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TOWARD CULTURAL ONCOLOGY: THE EVOLUTIONARY INFORMATION DYNAMICS OF CANCER

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Abstract

'Racial' disparities among cancers, particularly of the breast and prostate, are something of a mystery. For the US, in the face of slavery and its sequelae, centuries of interbreeding has greatly leavened genetic differences between 'Blacks' and 'whites', but marked contrasts in disease prevalence and progression persist. 'Adjustment' for socioeconomic status and lifestyle, while statistically accounting for much of the variance in breast cancer, only begs the question of ultimate causality. Here we propose a more basic biological explanation that

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extends the theory of immune cognition to include an elaborate tumor control mechanism constituting the principal selection pressure acting on pathologically mutating cell clones. The interplay between them occurs in the context of an embedding, highly structured, system of culturally-specific psychosocial stress. A Rate Distortion argument finds that larger system able to literally write an image of itself onto the disease process, in terms of enhanced 'risk behavior', accelerated mutation rate, and depressed mutation control. The dynamics are analogous to punctuated equilibrium in simple evolutionary systems, accounting for the staged nature of disease progression.

We conclude that 'social exposures' are, for human populations, far more than incidental cofactors in cancer etiology. Rather, they are part of the 'basic biology' of the disorder. The aphorism that 'culture is as much a part of human biology as the enamel on our teeth' appears literally true at a fundamental cellular level.

KEY WORDS: Cancer, cellular cognition, culture, evolution, information theory, interpenetration, mutator, punctuation, renormalization, second order selection, tumorigenesis, universality.

Introduction

Cardiovascular disease and cancer are major causes of mortality in the United States structured by 'race', class, and gender [28]. Cancers of the breast and prostate - 'hormonal' cancers - particularly show large disparities by ethnicity and economic class in incidence among young adults, stage at presentation, and mortality rate (e.g. [39]).

Although certain genetic alleles predispose individuals to higher susceptibility for these cancers (e.g. [23] for prostate cancer), recent changes of incidence and mortality in time and geography indicate genes alone do not explain the expressed population-level patterns. At present, African-American women under age 35 suffer an approximately two-fold higher age-specific rate of breast cancer, compared to white women, and the mortality rate is about three times higher [44]. For prostate cancer, African-American men have a 2-fold higher mortality rate, and 50 percent higher incidence rate, than their white counterparts [43].

During the 1980's, when ideologies of individualism particularly influenced US scientific thinking, interest in health differentials waned. In its stead, the life style doctrine arose: people get sick because they don't take

responsibility for their own health. The connection between diet and breast cancer was an often-cited example of how life style affects health. By the 1990's, however, a large literature on determinants of risk behaviors explored the bases of 'life style' decisions and found them rooted in social and economic processes (e.g. [11, 22, 30, 58, 59]).

Many of the risk behaviors associated with AIDS, drug abuse, and violence, were shown to be coping mechanisms for dealing with frustration, pain, deprivation, humiliation, and danger (e.g. [7, 58, 59]). The particular modes of coping spread, first between social networks and then within social networks by branching processes [32]. Indeed, one of the classic studies of drug use, *The Heroin Epidemics*, described all these contagious small-scale processes early on [29]. Risk behaviors may explain part of the pattern in hormonal cancers.

Such behaviors, however, may not totally explain population differentials in hormonal cancer incidences and mortality rates.

We propose an approach that more fully integrates the biocultural processes that shape the development of humans, their cancers, and differentials in both their susceptibility and pathways of disease progression. We begin with Nunney's [37] evolutionary history of cancer, as opposed to more conventional local evolutionary dynamic theories of tumorigenesis within an organism (e.g. [8]). Nunney's analysis suggests that in larger animals, whose lifespans are proportional to about the 4/10 power of their cell count, prevention of cancer in rapidly proliferating tissues becomes more difficult in proportion to their size. Cancer control requires the development of additional mechanisms and systems to address tumorigenesis as body size increases – a synergistic effect of cell number and organism longevity.

As Nunney puts it [37],

> "This pattern may represent a real barrier to the evolution of large, long-lived animals and predicts that those that do evolve... have recruited additional controls [over those of smaller animals] to prevent cancer".

