Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/mbe

MBE, 23(9): 2698–2719.
DOI: 10.3934/mbe.2026097
Received: 29 June 2026
Revised: 24 August 2026
Accepted: 03 September 2026
Published: 08 September 2026

Letter

Hauntings in the field: The evolutionary dynamics of semiotic corruption and tissue normativity in carcinogenesis

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Abstract: Field cancerization is the process by which carcinogenic insults cause genetic and epigenetic alterations in the tissue field, predisposing it to cancer. Current mereological, temporally synchronic explanatory paradigms struggle to explain why the complete clearance of malignant cells in the field is so often followed by local recurrence. We argue that a more complete account requires a process-ontological framework that captures both synchronic reflexive causation across levels of organization and the diachronic constitution of tissue states by their histories. We formalize these conceptual ideas using a mathematical model that tracks the frequencies of normal and malignant cells and the levels of tissue damage, resilience, and semiotic corruption. We derive a closed-form expression for the escape crossover, which specifies the level of semiotic corruption under which malignant cells acquire a fitness advantage over normal cells. We find that the system exhibits hysteresis, thereby requiring significantly more effort to destabilize a malignant state than to maintain the system at homeostasis. We identify regions of the state space that guarantee malignant escape or containment, and demonstrate a connection between repeated injuries and chronic disease, which tilts the system's disposition towards malignancy. We show that although tissues effectively recover from acute injuries, repeated insults accumulate tissue damage, erode resilience, promote semiotic corruption, and eventually trigger malignant escape. Surgery, even if it clears all malignant cells, leaves the tissue in poor health with semiosis corrupted and leads to recurrence. On the other hand, field-directed therapies restore tissue health and semiotic integrity, leading to durable responses and tissue normalcy. These findings reframe field cancerization as an inherently multi-scale phenomenon of semiotic corruption whose present state is actively constituted by traces from the past.

Keywords: field cancerization; evolutionary dynamics; hauntology; normativity; biosemiotics; semiotic corruption; Derrida; Canguilhem

1. Introduction

Field cancerization (FC) refers to the phenomenon whereby carcinogenic insults induce genetic and epigenetic aberrations in an epithelial tissue, thus increasing its susceptibility to malignant transformation. Originally identified in oral squamous cell carcinomas [1], FC has since been documented in many organs including the head and neck [2, 3], esophagus [4, 5], skin [6–8], lung [9–11], colon [12–14], stomach [15–17], gallbladder [18], prostate [19–21], pancreas [22], vulva and cervix [23, 24], ovaries [25, 26], breast [27–29], and bladder [30]. Clinically, FC remains a major obstacle to effective intervention. Despite substantial progress in understanding its molecular mechanisms, it remains unclear why surgical removal of malignant lesions often only provides temporary benefits, with patients frequently experiencing local recurrence after resection [31–33]. Under the dogma of the somatic mutation theory, which contends that cancer is the result of the uncontrolled proliferation of cells that have acquired somatic mutations in their genome [34, 35], it is difficult, on epistemological grounds, to explain why the removal of all malignant cells is frequently followed by local recurrence [36, 37].

In this paper, we propose that a more complete understanding of FC requires a new philosophical paradigm that, to summarize, accounts for both synchronic reflexive causation across levels of organization and the diachronic mode of temporal constitution, in which prior tissue injuries actively contribute to tissue individuation (*sensu* Simondon [38]) in present conditions. In other words, levels of biological organization cannot be mereologically separated: cells actively contribute towards tissue individuation over time and, simultaneously, the tissue imposes constraining relations on cells and influences their behavior. Furthermore, the present state of the tissue is actively constituted by the lingering effects of prior tissue injuries–temporally synchronic perspectives that solely focus on current tissue "normalcy" (*sensu* Canguilhem [39]) will miss this Derridean trace entirely. As described in our earlier work, this entails the corruption of signaling integrity within the society of cells in the tissue, particularly between immune and cancer cells [40].

After developing this philosophical perspective further, we turn to mathematical modeling to formalize and qualitatively explore its implications. Our model tracks the frequency dynamics of normal (x_N) and malignant (x_M) cells in the tissue, along with a haunting index ε that represents the extent of semiotic corruption, tissue damage D that captures the transient effects of injury, and tissue resilience R that encodes, at the tissue-level, how effectively cell-level signaling integrity can be restored. We show that there exists a unique threshold $\varepsilon^\times$ such that normal cells have a higher fitness than malignant cells for $\varepsilon < \varepsilon^\times$, whereas malignant cells are fitter for $\varepsilon > \varepsilon^\times$. We show that tissues can recover from single insults, but repeated injuries lead to an accumulation of tissue damage (chronic disease) that erodes resilience, thus paving the path for semiotic corruption and malignant cell escape. To conclude, we demonstrate that even surgery that eliminates all malignant cells may lead to recurrence as it leaves semiotic corruption intact. However, field-directed therapies that restore semiotic fidelity effectively shift the selection pressures in the tissue against malignant cells, thus promoting malignant cell clearance and durable tissue homeostasis.

2. Philosophical preliminaries

Although FC has been observed for over 70 years, an adequate explanation of local tumor reconstitution after even complete removal of malignant cells remains elusive. This explanatory gap is

symptomatic of the shortcomings of the constitutive molecular mechanistic tradition that is ubiquitous in cancer research. These explanations are typically mereological, reductionistic, and bottom-up, aiming to understand complex biological phenomena by breaking them down into their most fundamental constituent parts (e.g., cells, genes, molecules), understanding their properties and interactions, and then building the complex phenomena back up [41]. This view is inherently substance-ontological and ignores the complex bidirectional causation across levels of organization. Although this perspective has undoubtedly proven invaluable for identifying druggable, cancer-associated genes, it struggles to address fundamental questions in cancer metaphysics. For instance, it is unclear if cancer-driving genes cause cancer or vice versa. Perplexing explananda such as spontaneous cancer reversion, the existence of cancers without mutations, and inert foreign body carcinogenesis remain unexplained [40]. Moreover, of relevance here, why frequent local recurrence occurs even after complete clearance of cancer cells remains unknown. Answering these questions is not merely an abstract ontological exercise, but has critical implications for the way we conceptualize and design treatment strategies.

To begin to address these questions, we propose that a new philosophical paradigm is needed, grounded in a process relational ontology that spans across levels of organization and time. Modern cancer research is replete with traditional substance ontological thinking, in which homeostasis is taken for granted and the focus lies in identifying molecular mechanisms that cause change. However, homeostasis is a terribly complex process with much to be explained; pathologies such as cancer may then be seen as a breakdown in the mechanisms that maintain homeostasis. Simplistically, homeostasis is maintained by an exquisite balance between proliferation and control, and cancer occurs when this balance is disrupted in favor of proliferation. But how must we understand the processes of proliferation and control? This is inherently a multiscale question that involves molecules, genes, cells, tissues, and so forth. Notably, these interactions across levels of organization are synchronic and reflexive. For instance, genes are undoubtedly active contributors to cellular identity and phenotype. However, simultaneously, the cell's behavior in its dynamically changing environment (that it also contributes to in a myriad of ways) impacts expression patterns of its genes. Thus, a more complete account of cancer must span levels of organization, while remaining interpretable enough to provide insight into the specific question of interest.

Homeostasis is also influenced by history: the environments that cells and tissues (and humans and societies) encounter shape their phenomenology and the mechanisms that constitute their ongoing individuation. A fertile philosophical substrate to explore this idea is Derrida's notion of hauntology, which provides a framework to understand how past events persist as organizing forces in the present environment, even as those events are unidentifiable in the current state [42]. In the context of FC, prior carcinogenic insults may have resolved, but their effects remain as "traces" in the corrupted semiotic landscape of the tissue, actively constituting malignant tissue identity in the present rather than merely remaining causal residues from the past. In our model, this notion is captured by the dynamics of what we call the "haunting index", ε. As our modeling will show, effective therapies must reckon with these specters of the past–solely addressing present conditions is insufficient. This idea is related to the distinction that Canguilhem makes between normalcy and normativity or health: "Being healthy means being not only normal in a given situation but also normative in this and other eventual situations ... To be in good health means being able to fall sick and recover" [39]. Thus, what we often consider to be health (e.g., the absence of malignant cells in a tissue) may just be normalcy rather than true health.

