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Of criminals and cancer: The importance of social bonds and innate morality on cellular societies

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ABSTRACT

The current dogma in cancer biology contends that cancer is an identity problem: mutations in a cell's DNA cause it to "go rogue" and proliferate out of control. However, this largely ignores the role of cell-cell interaction and fails to explain phenomena such as cancer reversion, the existence of cancers without mutations, and foreign-body carcinogenesis. In this proof-of-concept paper, we draw on criminology to propose that cancer may alternatively be conceptualized as a relational problem: Although a cell's genetics is essential, the influence of its interaction with other cells is equally important in determining its phenotype. We create a simple agent-based network model of interactions among normal and cancer cells to demonstrate this idea. We find that both high mutation rates and low levels of connectivity among cells can promote oncogenesis. Viewing cancer as a breakdown in communication networks among cells in a tissue complements the gene-centric paradigm nicely and provides a novel perspective for understanding and treating cancer.

1. Introduction

1.1. The somatic mutation theory

Cancer is a leading cause of death worldwide, taking the lives of over 10 million people per year (Pienta et al., 2020; Siegel et al., 2020). Yet despite hundreds of billions of dollars being spent every year on research for decades, an understanding of what cancer is evades us. In the 1970s, molecular biology began to address the issue of cancer etiology (Bister, 2015) with the discovery of (proto-)oncogenes such as Src, MYC, and EGFR that explicitly linked genetic mutations with cancer progression (Bister and Duesberg, 1979; Duesberg et al., 1977; Duesberg and Vogt, 1970; Stehelin et al., 1976; Wang et al., 1978). These findings led to the somatic mutation theory (SMT), an explanatory framework for understanding cancer initiation and progression. The SMT proposes that mutations produce rogue cancer cells that proliferate uncontrollably and wreak havoc on their host (Vaux, 2011).

The ensuing decades brought with them a plethora of breakthroughs in cancer research, from the discovery of tumor suppressor genes to the role of stem cells and epigenetics (Hanahan and Weinberg, 2011). Along with these discoveries came a proliferation of perspectives of cancer etiology: the clonal genetic model, the stochastic model, the multigenic multiphasic model, the epigenetic progenitor model, the hierarchical model, and the evolutionary model (see (Bertolaso, 2016) for a more detailed discussion of these paradigms). Although these frameworks differ on what constitutes a cancer-promoting mutation, how many and what kind of mutations cancer requires, whether mutations in specifically stem cells drive cancer, or their implications for therapy regimens, they all fundamentally agree with the SMT that cancer is a product of the clonal expansion of mutated cells. As a result, the SMT has been regularly modified to take into account new findings, but still remains the dominant (and arguably only) paradigm used in cancer research and clinical practice today.

1.2. Failings of the SMT

However, there are many well-documented phenomena that the cell-centric SMT cannot explain. For instance, consider cancer reversion: the adoption of a normal phenotype by cancer cells (Kenny and Bissell, 2003).

The first clinical observation of spontaneous cancer regression was made by Swiss pathologist Max Askanazy in 1907. Askanazy noticed

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spontaneous differentiation of ovarian teratomas in an embryonic microenvironment into normal cells (Askanazy, 1907). More thorough examination of this process was possible after the advent of the 129/SvJ mouse model of teratoma by Stevens and Little in 1954 (Pensotti et al., 2023; Pierce et al., 1959; Pierce and Verney, 1961; Stevens and Little, 1954). Notably, studies by Brinster (Brinster, 1974) and, more extensively, by Mintz and Illmensee (Mintz and Illmensee, 1975) showed that embryonal carcinoma cells that were injected into blastocysts and implanted into 129/SvJ mice contributed to the development of normal tissues and organs, supporting Askanazy's observation of the normalizing effect of the embryonic microenvironment.