Nunney's work implies, in particular, that different tissues may have evolved markedly different tumor control strategies. All of these, however, are likely to be energetically expensive, permeated with different complex signaling strategies, and subject to a multiplicity of reactions to signals. For modern humans, large animals whose principal selective environment is other

humans, this suggests a critical role for the 'signal' of psychosocial stress, as mediated by a local 'sociocultural network', i.e. an embedding cognitive social structure linked to a cultural practice and history.

Contemporary evolutionary anthropology (e.g. [18]) emphasizes that culture, largely defining what social relations are particularly helpful or stressful, has become inextricably intertwined with human biology. Recent analysis (e.g. [21]) suggests that psychosocial stress is a very strong signal indeed and severally affects the stages of mutation control: immune surveillance, both DNA damage and repair, apoptosis, and rates of somatic mutation – the 'mutator phenotype' we will explore at length below.

Atlan and Cohen [3] and Cohen [12] go even further, finding the immune system is itself cognitive. The immune system compares incoming signals of immune challenge with a stored picture of the world in a kind of immune memory and then chooses a fairly precise response from a much larger repertoire. We have extended this characterization [53, 56] to show how an embedding sociocultural network, the local 'extended family' in which every human finds him or herself, can interact with both an individual's central nervous and immune systems. We characterize this synergism as a 'cognitive condensation' that links social to psychoneuroimmunologic function. According to our analysis, a systematic pattern of externally-imposed stressors constitutes a 'language' that can interact with this condensation. The 'signal' of imposed coherent stress then literally writes a distorted image of itself onto the cognitive condensation, and ultimately onto the functioning of the immune system.

Here we will extend that work to look at the effect of structured external stress on tumorigenesis. We will describe the 'local evolution' of cancer within a tissue in terms of a 'punctuated interpenetration' between a tumorigenic mutator mechanism and an embedding cognitive process of mutation control, including but transcending immune function.

Punctuated biological processes are found up and down temporal scales. Evolutionary punctuation is a modern extension of Darwinian evolutionary theory that accounts for the relative stability of a species' fossil record between the time it first appears and its extinction (e.g. [24]). Species appear 'suddenly' on a geologic timescale, persist relatively unchanged for a fairly long time, and then disappear suddenly, again on a geologic timescale. Evolutionary process is vastly speeded up in tumorigenesis, but we believe it to be subject to a version of 'punctuation' that accounts for the staged nature of the disease.

In essence, the mutation control process constitutes the Darwinian selection pressure determining the fate of the (path dependent) output of the mutator. Externally-imposed structured psychosocial stress then jointly increases mutation rate while decreasing mutation control effectiveness through an additional level of punctuated interpenetration. We envision this as a single, interlinked process, and, extending Nunney's work, find the evolutionary anthropologist Robert Boyd's aphorism that 'culture is as much a part of human biology as the enamel on our teeth' likely true at the level of very basic biological mechanisms.

For human populations, different forms of 'social exposures' can act as carcinogens. Hormonal cancers, since they explicitly involve 'signaling molecules', should be especially amenable to the information dynamics formalism we have adapted to our analysis.

The central mystery we are addressing does not involve such detailed questions as the relationship between metastatic spread and primary tumor size or the like. We are, instead, focusing on the basic biology of population-level differences in disease expression. However, the approach does provide an explanation of the temporally staged nature of cancer, in terms of multiple phase-change-like punctuations.

What we attempt is not without precedence. Adami et al. [1] envision genomic complexity as the amount of information a gene sequence stores about its environment. Something similar can be said of a reverse process: environmental complexity is the amount of information organisms introduce into the environment as a result of their collective actions and interactions [33]. Extending that perspective [57], we have invoked an information theory formalism, imposing invariance under renormalization on the mutual information characterizing the Rate Distortion Theorem applied to Adami's mapping. The result is a description of how a structured environment, through adaptation, literally writes a (necessarily) distorted image of itself onto the genetic structure of an organism in a punctuated manner.

We have adopted a version of Wilson's [60] classic renormalization strategy [51, 52, 54-7] to treat the dynamics of such 'languages-on-networks', finding their punctuated phase-transition splittings and coagulations to represent, respectively, speciation and coevolution. Application of the Rate Distortion and Joint Asymptotic Equipartition Theorems produced a theory whose qualitative behavior was free of the details of the chosen renormalization relations [56, 57]. Here we use those details to extend that theory, as it applies to the interaction of mutating cancer cells and a set of related tumor

control strategies which we infer must be cognitive. This set may include, but likely transcends, Cohen's vision of immune cognition.

