





# Insights From the Ecology of Information to Cancer Control

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## Abstract

Uniquely in nature, living systems must acquire, store, and act upon information. The survival and replicative fate of each normal cell in a multicellular organism is determined solely by information obtained from its surrounding tissue. In contrast, cancer cells as single-cell eukaryotes live in a disrupted, heterogeneous environment with opportunities and hazards. Thus, cancer cells, unlike normal somatic cells, must constantly obtain information from their environment to ensure survival and proliferation. In this study, we build upon a simple mathematical modeling framework developed to predict (1) how information promotes population persistence in a highly heterogeneous environment and (2) how disruption of information resulting from habitat fragmentation increases the probability of population extinction. Because (1) tumors grow in a highly heterogeneous microenvironment and (2) many cancer therapies fragment tumors into isolated, small cancer cell populations, we identify parallels between these 2 systems and develop ideas for cancer cure based on lessons gleaned from Anthropocene extinctions. In many Anthropocene extinctions, such as that of the North American heath hen (*Tympanuchus cupido cupido*), a large and widespread population was initially reduced and fragmented owing to overexploitation by humans (a “first strike”). After this, the small surviving populations are vulnerable to extinction from environmental or demographic stochastic disturbances (a “second strike”). Following this analogy, after a tumor is fragmented into small populations of isolated cancer cells by an initial therapy, additional treatment can be applied with the intent of extinction (cure). Disrupting a cancer cell’s ability to acquire and use information in a heterogeneous environment may be an important tactic for causing extinction following an effective initial therapy. Thus, information, from the scale of cells within tumors to that of species within ecosystems, can be used to identify vulnerabilities to extinction and opportunities for novel treatment strategies.

## Keywords

Anthropocene extinction, ecology of information, environmental heterogeneity, habitat fragmentation, integrins, cytoskeleton, stochasticity

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## Introduction

Uniquely in nature, living system must acquire, store, and act upon information. While biology tends to focus on information dynamics in the genome, survival, and proliferation of each organism requires continuous assessment of myriad types of cues and signals, which provide information from their environment to which they must respond physiologically and behaviorally.<sup>1-3</sup> A subdiscipline within behavioral ecology, the ecology of information,<sup>4,5</sup> explicitly considers information in an ecological context—how obtaining and processing

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information and producing phenotype adjustments to their local environment is vital to individual survival and population persistence—but also how obtaining and making use of information may be affected by the environment. Schmidt<sup>4</sup> developed an algebraic model that, in combination with an agent-based model, illustrates how spatial heterogeneity in habitat quality interacts with information to affect per capita reproductive success and population growth or decline. Specifically, habitat loss (eg, through destruction and fragmentation) decreases the ability of organisms to acquire and use information to enhance reproductive success. The reduction in breeding sites driven by habitat fragmentation causes declines in per capita reproductive success, which may result from information-mediated Allee effects, ultimately increasing vulnerability to population extinction. In this commentary, we argue that these results provide potential insights into novel strategies for controlling cancer within the context of evolutionary dynamics of Anthropocene extinctions.<sup>6</sup>

### Schmidt Model

Schmidt's<sup>4</sup> (2017) model considered a species living in a mosaic of 2 habitats. Habitat A is one in which the species thrives (net reproductive rate,  $R_0 > 0$ ) because, for example, it has abundant resources and few predators. Habitat B has net negative reproductive rate ( $R_0 < 0$ ). In our example, habitat B might have fewer resources and/or more predators. Thus, habitat A is termed a “source” habitat, with habitat B being a “sink.” The overall population growth rate ( $\lambda$ ) of the species is determined by the sum of the proportional use of the source and sink habitats, respectively, together with the habitat-specific  $R_0$ .

A second component of this model is that of information obtained and used by individuals or groups within the species. In a habitat that has high spatial diversity so that the density of resources or predators can be highly variable, information regarding the habitat has high value to individuals or groups. In other words, if there are patches within the habitat that are particularly resource-rich or have a high density of predators, optimal survival and proliferation requires individuals or groups (eg, herds) to have the ability to detect those patches and respond appropriately. This contrasts with a habitat that is relatively uniform over space and time in which the value of habitat information is low. In other words, uniformity reduces the value of information because individual organisms do not need to differentiate between good and poor habitats. Likewise, the value of information is higher for rare events or places because mass action will “find” what is common. To find what is rare through random sampling is not efficient.

