traits in a given environment, but only that this is a plausible hypothesis. For instance, Aktipis et al. (2013) write, "The exact nature of tradeoffs between these mechanisms has yet to be determined in most cases." Gallaher et al.'s (2019) is an ingenious simulation, using agent-based modeling to represent how these trade-offs could evolve in a population of cancer cells. However, the paper presupposes, rather than documents, the trade-offs in question. Likewise, Gillies et al. (2018), discussion is about how it is plausible that various trade-offs are at play in the EMT (epithelial-mesenchymal transition), associated with changes in blood flow in the tumor, not a test of this hypothesis. While they provide evidence suggesting that this hypothesis is a plausible explanation of patterns and processes of changes in tumors, it is not an attempt at systematically testing the hypothesis. Hatzikirou et al. (2012), also cite experiments with cultures of glioma cells (Giese et al., 2003) that have shown a "relationship between migratory and proliferative behavior, indicating cell motion and proliferation are mutually exclusive processes since highly motile glioma cells tend to have lower proliferation rates." (Giese et al., 1996a,b; Godlewski et al., 2010). However, the Hatzikirou et al. (2012) do not themselves conduct any experiments; the paper is *simulation of how the trade-off is likely* to play out in glioma. So, such studies do not provide the kinds of tests of life-history trade-offs Stearns takes to be exemplary; much of the evidence is indirect, at best.

On the one hand, one might argue that holding cancer researchers to the same standards of testing trade-offs typical in whole organism ecology is inappropriate. After all, cancers are often discovered well after the selective processes in question occurred. Unlike in whole organism biology and ecology, we cannot do a controlled study of exactly how and how much cancer cells vary with respect to these trade-offs *in situ*. Simulations are as close to tests of such hypotheses as can be provided (Parke, 2014). In the best case scenario, and perhaps with advances in sampling of tumor biomarkers, we may be able to describe the dynamics of cancer's evolution, during the course of treatment. Just as in testing any evolutionary hypotheses for which the evidence is long in the past, we can use experimental or computer simulations of *close enough* evolutionary processes (Vasi et al., 1994; Sniegowski et al., 1997).

On the other hand, it does seem worth considering whether ecological models and evidence in cancer should be held to lesser standards of. In order to test hypotheses that selective trade-offs are at work, or that various optima explain the presence or absence of this variant distribution in a population, whole organism ecologists are typically expected to generate a

function relating fitness and variable phenotypes (and trade-offs among them), and describe a *how* these fitness trade-offs can be varied to yield quantitative differences in outcome. Hausser and Alon (2020) do not provide anything this precise, nor do they experimentally test the link by manipulating these variables. Determining whether such fitness trade-offs are at work might require more precise, quantitative measures. Such context-specific information may be rather important to have, especially in treatment contexts.

Indeed, as Hausser et al. suggest, local selective (i.e., ecological) conditions may vary significantly across cancers. Arguably, different tumor microenvironments present quite distinctive challenges, and thus different selective "tasks" for different cancers, and different trade-offs, other than those they consider. It seems one important avenue for future work is to consider more seriously the role of local ecology – and potentially also, a role for niche construction. While it seems plausible that cancer cells from a variety of tissues and organs have relatively similar "driver" or hallmark gene expression profiles, it's also plausible that local conditions vary significantly (cf., Pong and Gutmann, 2011).

CONCLUSION

Multitask evolutionary theory is potentially a quite fruitful theoretical framework for generating and testing hypotheses that may explain the massive heterogeneity within and across cancer types and subtypes. It seems plausible, as Hausser et al., argue, that a variety of selection processes, and thus fitness optima, are universal to all cancers, and that there are trade-offs among various gene expression profiles. However, a significant portion of the cancers Hausser et al. studied did not fall within the archetypal framework. There are many possible explanations – ranging from the way the data were generated, to the means of analysis. I've argued here that it is worth exploring how cancers' dynamics might be governed by different ecological conditions, in different tissue microenvironments. Another consideration is drift; selection optimizes only given sufficient variation to act upon. Drift may play a significant role in some cancers' dynamics, limiting variation available for selection. Cancer stem cells may effectively function as genetic "bottlenecks," governing the variation available for selection in a tumor (Laplane, 2018; Lyne et al., 2020). Such bottlenecks could be limiting the possible scope of evolutionary change in some cancers.

I've also described two other reasons to be cautious in interpreting their results in light of the data used. When we set up an analysis of genomic data, we should be careful to assess whether the options are "forced" by the data or model considered. There are two ways in which this forcing could have come about here; first, their framework required that cancer types or subtypes be subject to trade-offs in ways that force the choice between "generalists" or "specialists." Second, the "tasks" that they identify were arguably "baked in": they are the very same tasks that cancer genomics researchers have been seeking to link to cancer drivers: the "hallmarks" of cancer. That said, it's not implausible that different cancer types in very different tissue microenvironments have distinctive ecological conditions, and thus selective trade-offs, at play.

Life history trade-off hypotheses may be easy to develop, but tests of such hypotheses can be forbiddingly difficult to carry out. As attested by Stearns (1989), examples of successful tests in whole organism biology often required decades of field work and experimental manipulation. On the one hand, it is widely agreed that life history theory, hypotheses about adaptation to local environments, and adaptive optima, can be fruitful. On the other hand, to establish exactly how various trade-offs are at work (such as a limited supply of energy, time, biomass, or nutrients), we should in principle give quantitative measures of each traits' relative effects on fitness. Even better, we should demonstrate how they change over time, drawing upon some form of experimental manipulation. Please see the attached figure for a summary of key parameters of relevance to testing hypotheses about ecological trade-offs in cancer.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fevo.2021.666262/full#supplementary-material

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