An essential character of physical systems subject to phase transition is that they belong to particular 'universality classes'. This means that the exponents of power laws describing behavior at phase transition will be the same for large groups of markedly different systems, with 'natural' aggregations representing fundamental class properties (e.g. [9]).

It is our contention that biological or social systems undergoing phase transition analogs need not be constrained to such classes, and that 'universality class tuning', meaning the strategic alteration of parameters characterizing the renormalization properties of evolutionary punctuation, might well be possible, especially in response to selection pressure or other stressors. Here we focus on the tuning of parameters within a single, given, renormalization relation. Clearly, however, wholesale shifts of renormalization properties in response to adaptation pressure must ultimately be considered as well.

Universality class tuning has been observed in models of 'real world' networks. As Albert and Barabasi [2] put it,

> "The inseparability of the topology and dynamics of evolving networks is shown by the fact that [the exponents defining universality class] are related by [a] scaling relation..., underlying the fact that a network's assembly uniquely determines its topology. However, in no case are these exponents unique. They can be tuned continuously..."

We extend these results to an information dynamics model of the adaptive mutator, with particular emphasis on cancer etiology and the effects of larger embedding cultural structures on population differences in disease incidence and virulence.

The literature on the mutator is vast and growing (see, e.g., [35, 48]). In sum, Thaler [48] finds "...it is conceivable that the mutagenic effects associated with a cell sensing its environment and history could be as exquisitely regulated as transcription...". Thus a structured environment may, in a higher iteration which Tenaillon et al. [49] characterize as 'second-order selection', write itself, in a punctuated manner, onto the very internal workings of evolutionary punctuation itself, with evident implications for understanding tumorigenesis.

We begin with a brief review of the appropriate information dynamics formalism, describe the 'tuning' of evolutionary phase transition, and finally

couple selection pressure to the internal structure of renormalization in a 'natural' iterated punctuation. In short, we model a mutator in its most general nature.

We next speculate that internal cellular mechanisms controlling cancers may be actively cognitive. This cognitive internal process may itself become linked with the structured system of external selection pressures affecting the mutator. The resulting synergism affects tumorigenesis by means of a punctuated interpenetration between a process of 'socio-cellular' cognition and adaptive clonal responses. Culturally crafted, systematic patterns of psychosocial stress are seen as literally writing an image of themselves onto tumorigenesis in a highly plieotropic manner, involving far more than just chronic inflammation. In this we are implicitly critical of currently popular biomedical 'inflammation' models of tumorigenesis which seem reflexively reductionist and distinctly unwilling to confront the full complexities of human biology (e.g. [13]).

Under this revised paradigm, cancer becomes a complicated disease of human ecology, likely to respond at the population level only to multifactorial, multiscale strategies which include redressing patterns of past and continuing social and economic injustice.

Review of formalism

Before beginning the formal treatment, we highlight several important points:

First, information theory is notorious for providing 'existence theorems' whose application is arduous indeed. For example, while the Shannon Coding Theorem implied the possibility of very efficient coding schemes as early as 1949, it took more than forty years for practical 'turbo codes' to be created. Our adaptation of the Shannon Source Coding Theorem is unlikely to be less difficult.

Second, we are invoking information theory variants of the fundamental asymptotic limit theorems of probability. These are independent of exact mechanism, but constrain the collective behavior of such mechanisms. For example, although not all processes involve long sums of individual stochastic variables, those that do, regardless of the individual variable distributions, follow a Normal distribution as a consequence of the Central Limit Theorem. Similarly, the games of chance in a Las Vegas casino are all quite different, but nonetheless the possible success of 'strategies' for playing them

is strongly and systematically constrained by the Martingale Theorem, regardless of game details. We similarly propose that languages-on-networks and languages-that-interact, as a consequence of the limit theorems of information theory, will be subject to regularities of punctuation and 'generalized Onsager relations', regardless of detailed mechanism, as important as the latter may be.

Finally, just as we often impose parametric statistics on sometimes questionable experimental situations, relying on the robustness of the Central Limit Theorem to carry us through, we will invoke a similar heuristic approach in our applications of the information theory limit theorems.

1. Cognition as language Since a large part of our argument revolves about the interaction of cognitive processes with embedding structures represented as information sources, it is first necessary to review how a cognitive process can itself be expressed as an information source.