The model identifies critical thresholds of information required for population persistence. A counterintuitive prediction of the model is that species persistence in habitats of low spatial heterogeneity requires a greater proportion of individuals to settle in habitat A (the source habitat), which requires a biased habitat selection. That is, for the species to persist when their source and sink habitats have low spatial heterogeneity,

individuals must maintain environmental information that is less valuable per capita than the same information in a high heterogeneity environment. Thus, the resource cost of maintaining information that has little or no fitness value must be compensated by increasing the number of individuals within the higher resource habitat.

The expectation that greater resource debt is incurred from maintenance of unused information when a population persists in low spatial heterogeneity was tested explicitly with an agent-based model. In this model, agents use the informed habitat selection rule of win-stay, lose-switch (WSLS). If proliferation in year 1 is successful, the agent returns to that site in the subsequent year. If unsuccessful, the agent switches to the second site.<sup>7</sup> Agents combine WSLS (information) with prospecting for conspecific breeding success or failure within a spatially complex and heterogeneous environment. This prospecting for conspecific breeding success allows an agent to become more informed about the distribution of quality of the available breeding sites within the overall environment. Schmidt<sup>4</sup> then used the agent-based model to examine how habitat loss, spatial heterogeneity in habitat quality, and increased information resulting from conspecific prospecting impact population persistence. Habitat loss resulted in a reduction in per capita reproductive success, consistent with a behavior-mediated Allee effect.<sup>8</sup> Together, Schmidt<sup>4</sup> models suggest that environmental disturbances, like human-driven habitat fragmentation and loss, may contribute to population declines and extinctions via the disruption in the ability of individuals to gather and effectively implement environmental information to make more informed decisions about where to breed. Holt<sup>9</sup> and Lüring and Scheffer<sup>10</sup> reached similar conclusions.

### Information at the Scale of Cells and Tissues: Implications for Cancer Ecology

Like organisms themselves, cells making up multicellular organisms live in a heterogeneous environment with opportunities and hazards.<sup>11–14</sup> Cells possess multiple adaptations for sensing properties of the microenvironment—including physical properties like oxygen concentration and pH, as well as macromolecular composition (eg, collagen, elastin) of the extracellular matrix (ECM) and the cellular components of the environment including fibroblasts, endothelial cells, and inflammatory cells (ECM).<sup>15,16</sup> In addition, the environment contains multiple diffusible elements (oxygen, cytokines, growth factors), which can be delivered by blood (oxygen<sup>17</sup>), produced by cellular components of the ECM (eg, cytokines<sup>18</sup>), or by the tumor cells themselves (cytokines and autocrine growth factors<sup>19</sup>).

The cell membrane of each cancer cell is its interface with its surrounding microenvironment and the site where information from the environment is received, processed, and transmitted internally to internal organelles.<sup>20</sup> The cell membrane thus provides the key target for therapeutic information disruption.

We see parallels between Schmidt's<sup>4</sup> model of the effects of environmental disturbance on the role of information in extinction vulnerability and a proposed strategy to eradicate cancer based on Anthropocene extinctions.<sup>6,21</sup> The essence of this strategy is to apply a sequence of powerful and effective chemotherapies in quick succession. Better yet, this strategy can be extended to targeted agents and immunotherapies, as well as combinations of both with chemotherapy. Indeed, such combinatorial approaches are actively tested in clinic trials for specific type of cancers and showing some promising results.<sup>22,23</sup> In many Anthropocene extinctions, human persecution (eg, overhunting) drove a species to small and fragmented subpopulations, and a later environmental or demographic perturbation subsequently eliminated the last remaining vestiges of the species, resulting in global extinction.<sup>6</sup> By analogy, the "First Strike–Second Strike" strategy would take advantage of the reduction in size and diversity of dispersed cancer populations following an initial application of a cancer drug at maximum tolerated dose by a rapid application of a "second strike" application of an alternative cancer drug that works with a different mode of action. Schmidt's<sup>4</sup> model suggests that 1-second tactic might come in the form of chemotherapies that preclude surviving cancer cells from gaining information about their surrounding microenvironment. In the following, we propose various methods by which treatment may disrupt information flow to cancer cells from the surrounding cells and the microenvironment.