Since these early experiments, several studies across different cancers and organisms have confirmed the finding that malignant cells can be reprogrammed to acquire a healthy phenotype that is subject to controlled proliferation and contributes to tissue-specific function (see (Cho et al., 2017; Pensotti et al., 2023) for detailed discussions). As outlined by Pensotti et al., these studies display cancer reversion in four ways: 1) spontaneous in vivo cancer regressions, 2) in vivo reversion of cancer cells placed in normal tissues, 3) in vivo reversion of cancer cells injected into blastocysts, and 4) in vitro reversion of cancer cells due to exposure to microenvironmental factors. What is clear from these studies is that, unlike the SMT suggests, a cancerous phenotype is not purely determined by genetics–tissue architecture and microenvironmental factors play an equally important role in influencing a cancer cell's phenotype and, at times, override underlying genetics.

This argument is bolstered by the existence of cancers without any cancer-associated mutations (Baker, 2014), an observation noted in several massive sequencing studies (Greenman et al., 2007; Imielinski et al., 2012; Kan et al., 2010; Lawrence et al., 2013). Apart from a few notable exceptions in ependymoma research (Mack et al., 2014; Michealraj et al., 2020), most articles ignore or only briefly mention the existence of cancers without mutations. The SMT, which inherently assumes that genetic mutations cause cancer simply cannot account for these observations. Another related observation is that of foreign body carcinogenesis, wherein inert substances inserted into animal hosts modify tissue architecture and cause local tumors (Bischoff and Bryson, 1964; Soto and Sonnenschein, 2011). Detailed studies on foreign body carcinogenesis show that the shape, not the composition, of the implanted material determines tumorigenesis (Karp et al., 1973; Turner, 1941). Namely, Karp et al. found that pore sizes smaller than 0.22 μm greatly promoted tumorigenesis, whereas pore sizes larger than 0.45 μm, tumor incidence was 0 (Karp et al., 1973). From this, the authors hypothesized that tumors arose from disruption of cellular communication networks. Since these inert substances have no genotoxic effects and, ostensibly, the disruption in tissue architecture as a result of implantation did not affect the cells' DNA, it is hard to explain these observations with the SMT.

Fundamentally, the SMT cannot explain phenomena such as cancer reversion, cancers with no mutations, and foreign-body carcinogenesis on epistemological grounds. The reductionist approach of the SMT inherently adopts a bottom-up view in which information flows from DNA to the phenotype, thereby deducing that a change in cellular phenotype is only possible with a change in genes (or gene expression). This paradigm has led cancer researchers for decades to attempt to understand oncogenesis at the genetic level. Indeed, perusal of the modern cancer literature will reveal a plethora of studies with a singular focus on elucidating mechanistic pathways at the cellular level for a wide range of oncogenic processes, from initiation to resistance to metastasis. However, the failings of the SMT call for a new perspective on cancer.

1.3. A new approach: Cancer, criminology, and corruption

Inspired by our prior work on cancer behavioral ecology (Bukkuri and Adler, 2021), we view cancer as a corruption of communication networks within and among agents in a society (Bukkuri and Adler, 2023). Although this definition extends the scope of cancer beyond the biomedical realm, we focus on the traditional formulation of cancer here (e.g., agents are cells and society is a tissue). Viewing cancer as a corruption of signaling integrity does not directly contradict the SMT. Indeed, we acknowledge the critical role genes play in influencing the cancer phenotype. However, unlike SMT, which attributes cancer entirely to genetics, or tissue organizational field theory (Soto and Sonnenschein, 2011), which attributes cancer entirely to disruption at the tissue level, we dispose of the mereological framework and adopt a synchronic reflexive causation one, presuming that a complex interplay between the microscopic and macroscopic levels gives rise to cancer. It is this interplay that our research program seeks to understand.