As we will show in this paper, a highly abnormal tissue may still retain normativity, whereas a fully normal tissue may be in poor health.

Concretely, what does semiotic corruption entail? To formalize this, we turn to biosemiotics, and specifically Peirce's triadic model of signs [43]. Briefly, this model posits that the process of semiosis involves a sign (representamen) that stands for something (an object), which is interpreted to generate meaning (by an interpretant). Of relevance to us, certain properties such as cell surface markers (representamen) may stand for a cell's identity (object), which is interpreted by the immune system (interpretant) as benign or malignant. Additionally, Peirce makes the distinction between the dynamic and the energetic interpretant: the former captures the meaning that is manifested by the sign in the interpretant (e.g., "this cell is malignant"), whereas the latter deals with the immediate action that the sign induces (e.g., latching onto the cell to release toxins). In cancer, we propose that there are three aspects of this structure that are corrupted. First, the representamen: malignant cells falsify their surface markers (e.g., via downregulation of MHC-1, NKG2D ligand shedding) to appear like normal cells to the immune system. Second, the dynamic interpretant: the immune *Umwelt* is recalibrated due to high levels of background stress and no longer registers malignant signals as "danger". Third, the energetic interpretant: even if immune cells detect and interpret malignant cells as dangerous objects to be killed, their execution may be inhibited via extracelluar matrix (ECM) stiffness or immunosuppressive cytokines in the environment. Together, these corrupting forces undermine the immune system's ability to detect, interpret, and eliminate malignant cells in the tissue.

3. Mathematical model

Few mathematical models of FC currently exist. Current models use stochastic approaches to consider how the size and geometry of the premalignant fields are influenced by tissue and genetic properties [44], quantify the effect of epithelial thickness on clonal spread and cancer initiation [45], link tissue-level FC dynamics to observed population incidence data [46], connect differential fitness between cellular populations to post-surgery recurrence times [47], and use cellular automata to investigate how carcinogen exposure at the tissue level impacts gene expression, thereby driving cellular dynamics of proliferation, quiescence, apoptosis, and differentiation [48]. Although these models illuminate numerous aspects of FC, they are heavily steeped in substance ontology and the somatic mutation theory. None consider synchronic reflexive causation between the cellular and tissue levels–causation is only unidirectional. No aspects of hauntology are considered: tissue injuries, if included at all, only exert their effects while they persist, and once resolved leave no trace behind. In addition, the focus of these models is solely on tissue normalcy rather than normativity. In this section, we develop a modeling framework that allows for the incorporation of these critical components.

To construct such a model, we begin with the frequency dynamics of normal (x_N) and malignant (x_M) cells in the tissue. We assume that the state vector $X = [x_N, x_M]$ evolves via standard replicator dynamics on the simplex $\Delta \subset \mathbb{R}^2$ where $x_N + x_M = 1$. The dynamics of the cell populations are given by the following:

$$\begin{aligned} \frac{dx_i}{dt} &= x_i(f_i - \bar{f}), \\ \bar{f} &= x_N f_N + x_M f_M, \end{aligned}$$

where the fitnesses of the normal and malignant cells are

$$f_N = r_N,$$
$$f_M = r_M - k\varphi(\varepsilon).$$

We assume that normal cells proliferate at a rate r_N and are not eliminated by the immune system at all, whereas malignant cells proliferate at rate $r_M > r_N$ and face immune elimination at rate $k\varphi(\varepsilon)$, where k is the elimination strength of the malignant cells by immune cells, and $\varphi(\varepsilon)$ is the probability of immune attack, defined as a decreasing sigmoid of the haunting index:

$$\varphi(\varepsilon) = \frac{\varphi_{\max}}{1 + \exp\left(\kappa_\varepsilon(\varepsilon - \varepsilon_{1/2})\right)}.$$

In a clean field ($\varepsilon = 0$), malignant cells face near-maximal detection: $\varphi(0) \approx 0.933$. However, in a fully corrupted field ($\varepsilon = 1$), they almost entirely evade detection: $\varphi(1) \approx 0.017$. We let $g(\varepsilon) := f_M(\varepsilon) - f_N$ capture the fitness advantage of malignant over normal cells, and $\Delta r := r_M - r_N$ denote the differential proliferation rates. Intuitively, $g(\varepsilon) < 0$ when the immune system suppresses malignancy and $g(\varepsilon) > 0$ during malignant escape. Figure 1 shows $\varphi(\varepsilon)$ and $g(\varepsilon)$ as functions of ε, illustrating the homeostatic and malignant escape regimes separated by $\varepsilon^\times = 0.48$.

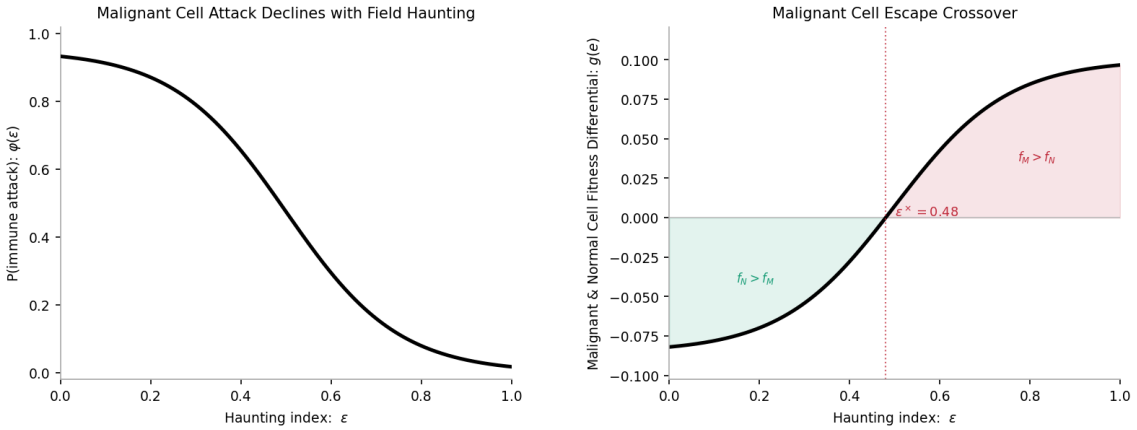

Figure 1. Immune attack probability $\varphi(\varepsilon)$ and escape crossover $\varepsilon^\times$. *Left*: $\varphi(\varepsilon)$ declines in a sigmoidal fashion as a function of tissue haunting. *Right*: fitness advantage of malignant over normal cells, $g(\varepsilon)$, as a function of tissue haunting. The unique threshold at $\varepsilon^\times = 0.48$, indicated by the dashed line, separates the regime for which malignant cells expand from the regime in which they decrease.