Atlan and Cohen [3] and Cohen [12] argue that the essence of immune cognition is comparing a perceived antigenic signal with an internal, learned picture of the world in such a way that the comparison evokes one small set of actual immune responses from a vastly larger repertoire of possible such responses. Following the approach of [55, 56], we make a very general model of that process.

Pattern recognition-and-response, as we characterize it, proceeds by convoluting (i.e. comparing) an incoming external 'sensory' antigenic signal with an internal 'ongoing activity' – the 'learned picture of the world' – and, at some point, triggering an appropriate action based on a decision that the sensory signal requires a response. We need not model how the pattern recognition system is 'trained'. Instead, regardless of the particular 'learning paradigm', we will model the general process with the Rate Distortion Theorem. We will, fulfilling Atlan and Cohen's [3] criterion of meaning-from-response, define a language's contextual meaning entirely in terms of system output.

The model is as follows.

A pattern of 'sensory' (e.g. antigenic) input is convoluted (compared) with internal 'ongoing' (e.g. memory) activity to create a path of convoluted signal $x = (a_0, a_1, ..., a_n, ...)$. This path is fed into a highly nonlinear 'decision oscillator' which generates an output $h(x)$ that is an element of one of two (presumably) disjoint sets B_0 and B_1. We take

$$B_0 \equiv b_0, ..., b_k,$$

$$B_1 \equiv b_{k+1}, ..., b_m.$$

Thus we permit a graded response, supposing that if

$$h(x) \in B_0$$

the pattern is not recognized, and if

$$h(x) \in B_1$$

the pattern is recognized and some action $b_j, k+1 \leq j \leq m$ takes place.

We are interested in paths x which trigger pattern recognition-and-response exactly once. That is, given a fixed initial state a_0, such that $h(a_0) \in B_0$, we examine all possible subsequent paths x beginning with a_0 and leading exactly once to the event $h(x) \in B_1$. Thus $h(a_0, ..., a_j) \in B_0$ for all $j < m$, but $h(a_0, ..., a_m) \in B_1$.

For each positive integer n let $N(n)$ be the number of paths of length n which begin with some particular a_0 having $h(a_0) \in B_0$ and lead to the condition $h(x) \in B_1$. We shall call such paths 'meaningful' and assume $N(n)$ to be considerably less than the number of all possible paths of length n – pattern recognition-and-response is comparatively rare. We further assume that the finite limit

$$H \equiv \lim_{n \to \infty} \frac{\log[N(n)]}{n}$$

both exists and is independent of the path x. We will – not surprisingly – call such a pattern recognition-and-response cognitive process *ergodic*.

We may thus define an ergodic information source $\mathbf{X}$ associated with stochastic variates X_j having joint and conditional probabilities $P(a_0, ..., a_n)$ and $P(a_n|a_0, ..., a_{n-1})$ such that appropriate joint and conditional Shannon uncertainties may be defined which satisfy the relations

$$H[\mathbf{X}] = \lim_{n \to \infty} \frac{\log[N(n)]}{n} =$$

$$\lim_{n \to \infty} H(X_n|X_0, ..., X_{n-1}) =$$

$$\lim_{n\to\infty} \frac{H(X_0, ..., X_n)}{n}.$$

We say this information source is *dual* to the ergodic cognitive process.

Different 'languages' will, of course, be defined by different divisions of the total universe of possible responses into different pairs of sets B_0 and B_1, or by requiring more than one response in B_1 along a path. Like the use of different distortion measures in the Rate Distortion Theorem (e.g. [14]), however, it seems obvious that the underlying dynamics will all be qualitatively similar.

Here, meaningful paths – creating an inherent grammar and syntax – are defined entirely in terms of system response, as Atlan and Cohen [3] propose. See [56] for explicit application of this formalism to mathematical models of neural process.

We will eventually parametize the information source uncertainty of this dual information source with respect to one or more variates. We can write $H[\mathbf{K}]$, where $\mathbf{K} \equiv (K_1, ..., K_s)$ represents a vector in an appropriate parameter space. Let the vector $\mathbf{K}$ follow some path in time, i.e. trace out a generalized line or surface $\mathbf{K}(t)$. We will, following the argument of Wallace (2002b), assume that the probabilities defining H, for the most part, closely track changes in $\mathbf{K}(t)$, so that along a particular 'piece' of a path in parameter space the information source remains as close to memoryless and ergodic as is needed for the mathematics to work. Between pieces we impose phase transition characterized by a renormalization symmetry, in the sense of Wilson [60].