To do this, we draw on studies of criminology and corruption. Criminology, with its focus on how deviant behavior arises is well-suited to help us understand how individual cells adopt a cancerous phenotype. In addition to examining factors within the microscopic level (e.g., innate morality or genetics), it assesses the impact of the macroscopic level (e.g., culture and social networks) on individuals. Corruption, with its focus on the systemic breakdown of broader networks, may help us understand how communication networks in a tissue are disrupted. In addition to examining factors within the macroscopic level (e.g., ecological factors or wounding), it assesses the impact of the microscopic level (e.g., deviant actors or cancer cells) on the societal network. Combining these perspectives will allow us to grasp the broader picture: how deviant actors arise and interact with external factors to promote the collapse of communication networks in their society, thereby facilitating their expansion. Intuitively, cancer reversion can be explained under this framework by the establishment of social bonds and communication networks, like how developing societies often have high levels of corruption until accountability measures arise. Cancers without mutations can be thought of as criminals without biological predisposition. Foreign body carcinogenesis can be viewed as the result of a disruption in signaling integrity, which prevents effective social control.

In this conceptual paper, we focus on cancer criminology and attempt to understand how deviant behavior manifests in cells due to their genetics and interactions with neighbors in their communication network. In criminology, there are several theories that suggest how deviant behavior arises, most of which focus on social factors. Of relevance to cancer is social control theory (Symons, 1951; Toby, 2017; Triplett et al., 2003), which suggests that people's social connections discourage them from engaging in deviant behavior. Thus, to prevent or reform criminal activity, the formation of social bonds is critical. However, many criminals exist from high socioeconomic status with strong social bonds to non-deviant actors. These findings are explained by the social push hypothesis (Raine, 2002), which argues that if no social factors exist that push an individual towards deviant behavior, then biological risk factors are more likely to explain the behavior. Indeed, the social push hypothesis is one aspect of a broader literature that investigates the biological basis to deviant behavior and crime. Much work over the recent decades has gone into connecting aspects of genetics (Beaver et al., 2007; Boutwell et al., 2014; Kolla and Bortolato, 2020; Tiihonen et al., 2015), physiology (Bertoldi et al., 2023; Latvala et al., 2015; Raine, 1990), and anatomy and brain factors (Brower and Price, 2001; Meijers et al., 2017; Pardini et al., 2014; Raine et al., 2000; Yang and Raine, 2009) to a predisposition to crime, with convincing results (Ling et al., 2019). Despite differences in the relative focus on biological or social factors, these theories acknowledge that social factors combine and interact with biology to shape deviant behavior. In cancer, the focus is currently entirely on the biological basis, with little to no consideration of social factors. We propose here that both social and biological factors are critical in influencing a cell's phenotype.

To examine the implications of our notion of cancer criminology, we develop an agent-based network model, wherein each node is occupied by cells that are normal or cancerous (to varying degrees). We develop rules for mutation and interaction that can change the phenotype of the cells and run simulations to examine how the frequency of normal and cancerous phenotypes in the network change over time. We investigate

the role of mutation rate (changes in innate morality) and network density (social bonds) on cancer expansion. These simulations demonstrate the importance of considering cell-cell interactions, in addition to genetics, in determining a cell's phenotype.

2. Agent-based network model

To create our agent-based network model, we first create the network. We generate a random simple graph with 1000 nodes and predetermined average node degree (default is 4). We initialize the population with 90 % normal cells and 10 % cancer cells (endowed with a deviance trait value of $\nu = 0$).

We now create the rules of the agent-based model (Fig. 1). At each time step, each agent can mutate with some probability (default is 0.1) or interact with a neighboring cell. If a mutation occurs and the agent is normal, it becomes cancerous. If a mutation occurs and the agent is cancerous, we let $\nu := \min(\nu + 0.3,1)$.