An interesting component of the implicit "bargain" between individual cells and the multicellular organism is that, in exchange for orderly cell division and behavior, individual cells will continuously be provided a stable and optimal environment for survival and (when necessary) proliferation. In less anthropomorphic terms, the cells in a multicellular organism do not need to expend energy to forage for substrate and can, therefore, use more of their energy budget to perform functions necessary for survival and proliferation of their multicellular host.

In contrast, cancer cells have a self-defined fitness function<sup>24</sup> so that survival and proliferation of each cell is determined by its ability to successfully forage for resources in competition with the foraging strategies of nearby cells in the population.

In this setting, cancer cell fitness will be strongly affected by its ability to gain information from the environment regarding opportunities to obtain substrate and avoid "predators" in the form of host immune cells. Here, the sensing mechanisms are limited to those encoded in the genome. However, memory can persist in the form of epigenetic changes in which DNA methylation and histone acetylation can increase or decrease their transcription in ways that allow a cell to respond quickly to the dynamic microenvironment of the tumor.<sup>25,26</sup>

### *Environmental Heterogeneity in Cancers*

The microenvironmental stability characteristic of multicellular organisms in physiological conditions is largely dependent

on the function of a well-organized vascular tree. Blood must not only flow to each region of normal tissue, it must do so without fluctuation. The architecture of arteries and veins allows continuous, coordinated flow of blood, and therefore, flow of information (metabolites). Cancer cells can act as loosely organized groups and promote ingrowth of blood vessels through production and excretion of vascular endothelial growth factor (VEGF) and other angiogenic molecules. However, these cells do not benefit (and may be negatively affected) by any further vascular modifications to allow vascular maturation that insures continuous downstream flow to other regions. As a result, blood flow in cancers, with a few notable exceptions, is typically unstable and chaotic, resulting in marked variations over time and space. In some regions of the tumor, for example, blood flow can vary from normal, to stasis, and reversed on a time scale that can vary from days to seconds.<sup>25,26</sup>

A unique environment for cancer cells is found at the tumor edge where cancer cells invade into the adjacent normal tissue. The cancer cells are typically scattered in small pockets or finger-like projections that are surrounded by normal cells. The vascular structure and blood flow, at least initially, remain normal so that the microenvironmental concentrations of substrate and metabolites remain relatively uniform. However, the normal tissue can mount vigorous defenses including the predator-like elements of the immune system as well as fibroblasts that can produce collagen to encapsulate the tumor and suppress proliferation. The dynamic landscape resulting from the interactions of such small populations of cancer cells with the surrounding normal cells may be highly heterogeneous in both space and time, much like the variation typical of landscapes in nature.

### *Habitats in Cancer*

Here, we divide cancer habitats into 4 distinct patterns:

1. Habitat A is relatively well-perfused so that it receives a steady blood flow (though often less than normal tissue) so the microenvironment is relatively uniform. Some host response (eg, infiltrating immune cells) elements exist but in small populations compared to the cancer cells.
2. Habitat B receives no blood flow. These regions, typically described as "necrotic," are uniform with only small populations of tumor cells scattered in a "sea" of fluid produced by dead cancer cells.
3. Habitat C contains a highly disordered vascular network resulting in stochastic temporal variations in blood flow so that environmental conditions can vary dramatically over time (eg, transitioning from normoxia to anoxia over a period of seconds). However, normal host immune cells cannot survive in such conditions so that the predatory risk is diminished.
4. Habitat D occupies the tumor–host interface—in ecological terms, it is an ecotone. Microenvironmental conditions are relatively stable, but the cancer cells are less

abundant than normal cells and are vulnerable to vigorous host responses including potentially lethal attacks from the immune system.