A small background mutation flux $\mu = 10^{-5}$ continually generates malignant cells from normal cells and produces an approximate mutation-selection equilibrium of $x_M^* \approx -\mu/g(0) \approx 0.012\%$:

$$\left.\frac{dx_N}{dt}\right|_{\text{mut}} = -\mu x_N, \qquad \left.\frac{dx_M}{dt}\right|_{\text{mut}} = \mu x_N.$$

This mutation-selection equilibrium can be viewed as a form of Canguilhem's static biological anomaly: a deviation from our conceptualization of the standard blueprint of a healthy tissue that

captures structural variation, rather than a disease-causing effect. Alongside the cellular dynamics, we track the haunting index $\varepsilon \in [0, 1]$, tissue resilience $R \in [0, 1]$, and tissue damage $D \geq 0$. We assume pulse-decay dynamics for tissue damage: D increases at injury events (occurring at times t_i) and decays between them:

$$\frac{dD}{dt} = \underbrace{\Delta D_{\text{ins}} \sum_i \delta(t - t_i)}_{\text{effect of injury}} - \underbrace{\delta_D D}_{\text{damage resolution}},$$

where $\delta(t - t_i)$ is the Dirac delta function centered at $t = t_i$. Tissue resilience is eroded by tissue damage and recovers over time. We let tissue recovery be a function of the frequency of normal cells in the tissue since normal epithelial stem cells are critical to wound healing [49–51], whereas a fully malignant field in which, for example, normal stromal cells are replaced by cancer-associated fibroblasts, loses the capacity for semiotic self-repair [52]. Explicit modeling of tissue resilience allows us to directly track Canguilhem's notion of health, rather than just focusing on normalcy (i.e., the frequency of malignant cells in the population):

$$\frac{dR}{dt} = \underbrace{-\alpha D R}_{\text{resilience degradation}} + \underbrace{\gamma_R x_N (1 - R)}_{\text{tissue resilience repair}}.$$

The haunting index ε is governed by malignant cell corruption and resolution via tissue resilience. Malignant cells drive ε upward at rate λ via active corruption of the semiotic structure, and tissue resilience resolves this corruption at the effective rate $\delta_0 R$. Although we treat ε as a single variable encoding the joint effects of semiotic corruption, in reality, it is decomposed as $\varepsilon = 1 - (1 - \varepsilon_R)(1 - \varepsilon_D)(1 - \varepsilon_E)$ where $\varepsilon_R, \varepsilon_D, \varepsilon_E \in [0, 1]$ capture the corruption of the representamen, dynamic interpretant, and energetic interpretant, respectively. This multiplicative structure arises from the nature of semiotic corruption–successful immune elimination of malignant cells requires three independent processes: cancer cells must exhibit signals that are sufficiently distinct from normal cells, immune cells must identify such signals as malignant, and immune cells must actually carry out the killing. Thus, corruption of any component of the semiotic structure is sufficient to impair the informational content it carries:

$$\frac{d\varepsilon}{dt} = \tau_\varepsilon \Big[\underbrace{\lambda x_M (1 - \varepsilon)}_{\text{malignant corruption}} - \underbrace{\delta_0 R \varepsilon}_{\text{tissue resolution}} \Big].$$

An acute injury, such as exposure to UV radiation or tobacco, is implemented via instantaneous increases in the following: 1) ε by $\Delta\varepsilon_{\text{ins}} = 0.30$ representing, for example, acute immune tolerance induction from DAMP signaling [53]; 2) x_M by $\Delta x_M^{\text{ins}} = 0.15$, directly seeding malignant clones from the mutagenic effects of the injury; and 3) D by $\Delta D_{\text{ins}} = 0.35$, capturing direct tissue damage.

The mechanisms and model structure considered here are the minimal set of components required to capture the two conceptual aspects we deem critical for a deeper understanding of cancer ontology: synchronic reflexive causation across levels of biological organization and the hauntological nature of tissue injuries, within a framework that allows tissue normalcy to be distinguished from normativity. Namely, two cell types (normal and malignant) are required to account for the evolutionary dynamics of carcinogenesis via semiotic corruption; the inclusion of a tissue layer allows for cross-scale interactions in a bidirectional manner; damage provides a physical mechanism for tissue injury to enter and recede

from the system so what remains in ε is a trace rather than just a persisting cause; resilience directly captures tissue health and normativity; and haunting reflects that prior injuries persist as traces that actively constitute the current state of the tissue. This minimal structure allows us to clearly understand the implications of our proposed philosophical framework.

As with all models, we make several simplifying assumptions for conceptual clarity and interpretability. Some of these components are already implicitly captured in the model (e.g., immune infiltration, exhaustion, and phenotypic switching between anti- and pro-tumor states are encoded in ε). Others, such as clonal heterogeneity within the normal and malignant cell populations, are excluded from the model as they would confound the metaphysics of presence argument we aim to make surrounding the trace of prior injuries on semiotic corruption in the current tissue state. Others, such as the assumption that the tissue is well-mixed, are excluded as they simply deal with different questions (e.g., monoclonal vs. polyclonal origins and the spread of semiotic corruption) that we aim to address in future work. The parameters, values, and interpretations of all model parameters are given in Table 1. Importantly, these parameter values were chosen to be biologically plausible, numerically convenient for simulation purposes, and to help clearly illustrate the conceptual points articulated in the paper in a qualitative fashion. They were not parameterized from any experimental data and are not meant to quantitatively recapitulate any specific *in vitro* or *in vivo* experiments.

Table 1. Model parameters.

Parameter	Value	Interpretation
r_N	0.10	Normal cell proliferation rate
r_M	0.20	Malignant cell proliferation rate
k	0.195	Strength of malignant cell elimination
$\varphi_{\max}$	0.95	Immune attack sigmoid saturation level
$\varepsilon_{1/2}$	0.50	Midpoint of immune attack sigmoid
κ_ε	8	Immune attack sigmoid steepness
λ	0.30	Field corruption rate by malignant cells
δ_0	0.24	Baseline field resolution rate
α	0.18	Damage-induced resilience degradation
γ_R	0.008	Baseline tissue resilience repair rate
δ_D	0.004	Damage decay rate
ΔD_{ins}	0.35	Damage added per insult
$\Delta\varepsilon_{\text{ins}}$	0.30	ε added per insult
Δx_M^{ins}	0.15	Malignant cells added per insult
τ_ε	0.10	Semiotic corruption timescale conversion
μ	10^{-5}	Normal-to-malignant mutation flux

4. Analytical results

Before we perform simulations under various physiological scenarios, we establish key analytical results of the model. We analyze the system for both repeated acute injuries wherein the damage path $D(t)$ dynamically changes over time, with impulse carcinogenic assaults followed by a period of recovery, and for constant chronic disease in which the damage path is set to a fixed $\bar{D} > 0$, which

allows for greater analytical tractability. First, we define the system and show that it is well-posed (Proposition 4.1). Then, we derive a closed-form expression for the unique escape crossover $\varepsilon^\times$ at which the fitness of malignant and normal cells are identical (Proposition 4.2). Next, we calculate the equilibria of the chronically damaged tissue (Proposition 4.3) and analyze its bifurcation properties (Proposition 4.4). Then, we provide sufficient conditions under which the tissue is certain to escape (Proposition 4.5) or be contained (Proposition 4.6). Finally, we show how repeated injuries lead to the accumulation of damage, thereby linking acute exposure to chronic disease (Proposition 4.7).

Since $D(t)$ evolves independently of the other state variables and only enters the system via a reduction in resilience, we treat damage as an exogenous, non-negative forcing and study the subsystem $z = (x, R, \varepsilon)$ where $x := x_M$ (and thus $1 - x = x_N$):

$$\begin{aligned}\frac{dx}{dt} &= f_1(z) := (1-x)(xg(\varepsilon) + \mu),\\ \frac{dR}{dt} &= f_2(z) := -\alpha DR + \gamma_R(1-x)(1-R),\\ \frac{d\varepsilon}{dt} &= f_3(z) := \tau_\varepsilon(\lambda x(1-\varepsilon) - \delta_0 R\varepsilon).\end{aligned}$$

Proposition 4.1 (Well-posedness & positive invariance)**.** *For every locally integrable damage path $D(t)$, the unit cube $I^3 = [0,1]^3$ is positively invariant and every solution with $z(0) \in I^3$ is unique and exists for all $t \geq 0$.*

Proof. Since our system is continuous in z, measurable in t, and locally integrably bounded on I^3, the Carathéodory existence theorem gives local existence. Furthermore, since $D(t)$ enters $f = (f_1, f_2, f_3)$ linearly only via f_2, the map $f(t, z)$ is locally Lipschitz in z on I^3 with the Lipschitz constant bounded by $C + \alpha D(t)$. Since $D(t)$ is assumed to be locally integrable, we have uniqueness.