If a mutation does not occur, an interaction with a neighboring cell is possible. A random cell in the set of neighboring agents is chosen for a potential interaction. If both agents are normal, we do nothing and move to the next agent. If both agents are cancerous, they interact with probability 0.9. If an interaction occurs, the less cancerous cell becomes more cancerous, adopting the average deviance trait value of the two agents. If an interaction does not occur, we do nothing and move onto the next agent. If one agent is normal and the other is cancerous, four possibilities exist: no interaction, cancer cell is killed and replaced by a normal cell, cancer cell becomes less cancerous, or the normal agent becomes cancerous. Which event occurs depends on the trait value of the cancer cell, ν. The probability of interaction is given by $\exp(-2\nu) - 0.1$, i.e., the more deviant the cancer cell is, the less likely it is to interact with a normal neighbor. The probability that the cancer cell is killed is given by $1.05 - \exp(-1.2\nu)$, i.e., the more deviant a cancer cell is, the more likely it is identified as such and eliminated by its neighbor (e.g., in an immune-mediated fashion). The probability that a cancer cell converts its normal neighbor into a cancer cell is given by $.2\tanh(\nu)$, i.e., the more deviant a cell is, the more likely it can convert its neighbor into a cancer cell (e.g., via exosomes). If none of these events occur, the cancer cell will become less cancerous ($\nu := \nu/2$). One time step in the simulation is completed once all agents have gone through this process. We simulate the agent-based model for 1000 time steps or until either normal or cancer cells take over the population. The rules proposed in this network model can be viewed through the lens of Henry Heng's innovative two-phased model of cancer evolution (Heng and Heng, 2021a; Heng and Heng, 2021b). This model posits that cancer evolution proceeds via two phases: an initial, punctuated macroevolutionary phase followed by a gradual microevolutionary phase. Briefly, the former involves altered karyotype coding prompted by stress-induced genome chaos and the subsequent selection of survivable genomes by punctuated macroevolution. The latter describes further gene-level adaptations via microevolution that increase the cancer cell's fitness.

The model presented here similarly proposes that cancer cells do not merely engage in different cellular behavior than normal cells, but represent the formation of an entirely new system with different forms of communication. In other words, rather than simply adopting different evolutionary strategies than normal cells, cancer cells are characterized by an entirely different evolutionary strategy set and fitness function. Once the macroevolutionary jump has been made from normal to cancer cells, our model allows them to adopt additional microevolutionary modifications via their deviance trait value. In addition, note that we do not allow for reversible evolution, i.e., cancer cells cannot revert their genome to become a normal cell. Thus, methods of control involve either killing cancer cells directly or by reducing their deviance and cancerous properties (note however, that their evolutionarily-feasible strategy set still encapsulates properties of the most deviant and malignant cancers).

It is worth recognizing the simplifying assumption we have made that population size is constant, set here to 1000 cells. In reality, the density of cells is dynamically changing and depends on a variety of factors, including tissue physiology and mechanical properties, environmental conditions such as aging and wounding, and cellular communication. In a similar vein, to keep our focus on cancer criminology, we have kept the network topology static. In reality, cells may interact with different groups of cells across time, interactions that may be influenced by stochastic or migratory effects or corruptive processes induced by cancer cells that disrupt communication networks in the tissue.

3. Results

We simulate our agent-based network model to probe how innate morality (mutation rate) and social bonds (network density) influence cancer expansion. To do this, we consider four cases: low mutation rate (probability of mutation is 0.05), high mutation rate (probability of mutation is 0.15), weak bonds (average of two neighbors), and strong bonds (average of six neighbors).