In the context of cancer and the 4 habitats described above, we propose Schmidt<sup>4</sup> model of environmental disturbance can be restated as cancer habitats in flux. That is, habitat A is relatively homogeneous with sufficient resources over space and time. Habitat B, the result of an extreme disturbance, is also spatially and temporally homogeneous but characterized by poor-resource availability. In contrast, habitat C is highly temporally dynamic with constantly changing blood flow. In turn, this can produce transient spatial variations as the micro-environmental response to sudden loss of blood flow can vary with differences in local cell density or perivascular diffusion dynamics. In other words, the populations of cancer cells subject to fluctuating environments may similarly alternate between evolutionary states in which they are far above or far below their carrying capacity. Finally, habitat D is undergoing dynamically transient spatial heterogeneity as cancer cells infiltrate into normal regions producing new environmental patches as well as complementary infiltration of immune cells seeking to eradicate the invaders.

### Cancer Cell Information

Normal cells must receive and process information from the local tissue to determine its spatial position and differentiated function. A normal cell's survival, proliferation, and death are completely governed by a circuitry designed to upkeep homeostasis within physiologically normal tissue. The reaction norm of normal cells is tightly controlled on a tissue level in a way that response to microenvironmental cues is within the fitness function of a tissue/whole organism.<sup>27</sup> In contrast, the fate of cancer cells is determined by the interactions of their phenotypic properties with the local microenvironment. Here, the cells must specifically not receive and/or process local tissue instructions. Instead, cancer cells must develop methods to accurately obtain information from their environment regarding both opportunities and threats. Furthermore, they must develop the ability to act upon that information so that they can, for example, move toward supplies of substrate and away from immune cells. In other words, cancer cells must deploy information receivers like those found in single-cell eukaryotes. Indeed, one can consider a cancer cell as a protist from an evolutionary perspective.<sup>28,29</sup>

Much of this new information state might be characterized as the equivalent of "fear responses" found in nature. For example, a cancer cell must be capable of responding rapidly to changes in oxygen in its environment and rapidly deploy the molecular machinery to metabolize glucose and other substrate molecules without oxygen. This is observed as "deregulated cellular energetics"—one of the "hallmarks" of cancer—and perhaps most evident in the Warburg effect in which cancer cells often maintain constant fermentative, glycolytic metabolism of glucose, even in physiologically normal oxygen

concentrations. This has been shown to be a "bet-hedging" strategy to maintain survival in a stochastically fluctuating environment.<sup>30</sup>

Similarly, cancer cells typically deploy receptors that detect interferon and other cytokines that signal proximity of immune predators, thus serving as an early warning system so that they can either move away or deploy surface molecules that prevent recognition and/or destruction by the immune cells.

### Schmidt Models in Cancer Biology

*Intratumoral habitats.* Consider adjacent tumor regions, one is habitat A and the other habitat C. This mimics the source and sink habitats in the Schmidt<sup>4</sup> model but with unequal heterogeneity because of the stochastic temporal changes in habitat C. Habitat A is a site in which cancer cells readily proliferate. Habitat C allows only limited proliferation, but conditions there strongly favor cells with a high level of accurate information about the extremely heterogeneous environment. Thus, the sink habitat will strongly select for cells with the ability to obtain maximal information regarding the environment.

Thus, cells in the sink habitat may be subject to selective pressure for more proficient or accurate habitat selection, thus evolving to diverge from the original "species." These individual cells evolve an increased competitive ability to obtain information and exploit opportunities within the habitat. Thus, for example, cells that can rapidly detect small changes in oxygen concentration may have an advantage, particularly if they can also rapidly deploy adaptive metabolic machinery. Cells that permanently upregulate energy metabolism derived from glycolysis will sacrifice efficiency in high oxygen concentrations for survival in low concentrations if the fluctuations are very rapid. Similarly, cells that detect small changes in oxygen concentration may deploy behavioral adaptations by rapidly moving up concentration gradients to invade small patches in which oxygen concentration may be slightly higher. In particular, the most obvious such patch is within the blood vessels. That is, even if flow has stopped, the oxygen within the vessel is not subject to cellular metabolism and will remain relatively constant. Cells that invasively follow oxygen concentration gradients will, therefore, often enter blood vessels. However, when flow is reestablished, these cells will be carried into the systemic circulation. Thus, temporal variations in blood flow will tend to select for high information cells (with increased levels of phenotypic plasticity and invasiveness) and that promote dynamics that drive them to invade the systemic circulation system, ultimately leading to increased opportunity for metastases formation.