We will call such an information source 'piecewise memoryless ergodic'.

Iterating the argument on paths of 'tuned' sets of renormalization parameters gives a second order punctuation in the rate at which primary interacting information sources come to match each other in a distorted manner, the essence of adaptation or interpenetration.

2. Information dynamic phase transitions The essential homology relating information theory to statistical mechanics and nonlinear dynamics has been described elsewhere [42, 51, 52, 57], and we truncate the discussion here, although Feynman [20] shows in great detail that, for certain simple physical systems, the homology is, in fact, an identity.

The definition of the free energy density for a parametized physical system is

$$F(K_1, ...K_m) = \lim_{V \to \infty} \frac{\log[Z(K_1, .., K_m)]}{V}$$

(1)

where the K_j are parameters, V is the system volume and Z is the 'partition function' defined from the energy function, the Hamiltonian, of the system.

For an adiabatically piecewise memoryless ergodic information source [57], the equivalent relation associates source uncertainty with the number of 'meaningful' sequences $N(n)$ of length n, in the limit

$$H[\mathbf{X}] = \lim_{n \to \infty} \frac{\log[N(n)]}{n}.$$

'Meaningful' sequences are those with a high degree of internal serial correlation, having grammar, syntax, and higher order structures, in the limit of 'infinite' length. $H[\mathbf{X}]$ then represents the 'splitting criterion' between small high and much larger low probability sets of sequences, which we call 'paths' (e.g. [17]).

Note that this approach, since it is asymptotic, precludes 'semantic' or 'semiotic' analysis of short symbol sequences.

We appropriately parametize the information source to obtain the crucial expression on which our version of information dynamics will be constructed, writing

$$H[K_1, ..., K_m, \mathbf{X}] = \lim_{n \to \infty} \frac{\log[N(K_1, ..., K_m)]}{n}.$$

(2)

The K_j represent the parameters.

To reiterate, the 'adiabatic' nature of the information source means that probabilities defining H closely track parameter changes, remaining as 'memoryless' as is necessary for the mathematics to work, along a 'piece' of underlying structure. Between such pieces, we impose 'phase transition' regularities described by renormalization dynamics.

While information systems do not have 'Hamiltonians' allowing definition of a 'partition function' and a free energy density, they may have a source uncertainty obeying a limiting relation like that of free energy density. Importing 'renormalization' symmetry gives phase transitions at critical points (or surfaces), and importing a Legendre transform gives dynamic behavior far from criticality.

As neural networks demonstrate so well, it is possible to build larger pattern recognition systems from assemblages of smaller ones. We abstract this process in terms of a generalized linked array of subcomponents that 'talk' to each other in two different ways. These we take to be 'strong' and 'weak' ties between subassemblies. 'Strong' ties are, following arguments from sociology [25], those which permit disjoint partition of the system into equivalence classes. The strong ties are associated with some reflexive, symmetric, and transitive relation between components. 'Weak' ties do not permit such disjoint partition. In a physical system these might be viewed, respectively, as 'local' and 'mean field' coupling.

We are, thus, concerned with languages 'spoken' on an underlying network, be it chemical, neural, social, ecological, or some mix of these. The network will be manifest in the properties of any language 'spoken' on it, and vice versa, if language process can affect network properties. It is this composite, interactive phenomenon we wish to model.

We fix the magnitude of strong ties, but vary the index of weak ties between components, which we call P, taking $K = 1/P$.

We assume the ergodic information source depends on three parameters, two explicit and one implicit. The explicit are K as above and an 'external field strength' analog J, which gives a 'direction' to the system. We may, in the limit, set $J = 0$.

The implicit parameter, which we call r, is an inherent generalized 'length' on which the phenomenon, including J and K, are defined. That is, we can write J and K as functions of averages of the parameter r, which may be quite complex, having nothing at all to do with conventional ideas of space; for example the degree of niche partitioning in ecosystems or separation in social structures.

For a given generalized language of interest with a well defined ergodic source uncertainty H we write

$$H[K, J, \mathbf{X}]$$

Imposition of invariance of H under a renormalization transform in the implicit parameter r leads to expectation of both a critical point in K, which we call K_C, reflecting a phase transition to or from collective behavior across the entire array, and of power laws for system behavior near K_C. The addition of other parameters to the system, e.g. some V, results in a 'critical line' or surface $K_C(V)$.