To verify positive invariance of I^3, we invoke Nagumo's theorem, which requires that f belongs to the tangent cone at every $z \in \partial I$. Since I^3 is a cube, we simply verify upper or lower bounds, as appropriate, on every face:

$$\begin{aligned} x = 0:&\quad f_1 = \mu \geq 0, & \qquad x = 1:&\quad f_1 = 0,\\ R = 0:&\quad f_2 = \gamma_R(1-x) \geq 0, & \qquad R = 1:&\quad f_2 = -\alpha D(t) \leq 0,\\ \varepsilon = 0:&\quad f_3 = \tau_\varepsilon \lambda x \geq 0, & \qquad \varepsilon = 1:&\quad f_3 = -\tau_\varepsilon \delta_0 R \leq 0.\end{aligned}$$

Thus, I^3 is positively invariant, and its boundedness guarantees global existence of the solutions. □

This proposition provides a sanity check, ensuring that the cell frequencies, resilience, and haunting remain within I^3. The biologically interesting regime in this cube occurs when, under an uncorrupted field, the immune system suppresses malignancy, and under a fully corrupted field, the malignant cells escape. These conditions are formalized as follows:

$$\text{C1: } k\varphi(0) > \Delta r \qquad \text{and} \qquad \text{C2: } k\varphi(1) < \Delta r.$$

Tissues that lie outside this region correspond to scenarios in which homeostasis or malignancy is certain regardless of damage history, and thus obviate the need for a hauntological account. Next, we calculate a tissue haunting level that partitions this regime into a region in which malignant cells have a fitness advantage and a region in which normal cells have a fitness advantage.

Proposition 4.2 (Escape crossover)**.** *Assume C1 and C2. Then, there exists a unique haunting level* $\varepsilon^\times \in (0,1)$ *such that* $g(\varepsilon^\times) = 0$*:*

$$\varepsilon^\times = \varepsilon_{1/2} + \frac{1}{\kappa_\varepsilon} \ln\left(\frac{\varphi_{\max} k}{r_M - r_N} - 1\right).$$

For our model parameters, $\varepsilon^\times = 0.48$.

Proof. Since $g(0) < 0$ and $g(1) > 0$ by assumption and $\varphi(\varepsilon)$ is a monotonically decreasing function, $g(\varepsilon)$ is monotonically increasing and $\varepsilon^\times$ is unique by the intermediate value theorem. Setting $\varphi(\varepsilon^\times) = (r_M - r_N)/k$ and solving gives the desired formula. □

To assess the robustness of the escape crossover and the impact of changes in parameters on $\varepsilon^\times$, we perform a sensitivity analysis via Latin hypercube sampling across the six parameters that influence its value (Figure 2). As we can see, more aggressive tumors lower the threshold for malignant escape, whereas immune efficacy (both in the probability and lethality of attack) raises it. Figure 1 visualizes this escape crossover. For $\varepsilon < \varepsilon^\times$, the frequency of malignant cells in the tissue decreases. Conversely, for $\varepsilon > \varepsilon^\times$, the frequency of malignant cells in the tissue increases.

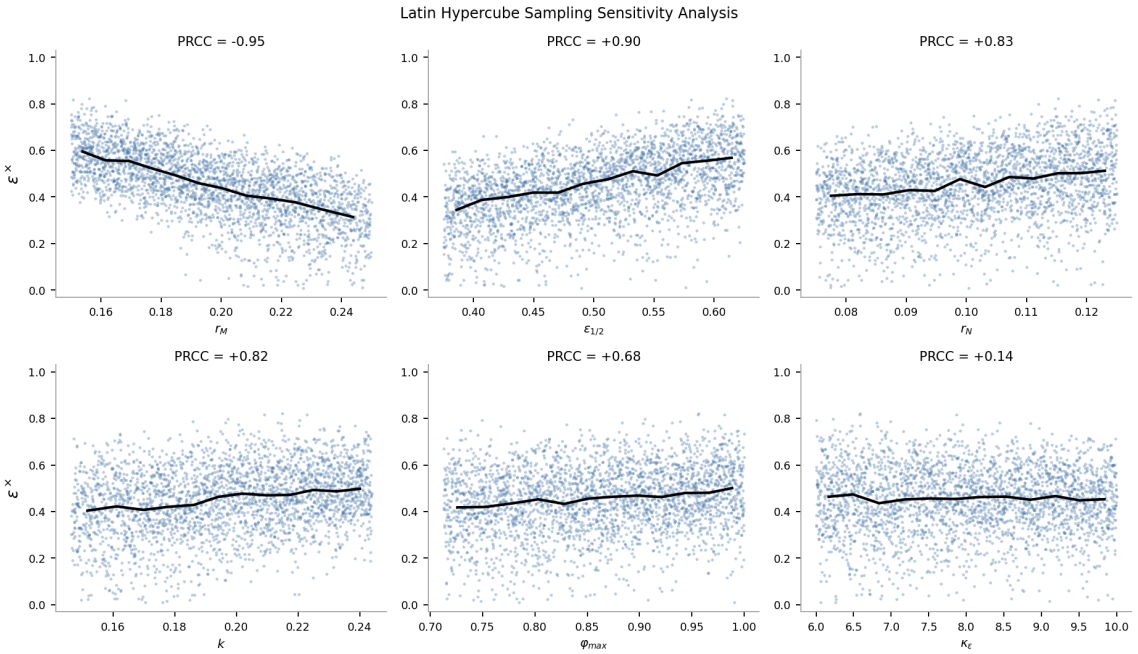

Figure 2. Latin hypercube sampling sensitivity analysis. 3000 sets of parameters are sampled per panel with a 25% variance about the values given in Table 1, except for $\varphi_{\max}$, which is bounded above by 1. Partial Rank Correlation Coefficients (PRCC) are provided for each parameter.

4.1. Chronic disease

In this section, we consider the properties of the system under a chronic disease setting in which we set $\mu = 0$ and $D(t) = \bar{D} > 0$. First, we calculate the equilibria and classify their stability properties.

Proposition 4.3 (Equilibria and stability)**.** *Assume C1 and C2. Then, the chronic disease system has three equilibria:*

$$E_0 = (0, R_0, 0), \quad E_1 = (1, 0, 1), \qquad E_s = (x_s, R_s, \varepsilon^\times),$$

where $R_0 := \frac{\gamma_R}{\alpha\bar{D}+\gamma_R}$, $x_s = \frac{1}{2}\Big[1+a+c-\sqrt{(1+a+c)^2-4c}\Big]$, $R_s = \frac{x_s}{c}$, $a := \frac{\alpha\bar{D}}{\gamma_R}$, *and* $c := \frac{\delta_0\varepsilon^\times}{\lambda(1-\varepsilon^\times)}$. E_0 *and* E_1 *are locally asymptotically stable, whereas* E_s *is a saddle with a two-dimensional stable manifold and a one-dimensional unstable manifold.*

Proof. First, we compute the equilibria. Setting $f_1 = 0$ gives three cases: $x = 0$, $x = 1$, or $x \in (0, 1)$ ($\varepsilon = \varepsilon^\times$). We consider each case separately.

$x = 0$. Setting $f_2 = 0$ gives $-\alpha\bar{D}R + \gamma_R(1 - R) = 0 \implies R = R_0$. Then, setting $f_3 = 0$ gives $-\tau_\varepsilon\delta_0 R_0\varepsilon = 0 \implies \varepsilon = 0$. Thus, we have E_0.