*The tumor–host interface.* Expansion of cancer populations often requires invasion of adjacent tissue by "pioneering" cancer cells. Singly or in small groups, these cells invade into normal tissue at the tumor edge. The ecological forces that drive this invasion are not clear but could be similar to the above dynamics in which some cancer cells move along concentration gradients toward regions of normal cells with well-developed

vasculature. While angiogenesis due to cancer cell signaling (eg, VEGF production and excretion) is extensively studied, it is also clear that some intratumoral blood vessels are “acquired” from adjacent normal tissue.<sup>31</sup>

In the context of the Schmidt model, here we have a patch within the cancer in which the malignant cell population is near some carrying capacity with only limited opportunity for additional proliferation. However, in the adjacent normal tissue, the cancer population is quite small so that there is an opportunity for rapid growth. In general, the relatively organized normal tissue, even though it is being invaded by cancer cells, will maintain a more homogeneous environment than that of the adjacent tumor edge.

### *Information Disruption as a Cancer Therapy*

Having established that the sorts of natural landscape habitat heterogeneity modeled by Schmidt may have analogs within the contexts of cancer populations and their microenvironment (habitats), we next propose that information may be a target for therapy. In the Schmidt model, information informs habitat selection in a way that allows a population to persist in the face of heterogeneity in reproductive success. Similarly, information may be vital for cancer cell persistence in the presence of the sorts of habitat heterogeneity presented above. Moreover, in the Schmidt model, habitat degradation disrupts the ability of individuals to use information or to gather new information to make informed habitat selection, making the population susceptible to net reproductive failure and eventual extinction. We argue that cancer treatment may similarly disrupt information gathering capabilities of cancer cells, and this insight may guide strategies to deploy cancer therapies that maximize their effectiveness and improve patient outcomes. Below we discuss 2 potentially exciting mechanisms for disrupting information flow to cancer cells. These are still in early stages of development, and we believe other mechanisms will be developed in the near future.

**Nutrient-sensing mechanisms in cancer cells.** Like all cells, cancer cells possess adaptations to allow them to sense the presence or absence of nutrients within the surrounding microenvironment.<sup>32,33</sup> Several recent publications suggest that targeting nutrient-sensing pathways may be useful in certain cancers. For instance, Albrecht et al<sup>34</sup> reported that administration of low-dose methotrexate interferes with Wnt signaling, which regulates endocytosis of extracellular proteins and lysosome activity. Methotrexate, along with changes in diet that reduce methionine intake, may disrupt the activity of the nutrient-sensing metabolite S-adenosylmethionine, a critical component of the Wnt signaling. Selwan et al<sup>35</sup> discuss tactics to interfere with a cancer cell’s ability to acquire nutrients, via membrane transporters, receptor-mediated (signal-dependent) uptake, micropinocytosis, and autophagy. The relative use of these nutrient acquisition strategies is dependent upon information processing, and Selwan et al<sup>35</sup> discuss therapies that antagonize or block those mechanisms. Further development of therapies

that disrupt the ability of nutrient sensing in cancer cells should hold great promise for cancer control.<sup>33</sup>

**Integrin–cytoskeleton interactions.** Integrins are a family of molecules involved in cell adhesion, communication, multidirectional signaling, and motility.<sup>36</sup> Integrins are intimately involved in cancer progression and metastasis.<sup>37</sup> Because they play a paramount role in communicating information between the ECM and the cell,<sup>38</sup> integrins provide a key target for information disruption.<sup>37</sup> A large number of drugs have been tested in clinical trials, and several have been approved for use in the clinic.<sup>38</sup> Several integrin receptors that are upregulated in cancer cells may be conjugated to drugs for delivery to tumors.<sup>39</sup> A recent review of clinical trials testing therapies targeting integrins reported a general failure to deliver successful results. However, we note that the lack of success may reflect treatment protocols that do not fully exploit the information role of integrins. For example, the information gathered by integrins might have the greatest fitness benefit when the environment is disrupted by, for example, angiogenesis inhibitors and chemotherapy or by the introduction of predators in the form of immune cells.