Let $\kappa = (K_C - K)/K_C$ and take χ as the 'correlation length' defining the average domain in r-space for which the information source is primarily dominated by 'strong' ties. We begin by averaging across r-space in terms of 'clumps' of length R. Then, taking Wilson's [60] physical analog as a starting point, we choose the renormalization relations as

$$H[K_R, J_R, \mathbf{X}] = f(R)H[K, J, \mathbf{X}]$$

$$\chi(K_R, J_R) = \frac{\chi(K, J)}{R},$$

(3)

with $f(1) = 1$ and $J_1 = J, K_1 = K$. The first of these equations states that 'processing capacity,' as indexed by the source uncertainty of the system, the 'richness' of the generalized language, grows monotonically as $f(R)$. The second just states that the correlation length simply scales as R. The first equation significantly generalizes Wilson's approach. First, since both $H[K_R, J_R]$ and $H[K, J]$ are dimensionless, $f(R)$ must itself be dimensionless. This is most easily done by assuming that we replace R with R/R_0, where R_0 is some 'characteristic length' of the system for which renormalization is a reasonable procedure. We then set $R_0 \equiv 1$, thus measuring in units of R_0. Wilson's equation (4) states that free energy density remains constant during renormalization: If $F[K_R, J_R]$ is the free energy of the clumped system,

and $F[K, J]$ the free energy density independent of renormalization, then $F[K, J] = R^{-3}F[K_R, J_R]$, or

$$F[K_R, J_R] = R^3 F[K, J].$$

Thus $f(R)$=R^3 for the free energy of a physical system, so that the free energy density remains constant with increasing R.

Here we assume that, as a network grows in size, language richness grows as some appropriate function of that size, but not, like free energy, as its cube. Thus other, (sometimes very subtle), symmetry relations – not necessarily based on the elementary physical analog we use here – may well be possible. For example [36, p.168] describes the highly counterintuitive renormalization relations needed to understand phase transition in simple 'chaotic' systems, an example we will revisit below. This is an important subject for future research, since we suspect that biological or social systems may alter their renormalization properties wholesale, and not merely the parameters associated with a particular renormalization.

The 'richness' of a biological 'language' is not likely to grow exponentially with increase in size of the system, rather it is likely to follow a much smaller rate of rise, or even approach an asymptotic limit. We explore more biologically reasonable forms of $f(R)$ in the Appendix, including

$$f(R) = m \log(R) + 1$$

$$f(R) = \exp[m(R - 1)]$$

$$f(R) = \exp[m(R - 1)/R].$$

The latter expression represents a system having a crude upper asymptotic limit. More realistic 'S'-shaped curves take us, unfortunately, beyond our ability to solve the renormalization equations at this point. Again, we have written a shorthand for dimensionless adjustment by the 'characteristic length' R_0, i.e. $f(R) \to f(R/R_0)$.

Using the simplest physical analog as a starting point, we take $f(R) = R^d$, for some real $d > 0$. See [9, 60] for details. Limiting K to a region near the 'critical value' K_C, if $J \to 0$, a simple series expansion and some clever algebra [9, 60] gives

$$H = H_0 \kappa^{\alpha}$$

(4)

where α is a positive constant. Again, more biologically relevant examples are presented in the Appendix.

Further from the critical point matters are more complicated, involving 'Generalized Onsager Relations' and a kind of thermodynamics associated with a Legendre transform [56].

An essential insight is that *regardless of the particular renormalization properties, sudden critical point transition is possible in the opposite direction for this model.* That is, we also can move from a number of independent, isolated and fragmented systems operating individually and more or less at random, into a single large, interlocked, coherent structure, once the parameter K, the inverse strength of weak ties, falls below threshold, or, conversely, once the strength of weak ties parameter $P = 1/K$ becomes large enough.

Thus, increasing nondisjunctive weak ties between them can bind several different 'languages' into a single, embedding hierarchical metalanguage which contains each as a linked subdialect.