$x = 1$. Setting $f_2 = 0$ gives $-\alpha\bar{D}R = 0 \implies R = 0$. Then, setting $f_3 = 0$ gives $-\tau_\varepsilon\lambda(1 - \varepsilon) = 0 \implies \varepsilon = 1$. Thus, we have E_1.

$\varepsilon = \varepsilon^\times$. Setting $f_3 = 0$ gives $\delta_0 R\varepsilon^\times = \lambda x(1 - \varepsilon^\times) \implies x = cR$. Then, setting $f_2 = 0$ gives $\alpha\bar{D}x/c = \gamma_R(1 - x)(1 - x/c) \implies ax = c - x - cx + x^2 \implies 0 = x^2 - (1 + a + c)x + c := \chi(x)$. From this, we know that the product of the two roots, r_1 and r_2, must be c and their sum must be $1 + a + c$. Since $\chi(0) = c > 0$ and $\chi(1) = -a < 0$, $0 < r_1 < 1 < r_2$, and we are only interested in the smaller root. By the quadratic formula, this is given by $x_s = \frac{1}{2}\Big[1 + a + c - \sqrt{(1 + a + c)^2 - 4c}\Big]$ and the equilibrium E_s follows.

Next, we consider the stability of the three equilibria. First, we compute the Jacobian:

$$J = \begin{bmatrix} (1-2x)g(\varepsilon) & 0 & (x-x^2)g'(\varepsilon) \\ -\gamma_R(1-R) & -(\alpha\bar{D}+\gamma_R(1-x)) & 0 \\ \tau_\varepsilon\lambda(1-\varepsilon) & -\tau_\varepsilon\delta_0\varepsilon & -\tau_\varepsilon(\lambda x+\delta_0 R) \end{bmatrix}$$

Consider E_0. Plugging in $x = 0$ makes the matrix lower triangular, and the eigenvalues can be read off the diagonal as $g(0)$, $-\alpha\bar{D} - \gamma_R$, and $-\tau_\varepsilon\delta_0 R_0$. All these eigenvalues are negative, so E_0 is locally asymptotically stable.

Consider E_1. Plugging in $x = 1$ makes the matrix lower triangular again, with eigenvalues of $-g(1)$, $-\alpha\bar{D}$, and $-\tau_\varepsilon\lambda$. All eigenvalues are negative, and hence E_1 is locally asymptotically stable.

This same trick does not work for E_s. However, recall that the determinant of the Jacobian is the product of its eigenvalues $\prod \lambda_i$ and the trace is their sum $\sum \lambda_i$. Since $\varepsilon = \varepsilon^\times$, $J_{11} = 0$ and we have $det(J) = J_{13}(J_{21}J_{32} - J_{22}J_{31}) \implies det(J) > 0$ by the signs of the relevant Jacobian entries. Additionally, $tr(J) = J_{11} + J_{22} + J_{33} < 0$. We know that the eigenvalues must either all be real, or there must be one real eigenvalue and one complex conjugate $\sigma \pm \psi i$. If all eigenvalues are real, $det(J) > 0$ means that there are either zero or two negative eigenvalues. Since $tr(J) < 0$, two are negative and one is positive. If there is a complex conjugate, then $\prod \lambda_i = \lambda_1(\sigma^2 + \psi^2) \implies \lambda_1 > 0$. Furthermore, $\sum \mathrm{Re}(\lambda_i) = \lambda_1 + 2\sigma < 0 \implies \sigma < -\lambda_1/2 < 0$. Thus, E_s is a saddle with a two-dimensional stable manifold and a one-dimensional unstable manifold. □

Note that chronic disease may not change the frequency of malignant cells in the tissue (Canguilhem's normalcy) under homeostatic conditions, but it may significantly impact the tissue's resilience and capacity to repair semiotic corruption (Canguilhem's health). This captures the idea of dispositional causation: the tissue's newly established degraded normativity does not directly cause

pathology, but rather increases its disposition towards it, thereby weakening its abilities to maintain homeostasis when confronted with subsequent insults.

Next, we analyze how the window of bistability changes as a function of the strength of malignant cell elimination, k. We define $k_- := \Delta r/\varphi(0)$ and $k_+ := \Delta r/\varphi(1)$. Basic algebra shows that $k \in (k_-, k_+)$ corresponds to the biologically interesting regime defined by conditions C1 and C2.

Proposition 4.4 (Window of bistability & hysteresis)**.** *As $k \downarrow k_-$, $\varepsilon^\times \to 0$ and $E_s \to E_0$. Conversely, as $k \uparrow k_+$, $\varepsilon^\times \to 1$ and $E_s \to E_1$. Each collision ends in a transcritical bifurcation.*

Proof. By Prop. 4.2, $\varepsilon^\times$ is strictly increasing in k with $\varepsilon^\times \to 0$ as $k \downarrow k_-$ and $\varepsilon^\times \to 1$ as $k \uparrow k_+$. Recall from Prop. 4.3 that x_s is the smaller root of $\chi(x) = x^2 - (1 + a + c)x + c = 0$. As $\varepsilon \to 0$, $c \to 0 \implies x_s \approx c/(1 + a) \to 0$. Then, we have $R_s \to 1/(1 + a) = R_0$. Putting these together, we see that $E_s \to E_0$. Similarly, as $\varepsilon \to 1$, $c \to \infty \implies x_s \approx c/(c + a) \to 1$ and $R_s \to 0$, giving $E_s \to E_1$. At each endpoint, the unstable interior equilibrium collides with a stable boundary equilibrium and exchanges stability: E_0 and E_1 are locally asymptotically stable when $k > k_-$ and $k < k_+$, respectively, and lose hyperbolicity exactly at the boundary (Prop. 4.3). When $k < k_-$, condition C1 fails and malignant cells always have a fitness advantage over normal cells, even in an entirely uncorrupted field–$g(0) > 0$, which turns E_0 into an unstable saddle, whereas E_1 remains stable ($g(1) > 0$); the biologically realistic interior equilibrium E_s disappears. When $k > k_+$, condition C2 fails and the same argument holds in reverse (E_1 becomes an unstable saddle and E_0 remains stable). The transcritical nature of this bifurcation is numerically apparent from Figure 3. The hysteresis exhibited by the system suggests that significantly more effort is required to destabilize a malignant tissue than to keep a tissue at homeostasis. □

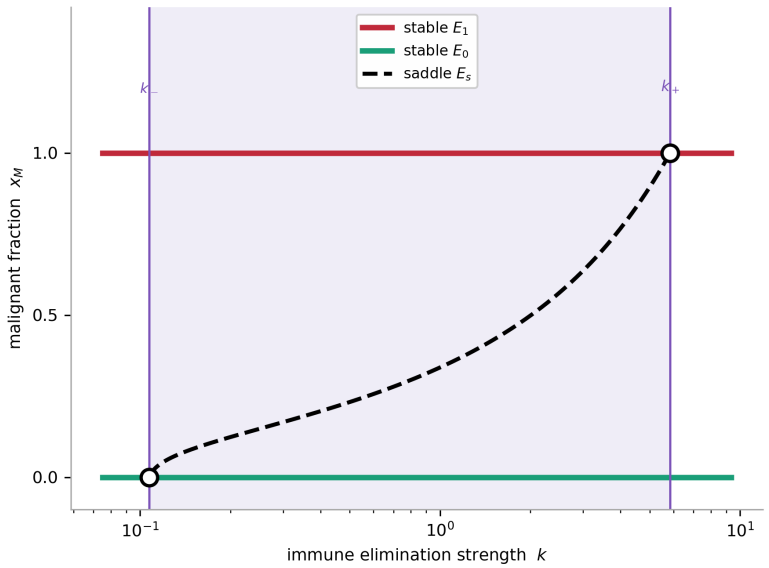

Figure 3. Bifurcation structure of the chronic disease system. Equilibria are plotted as a function of the immune elimination strength k at chronic damage $\bar{D} = 0.2$. The homeostatic (green) and malignant (red) states are stable throughout the bistable window (k_-, k_+) (shaded in purple). Each loses stability at the end of the window, when they collide with the saddle (dashed), which rises from $x_M = 0$ at $k_- \approx 0.1$ to $x_M = 1$ at $k_+ \approx 5.9$ (Prop. 4.4).