First, we consider the role of mutation rate (Fig. 2). As expected, we find that low mutation rates prevent cancer cells from expanding in the

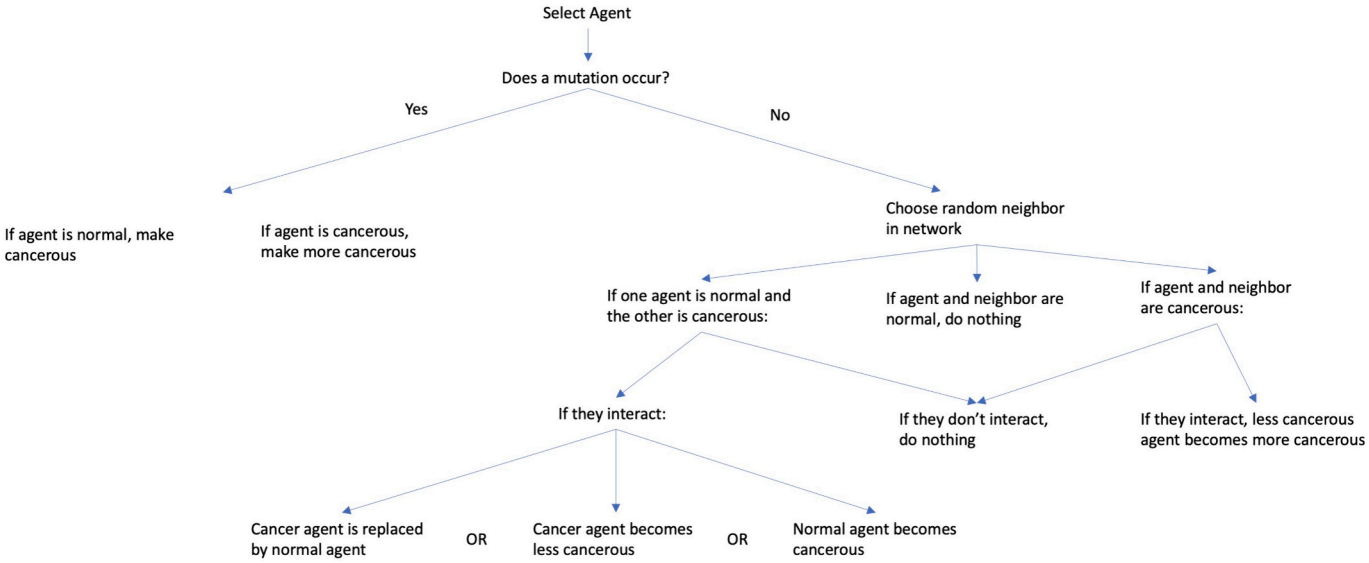

Fig. 1. Flowchart of ABM rules.