In a recent review, Alday-Parejo et al<sup>40</sup> concluded that integrins remain a viable target for cancer therapy but call for “agents with better pharmacological properties, alternative models for their preclinical evaluation, and innovative combination strategies for clinical testing (eg, together with immunology agents) are needed.” In the context of this article, targeting integrins may prove more effective when placed in the context of the “First Strike–Second Strike” therapeutic strategy.

Information is transmitted from the ECM to cell organelles along microfilaments,<sup>1,41</sup> which are largely composed of actin polymers. This suggests another potential target for information disruption could involve the actin components of the cytoskeleton. Two recent papers report cancer cell-specific mechanisms to disrupt the actin cytoskeleton. One targets specific isoforms of tropomyosin core components of actin filaments that are selectively upregulated in cancers.<sup>42</sup> This mechanism is an anti-tropomyosin compound that disables the cytoskeleton causing reduced motility and viability.<sup>42</sup> The second approach uses a natural compound, chondramide, produced by the myxobacterium, *Chondromyces crocatus*, which binds to and inhibits actin filament dynamics.<sup>43,44</sup> In vitro and in vivo studies indicate the potential for this compound to slow tumor progression,<sup>43</sup> inhibit metastasis,<sup>44</sup> and promote tumor cell death.<sup>43</sup> Both of these studies suggest that this class of drugs may provide other actin-targeting agents effective in cancer therapy.

### *Increasing Information Demand as Therapy*

While the above strategies focus on disrupting information dynamics, we note that treatments can also focus on further disrupting the cancer environment, thus increasing information demand and the demand for resources to support information

acquisition and processing. That is, like the state-dependent strategies<sup>45</sup> described in parasites, the cancer must always respond to changes in the host environment.

One treatment strategy will disrupt the intratumoral blood flow<sup>46</sup> using angiogenic inhibitors.<sup>47</sup> Interestingly, initial application of antiangiogenic agents frequently results in “normalization”<sup>48</sup> of blood flow with generally increased and more uniform blood flow. However, this is a transient effect, and after a few days, blood flow is substantially but heterogeneously diminished throughout the tumor volume.<sup>49</sup> Both the end-stage increase in heterogeneity and the fluctuations<sup>50</sup> that precede it may require increased information and associated resources. When combined with other therapies that increase resource demand for adaptive cellular measures, cancer cells may be unable to retain viability. Indeed, these synergistic effects have been observed clinically.<sup>51,52</sup> Finally, the generally diminished blood flow may increase isolation of small colonies of cancer cells so that their ability to provide mutual support is diminished. For example, when the cancer population is reasonably continuous, deaths in one region can be compensated by migration of tumors from adjacent sites. However, in a fragmented environment in which the cancer population exists in isolated islands separated by necrosis and fibrosis, this mutual support may be lost so that each small population is increasingly vulnerable to extinction from stochastic demographic and environmental fluctuations.

A second approach to increasing environmental heterogeneity is addition of a “predator”<sup>53</sup> in the form of immunotherapy. Because delivery and function of immune cells is influenced, but not fully dependent on regional blood flow,<sup>54</sup> this new selection force will also be subject to temporal and spatial fluctuations so that predator avoidance may impose an additional need for which local resources are not available.

## Conclusions

We have drawn upon the concept of the ecology of information to suggest potential avenues for new strategies to target information needs of cancer cells. Cancer cells must constantly obtain information from their environment to ensure survival and proliferation. Building upon an ecological modeling framework that highlights the importance of information for population persistence in the face of environmental heterogeneity, we present research that suggests mechanisms to target the sensory abilities of cancer cells to acquire information about the tumor microenvironment or their ability to transmit gained information to cell organelles via the cytoskeleton. Disrupting a cancer cell’s ability to acquire and use information in a heterogeneous environment may be an important tactic for causing extinction following an effective initial therapy.

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