4.2. Repeated carcinogenic insults

Having established the properties of the tissue under chronic disease, we now relax the constant damage and zero mutation assumptions and establish regions of state space in which escape is guaranteed, regardless of the future damage path, and regions of state space in which containment is guaranteed, assuming no subsequent tissue injuries occur.

Proposition 4.5 (Guaranteed Escape)**.** *Assume C1 and C2. Fix* $\varepsilon_1 \in (\varepsilon^\times, 1)$*, which sets* $g_1 := g(\varepsilon_1)$ *and* $c_1 := \frac{\delta_0 \varepsilon_1}{\lambda(1-\varepsilon_1)}$*. Additionally, define* $\rho_1 := \frac{\gamma_R c_1 - \mu}{g_1 + \gamma_R}$*. Then, let* $x_1 > max(\rho_1, 0)$ *and define the escape region as follows:*

$$\mathcal{E} := \{z \in I^3 | \varepsilon \geq \varepsilon_1, x \geq x_1, and\ x \geq c_1 R\}.$$

Then, for every locally integrable damage path $D(t)$ *for* $t \geq t_0$*,* $\mathcal{E}$ *is positively invariant and* $z(t_0) \in \mathcal{E}$ *is irreversibly destined for malignant escape.*

Proof. To verify invariance, we again invoke Nagumo's theorem and check the lower bounds on the three relevant faces.

$\varepsilon = \varepsilon_1$. $f_3 = \tau_\varepsilon \lambda(1 - \varepsilon_1)(x - c_1 R) \geq 0$ since $x \geq c_1 R$.

$x = x_1$. $f_1 = (1 - x)(x_1 g(\varepsilon) + \mu) \geq (1 - x) x_1 g_1 \geq 0$ since $g(\varepsilon) \geq g(\varepsilon_1) > 0$ in $\mathcal{E}$ and $x_1 > 0$.

$x = c_1 R$. Let $h := x - c_1 R$. Then, we have the following:

$$\begin{aligned} \frac{dh}{dt} &= (1 - x)(xg(\varepsilon) + \mu) + \alpha D x - \gamma_R (1 - x)(c_1 - x) \\ &\geq (1 - x)(x_1 g_1 + \mu) - \gamma_R (1 - x)(c_1 - x_1) \\ &= (1 - x)(x_1 (g_1 + \gamma_R) - (\gamma_R c_1 - \mu)). \end{aligned}$$

Since $x_1 > \frac{\gamma_R c_1 - \mu}{g_1 + \gamma_R}$ by assumption, $dh/dt \geq 0$ and we have that $\mathcal{E}$ is positively invariant.

To show that systems that start in $\mathcal{E}$ are doomed to malignancy, we show that $w := 1 - x \to 0$. Since $dx/dt \geq (1 - x) x_1 g_1$, we have that $dw/dt \leq -(1 - x) x_1 g_1$. Then, Grönwall's inequality gives $w(t) \leq w(t_0) e^{-x_1 g_1 (t - t_0)}$. As $t \to \infty$, $w(t) \to 0$. Thus, $x(t) \to 1$. □

Proposition 4.6 (Guaranteed Containment)**.** *Assume C1 and C2. Fix* $\varepsilon_2 \in (0, \varepsilon^\times)$ *such that* $g_2 := g(\varepsilon_2) \leq -\gamma_R$ *and* $c_2 := \frac{\delta_0 \varepsilon_2}{\lambda(1-\varepsilon_2)}$*. Let* $x_2 \in [-\mu/g_2, min(c_2, 1)]$ *and assume that no further tissue injuries occur after* t_0*, so that* $D(t) \leq D(t_0)$ *for all* $t \geq t_0$*. Then, if* $D(t_0) \leq \frac{(1-x_2)(\gamma_R c_2 - x_2(g_2 + \gamma_R) - \mu)}{\alpha x_2}$ *and if* $\mu < \gamma_R c_2$*, then the containment region*

$$C := \{z \in I^3 | \varepsilon \leq \varepsilon_2, x \leq x_2, and\ x \leq c_2 R\}$$

is positively invariant and $z(t_0) \in C$ *is destined for containment (i.e.,* $\limsup_{t \to \infty} x(t) \leq -\mu/g_2$*).*

Proof. The invariance proof follows that of Proposition 4.5. We invoke Nagumo's theorem and check the upper bounds on the three relevant faces.

$\varepsilon = \varepsilon_2$. $f_3 = \tau_\varepsilon \lambda(1 - \varepsilon_2)(x - c_2 R) \leq 0$ since $x \leq c_2 R$.

$x = x_2$. $f_1 = (1 - x_2)(x_2 g(\varepsilon) + \mu) \leq (1 - x_2)(x_2 g_2 + \mu) \leq 0$ since $g(\varepsilon) \leq g(\varepsilon_2) < 0$ in C and $x_2 \geq -\mu/g_2$.

$x = c_2 R$. Let $h := x - c_2 R$. Then, we have the following:

$$\begin{aligned} \frac{dh}{dt} &= (1 - x)(xg(\varepsilon) + \mu) + \alpha D x - \gamma_R (1 - x)(c_2 - x) \\ &\leq (1 - x)(x(g_2 + \gamma_R) + \mu - \gamma_R c_2) + \alpha D(t_0) x. \end{aligned}$$

Since $g_2 + \gamma_R \leq 0$, the function above is convex and attains its maximum at either endpoint. At $x = 0$, we have $\mu - \gamma_R c_2 < 0$ by assumption on mutation rates. At $x = x_2$, the condition on the damage ceiling ensures $dh/dt \leq 0$. Putting these together gives positive invariance of C. Confinement of the system to, at most, a mutation-selection floor of $-\mu/g_2$ directly follows. □

Next, we turn our attention to the monotonically increasing nature of damage accumulation from one insult to the next. Namely, repeated tissue injuries lead to an accumulation of damage, which manifests as chronic disease. Let D_k^- denote the value of D just before the k-th insult, with $D_0^- = 0$. Let $T > 0$ be the inter-insult interval. Then, we have the following proposition.

Proposition 4.7 (Damage Accumulation)**.** *Under repeated, equally-spaced insults, D_k^- is strictly increasing and converges to the following:*

$$D^*(T) = \frac{\Delta D_{ins}\, e^{-\delta_D T}}{1 - e^{-\delta_D T}}.$$

$D^*(T)$ is strictly decreasing in T: the longer the time between insults, the lower the accumulated damage levels will be.

Proof. Between insults, $D_{k+1}^- = (D_k^- + \Delta D_{\text{ins}})e^{-\delta_D T} = aD_k^- + b$ for $a = e^{-\delta_D T} \in (0, 1)$ and $b = \Delta D_{\text{ins}} e^{-\delta_D T} > 0$. The affine contraction has a unique fixed point $D^*(T) = b/(1 - a)$, strictly decreasing in T since $\partial D^*/\partial T = -\Delta D_{\text{ins}}\, \delta_D\, e^{-\delta_D T}/(1 - e^{-\delta_D T})^2 < 0$. Since $D_0^- = 0 < D^*$, orbits converge monotonically from below. □

Combining this with the results of Proposition 4.3, note that $x_s(D_k^-)$ is strictly decreasing with the number of insults and is strictly increasing with the time between insults, bounded below by $x_s(D^*(T)) > 0$. Tissue resilience, $\gamma_R/(\alpha D_k^- + \gamma_R)$, similarly decreases with insult count and increases with the time between insults. The effect of these accumulated damage levels is a gradual erosion of tissue resilience, which progressively reduces the effective rate of tissue resolution, allowing for semiotic corruption to rise above $\varepsilon^\times$ and leading to a self-sustained malignant escape (Figure 4). These results have a natural interpretation in terms of aging: as individuals experience repeated insults over the course of their lifetime, they simultaneously experience an erosion of the tissue's ability to restore signaling integrity. Eventually, this semiotic corruption provides a selective advantage to malignant cells (that are continually produced in the body), which allows for their expansion and culminates in cancer.