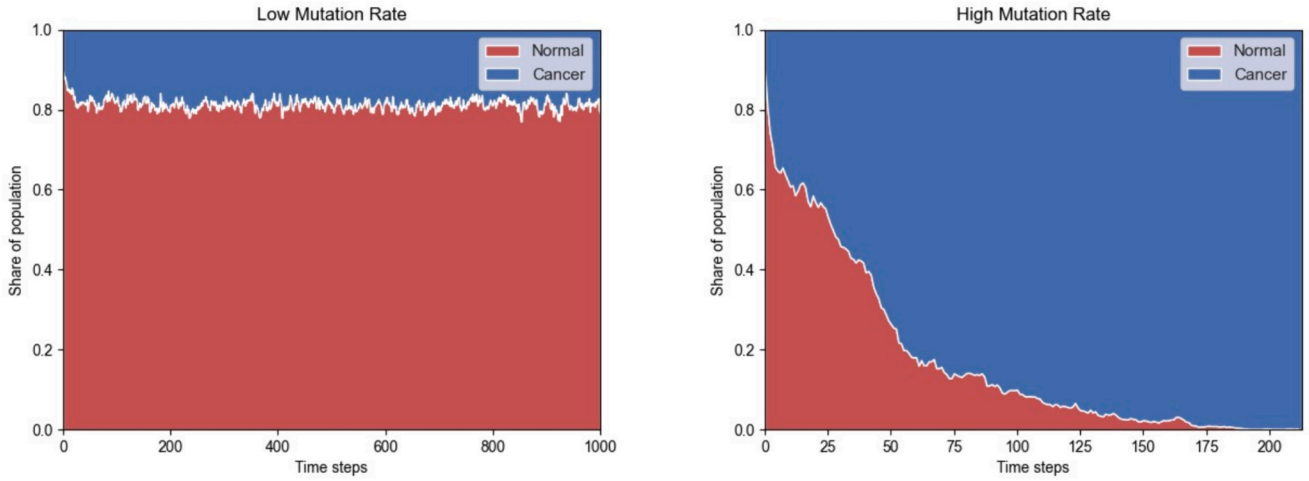

Fig. 2. Effects of mutation on cancer expansion. Red and blue regions represent the normal and cancerous shares of the population, respectively. Low mutation rates constrain cancer expansion, whereas high mutation rates allow cancerous cells to take over the population.

population. Since most of a cancer cell's neighbors will be normal cells and cancer cells will not mutate often to become more cancerous, they are likely to interact with their normal neighbors, typically resulting in cell death and replacement by a normal cell or reversion to a less deviant state. When the mutation rate is increased, cancer cells are more likely to be surrounded by other cancer cells and are more likely to mutate and become more cancerous. This leads to a higher survival rate, higher levels of deviance, and a higher conversion rate of normal cells to cancer cells. Eventually, this allows them to take over the population.

Next, we consider the impact of social bonds (Fig. 3). When social bonds are strong, i.e., network density is high (average node degree set to 6), cancer cells are surrounded by more (primarily normal) neighbors. Although we do not allow the number of neighbors to influence the probability of interaction, this increases the probability of interacting with normal cells rather than other cancer cells, and thereby constrains their expansion. When the number of neighbors is decreased (average node degree set to 2), rare mutations are less likely to impact the phenotype of their neighbors. In other words, the strength of social bonds provides a buffer against neighbor-mediated deviance.

To see if these trends hold for a wide range of mutation rates and network densities, we simulate the model for a range of mutation rates (0 to 0.2) and average node degrees (0 to 8). Fig. 4 summarizes the result of 2560 total runs of the model. As expected, higher mutation rates and sparser networks promote cancer expansion more generally. This is in accordance with our expectations from criminology theory: both biological and social factors are critical in influencing deviant behavior outcomes.

4. Conclusion

Cancer has traditionally be seen as a disease of the genes, wherein mutations in a cell's DNA induce a phenotype of "uncontrolled proliferation." However, this paradigm fails to consider the impact of cell-cell communication on phenotypic manifestation, a view that is analogous to ascribing all deviant behavior to underlying biological factors. We instead suggest that cancer should be viewed as a corruption of signaling integrity in a tissue that results from the interplay between deviant agents within the tissue (commonly referred to as cancer cells) and external factors. In this conceptual paper, we focused on the former aspect of cancer criminology and asked the question: How does deviant behavior arise? We developed an agent-based network model to examine the implications of our cancer criminology theory: that both innate morality (mutation rate) and social bonds (tissue network density) play a role in oncogenesis. We showed that a both high mutation rates and low social bonds promote cancer expansion, in line with expectations from the criminology literature.