5. Numerical simulations

Now, we perform simulations to further explore the model. For each simulation, a time-series plot of cellular and tissue dynamics will be shaded red or green when the system enters regions of guaranteed escape or containment, respectively. To visualize how the system enters these regions, each time series plot will be accompanied by a plot of the dynamics in z space, with red regions corresponding to $\mathcal{E}$ ($\varepsilon_1 = 0.509$) and green regions corresponding to C ($\varepsilon_2 = 0.232$). The simulations in Figure 4 are initialized in a healthy, unperturbed tissue with $x_N = 1, x_M = 0, R = 1, D = 0$, and $\varepsilon = 0$. Simulations in Figure 5 are initialized at the system state when $x_N = x_M$ after the second injury: $x_N = 0.5, x_M = 0.5, R = 0.11, D = 0.23$, and $\varepsilon = 0.63$. First, consider the case of an acute

injury (Figure 4). For the first 200 time steps, we let the tissue remain at homeostasis. Here, the tissue is almost entirely comprised of normal cells (except for a vanishingly small malignant cell fraction produced by the background mutation flux). Tissue resilience remains at $R = 1$ and semiotic corruption and damage remain minimal. Upon an acute injury at $t = 200$, there is an increase in the malignant cell fraction, the haunting index, and tissue damage, along with a drop in resilience. However, since $\varepsilon < \varepsilon^{\times}$ throughout, $g(\varepsilon) < 0$ and the malignant cells monotonically decrease in frequency immediately after the insult. Accompanying this is a gradual recovery of resilience, resolution of damage, and reduction in tissue haunting. Eventually, the system enters C at $t \approx 259$ and homeostasis ensues.

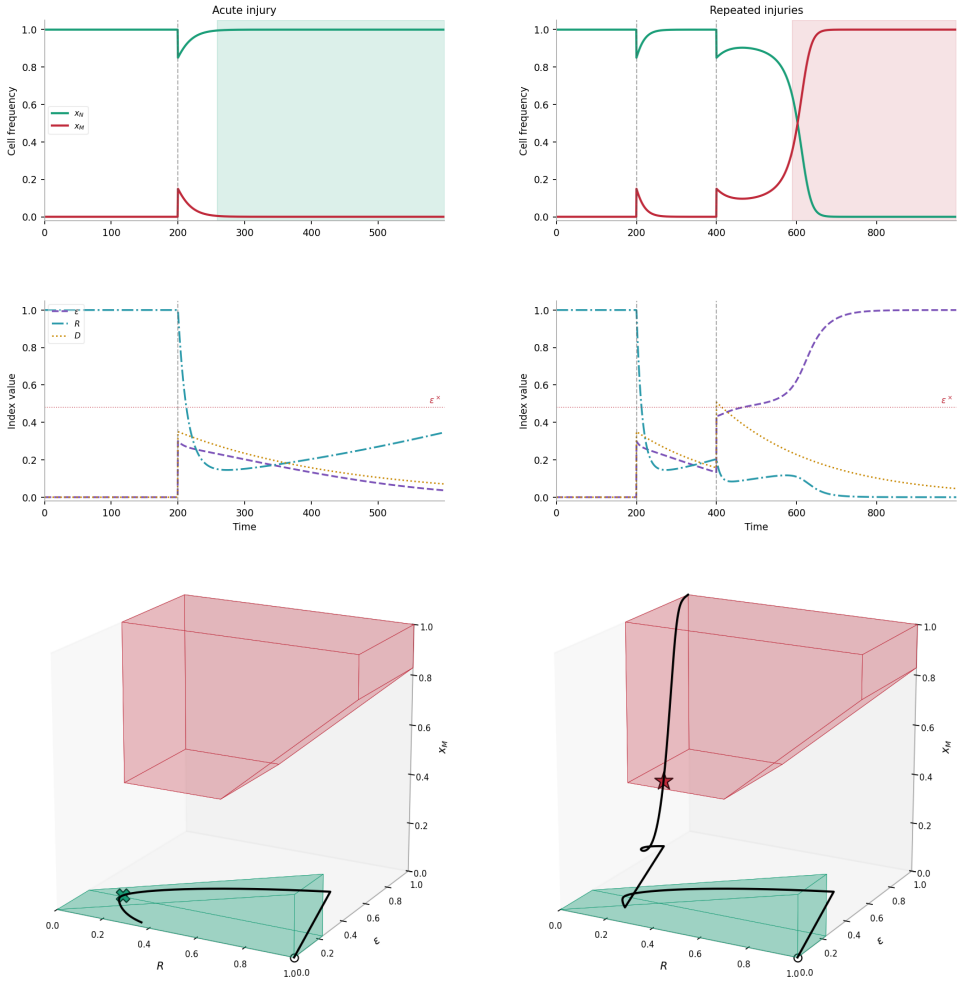

Figure 4. Tissue injury: recovery vs. escape. Upon an acute injury at $t = 200$, malignant cells are seeded into the tissue, along with an increase in tissue damage and haunting, leading to a degradation of tissue resilience. However, the field is not sufficiently haunted to provide the malignant cells with a fitness advantage over the normal cells. Thus, they are rapidly eliminated from the population and homeostasis is restored, with the system entering C at $t \approx 259$ (green cross). However, upon the second insult, higher levels of damage are suffered, eroding tissue resilience further and allowing ε to surpass $\varepsilon^{\times}$ at $t \approx 465$. This allows the malignant cells to expand in the tissue, with the system eventually entering $\mathcal{E}$ at $t \approx 589$ (red star).

Next, consider what happens if the tissue suffers another injury at $t = 400$ (Figure 4). 65 time steps after this second insult, tissue resilience has significantly eroded, allowing ε to rise above $\varepsilon^{\times}$, thereby conferring malignant cells with a fitness advantage over normal cells. Note that this advantage could, in principle, be reversed if damage was instantaneously resolved. However, absent that, tissue health continues to degrade and enters $\mathcal{E}$ at $t \approx 589$, at which point escape is guaranteed regardless of the future damage path (Proposition 4.5). The temporal distance from the system's entrance into $\mathcal{E}$ and its takeover of the tissue captures Derrida's notion of the arrivant, the idea that ghosts from the past not only serve as organizing forces in the present, but also the future. Seen through Derrida's deconstructive perspective on time and the metaphysics of presence, the never fully self-contained present contains both the past and the future: malignant transformation already exists within the milieu of the pre-malignant tissue, most clearly when the system inhabits $\mathcal{E}$.

To build on these results, we next consider the impact of two types of therapy: surgery and field-directed therapy (Figure 5). For both interventions, we allow for a 50 time step pre-therapy window that captures the dynamics from when $x_M \approx x_N$ to when malignant cells dominate the population. Following this, we implement therapy. Surgery instantaneously leads to clearance of the malignant population ($x_M \to 0$), but does not directly target ε, R, or D. Conversely, field therapy is applied over 40 time steps, reducing ε and D at rate 0.05 and increasing R at rate 0.05, but does not directly target x_M. Examples of therapies that have these effects include MEK inhibitors such as trametinib that reduce cancer cells' production of immunosuppressive factors and recruitment of monocytic myeloid derived suppressor cells (reducing λ and thereby ε) [54], anti-inflammatory agents such as TGF-β inhibitors (increasing δ_D and thereby reducing D), and anti-fibrotic or stromal-normalizing drugs such as losartan and pirfenidone that reverse cancer-associated fibroblast activation and improve cell-cell communication fidelity (increasing γ_R and thereby R).