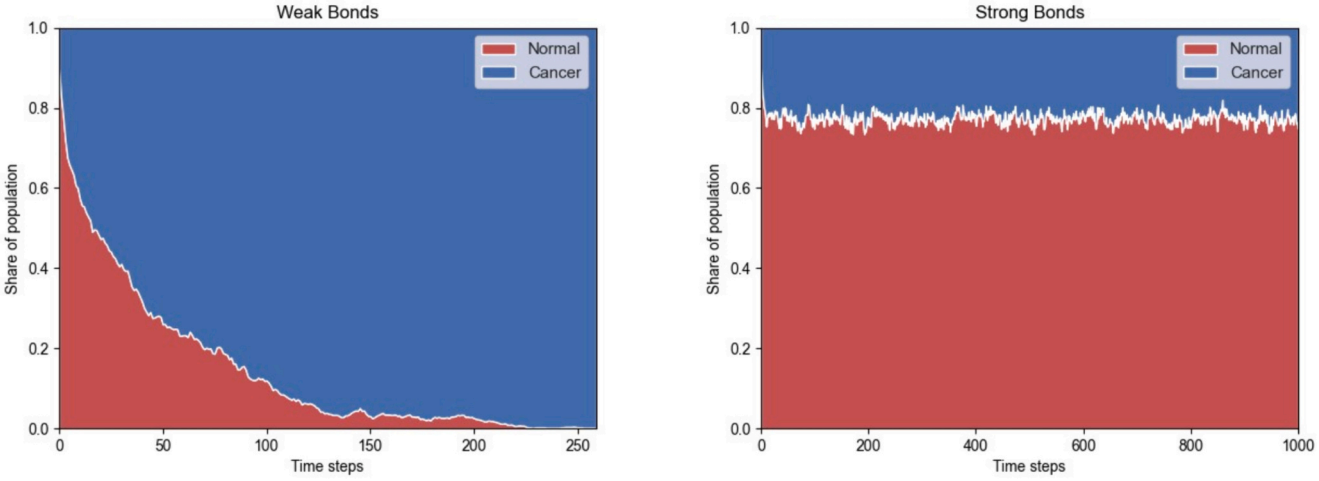

Fig. 3. Effects of social bonds on cancer expansion. Red and blue regions represent the normal and cancerous shares of the population, respectively. Strong social bonds keep cancer cells in check, whereas weak social bonds allow cancer cells to expand and invade the population.

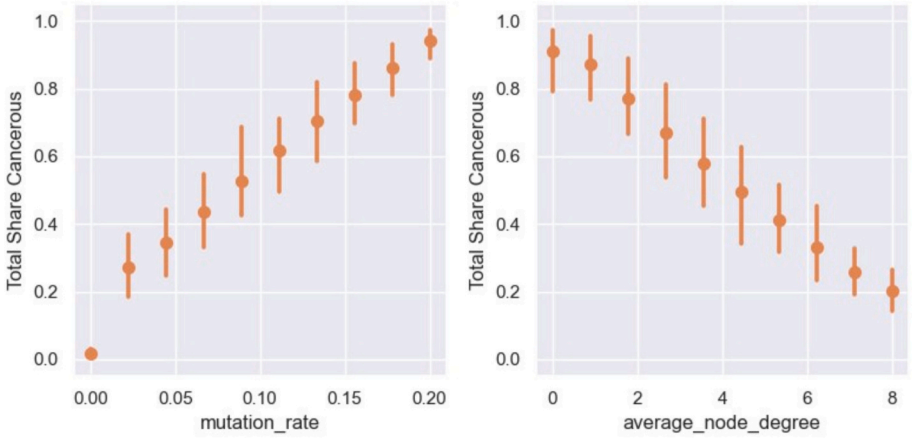

Fig. 4. Effects of mutation and social bonds on cancer expansion.

It is likely that different cancers are subject to different influences of genetics and social bonds. Some, like chronic myeloid leukemia, may be driven by the former, whereas epigenetic cancers like ependymomas may be controlled by the latter. In future work, we will aim to develop a classification scheme that places cancers on a sociality spectrum, based on how readily they respond to social control. Highly responsive cancers may be good candidates for cancer reversion efforts, whereas non-responsive cancers may be best treated via direct killing. We will build on the agent-based network model proposed here to explore how deviant agents interact with environmental factors such as aging or wounding to promote oncogenesis via assortative bond formation and co-option of healthy agents.

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CRediT authorship contribution statement

Anuraag Bukkuri: Software, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization, Writing – review & editing, Writing – original draft. **Frederick R. Adler:** Funding acquisition, Conceptualization, Writing – review & editing.

Declaration of competing interest

None declared.

Data availability

Code is available at: https://github.com/abukkuri/OfCriminalsandCancer

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