It is worth noting that these are intentionally simplified representations of how surgery and field therapy work. Empirical evidence suggests that surgical excision can induce tissue damage, transient immunosuppression, and pro-metastatic wound healing cascades [55–59], promoting a pro-cancer environment. Indeed, many of the anti-tumor effects of surgery come from the removal of tumor-mediated immunosuppression, including neutrophilia-associated suppression of anti-tumour immunity [60, 61]. Such effects are already implicitly captured in our model through the removal of the cancer cells' active constitution of the haunted environment. Furthermore, some field therapies can directly impact cancer cells (e.g., HDAC inhibitors promote apoptosis, cell cycle arrest, and differentiation) [62, 63]. Although these effects improve the effectiveness of field therapy, we do not include them in our model for simplicity. Rather, the distinction we aim to make by comparing surgery and field therapy is between therapies that aim to restore tissue normalcy vs. those that aim to improve tissue health.

Surgery effectively eliminates the malignant cells in the population; this is accompanied by a transient improvement of tissue resilience and haunting. However, as is clear from the 3D plot, ε remains high for the entire duration of the simulation and never approaches the containment wedge. Eventually, the system enters $\mathcal{E}$ at $t \approx 190$ and recurrence follows. In other words, surgery treats the abnormality of the tissue without resolving its underlying pathology. On the other hand, field therapy targets the structure of the underlying evolutionary game itself – ε, R, and D – without directly modifying player (x_M and x_N) proportions. The post-therapy haunting levels are reduced below $\varepsilon^{\times}$, the restored tissue resilience moves the system into C at $t \approx 175$, and homeostasis follows. Viewed

through the lens of mechanism design, field therapy succeeds not because it directly targets the players in the evolutionary game (e.g., by killing all malignant cells and restoring tissue normalcy), but rather because it changes the rules of the game to achieve desired outcomes (i.e., by restoring tissue resilience and signaling integrity to create a healthy tissue environment that selects against malignant cells).

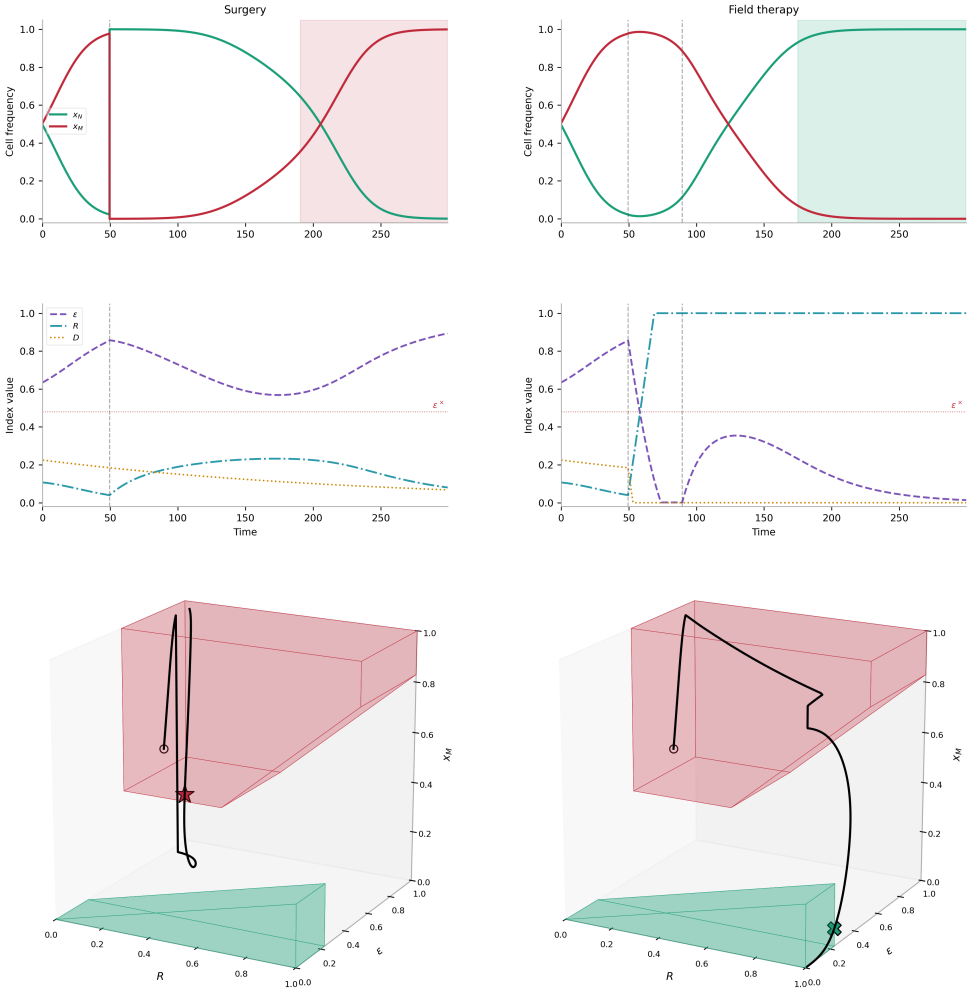

Figure 5. Effects of surgery vs field-directed therapy. Although surgery rapidly eliminates malignant cells, it leaves the tissue haunted and with low resilience. As a result, recurrence occurs, with the system entering $\mathcal{E}$ at $t \approx 190$ (red star). Field therapy targets the haunting index, tissue damage, and resilience. This shapes the tissue microenvironment such that malignant cells are selected against, leading to durable low-level containment with the system entering C at $t \approx 175$ (green cross).

6. Conclusions

In this paper, we argued that field cancerization cannot be adequately understood using a mereological, temporally synchronic perspective, but must rather be conceptualized as a multi-scale phenomenon in which the effects of prior tissue injuries on semiotic integrity persist through time as a

Derridean trace. To formalize this philosophical framework, we created a mathematical model that captures the interplay between cellular and tissue dynamics, while also encoding the lingering effects of semiotic corruption.

We found that there exists a unique threshold $\varepsilon^{\times}$ that determines when the fitness of malignant cells will exceed that of normal cells. We showed that the system exhibits bistability and hysteresis: the immune strength needed to destabilize a malignant system is significantly higher than what is required to keep the system at homeostasis. We defined regions in state space in which escape is inevitable, regardless of the future damage path, or containment is guaranteed assuming no subsequent insults occur. Additionally, we showed how repeated acute injuries can lead to damage accumulation and chronic disease, which may not change the normalcy of the homeostatic state, but changes its health and thereby the tissue's disposition towards malignancy.

Then, we explored the implications of these findings for therapy. Surgery promotes tissue normalcy by removing malignant cells but does not directly contribute to tissue health, leaving the corrupted semiotic structure intact and leading to recurrence. On the other hand, field therapy restores semiotic integrity and tissue resilience, promoting health. Although this therapeutic modality does not directly target tissue normalcy, it changes selective pressures in the tissue microenvironment to select against malignant cells, eventually leading to containment. Overall, our results stress the importance of considering multi-scale interactions, semiotic fidelity, and the persistence of the effects of prior tissue injuries as organizing forces in the present state.

Use of AI tools declaration

The author declares the use of Claude Opus 4.8 for copyediting purposes and to help in generating code for Figures 1–4. All results have been verified for accuracy by the author.

Conflict of interest

The author declares there is no conflict of interest.

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