This heuristic insight can be made exact using a rate distortion approach (or, more generally, using the Joint Asymptotic Equipartition Theorem). The argument goes as follows [56, 57]:

Suppose that two ergodic information sources $\mathbf{Y}$ and $\mathbf{B}$ begin to interact, to 'talk' to each other, i.e. to influence each other in some way so that it is possible, for example, to look at the output of $\mathbf{B}$ – strings b – and infer something about the behavior of $\mathbf{Y}$ from it – strings y. We suppose it possible to define a retranslation from the B-language into the Y-language through a deterministic code book, and call $\hat{\mathbf{Y}}$ the translated information source, as mirrored by $\mathbf{B}$.

Take some distortion measure d comparing paths y to paths $\hat{y}$, defining $d(y, \hat{y})$ [14]. We invoke the Rate Distortion Theorem's mutual information $I(Y, \hat{Y})$, which is the splitting criterion between high and low probability pairs of paths. Impose, now, a parametization by an inverse coupling strength

K, and a renormalization symmetry representing the global structure of the system coupling. This may be much different from the renormalization behavior of the individual components. If $K < K_C$, where K_C is a critical point (or surface), the two information sources will be closely coupled enough to be characterized as condensed.

Wallace and Wallace [51, 52] use this technique to address speciation, coevolution and group selection in a relatively unified fashion. These papers, and [56, 59], further describe how biological or social systems might respond to gradients in information source uncertainty and related quantities when the system is away from phase transition. Language-on-network systems, as opposed to physical systems, appear to diffuse away from concentrations of an 'instability' construct related to a Legendre transform of information source uncertainty. This is much the same way entropy is the Legendre transform of free energy density in a physical system. The parametized 'instability', $Q[K]$, is defined from the principal splitting criterion by the relation

$$Q[K] = -KdH[K]/dK$$

$$Q[K] = -KdI[K]/dK.$$

(5)

$H[K]$ is the information source uncertainty in the Asymptotic Equipartition Theorem and $I[K]$ the mutual information in the Rate Distortion and Joint Asymptotic Equipartition Theorems, describing the cross-talk between two information sources.

Universality class tuning

We suppose that a structured environment, which we take itself to be an appropriately regular information source $\mathbf{Y}$, 'engages' a modifiable system through selection pressure, and begins to write itself on that system's genetic sequences or other internal structures in a distorted manner permitting definition of a mutual information $I[K]$ splitting criterion according to

the Rate Distortion or Joint Asymptotic Equipartition Theorems. K is an inverse coupling parameter between system and environment [56, 57]. According to our development, at punctuation – near some critical point K_C – the systems begin to interact very strongly indeed, and we may write, near K_C, taking as the starting point the simple physical model of equation (4),

$$I[K] \approx I_0[\frac{K_C - K}{K_C}]^{\alpha}.$$

For a physical system α is fixed, determined by the underlying 'universality class'. Here we will allow α to vary, and, in the section below, to itself respond explicitly to selection pressure.

Normalizing K_C and I_0 to 1, we obtain,

$$I[K] \approx (1 - K)^{\alpha}.$$

(6)

The horizontal line $I[K] = 1$ corresponds to $\alpha = 0$, while $\alpha = 1$ gives a declining straight line with unit slope which passes through 0 at $K = 1$. Consideration shows there are progressively sharper transitions between the necessary zero value at $K = 1$ and the values defined by this relation for $0 < K, \alpha < 1$. The rapidly rising slope of transition with declining α is, we assert, of considerable significance.

The instability associated with the splitting criterion $I[K]$ is defined by

$$Q[K] \equiv -KdI[K]/dK = \alpha K(1 - K)^{\alpha - 1},$$

(7)

and is singular at $K = K_C = 1$ for $0 < \alpha < 1$. Following [51, 52, 56, 59], we interpret this to mean that values of $0 < \alpha \ll 1$ are highly unlikely

for real systems, since $Q[K]$, in this model, represents a kind of barrier for information systems.

On the other hand, smaller values of α mean that the system is far more efficient at responding to the adaptive demands imposed by the embedding structured ecosystem, since the mutual information which tracks the matching of internal response to external demands, $I[K]$, rises more and more quickly toward the maximum for smaller and smaller α as the inverse coupling parameter K declines below $K_C = 1$. That is, *systems able to attain smaller α are more adaptive than those characterized by larger values*, in this model, but smaller values will be hard to reach, and can probably be done so only at some considerable physiological or other cost.

Again, more biologically realistic renormalization strategies – based on different forms of $f(R)$ – are given in the Appendix. These produce sets of several parameters defining the 'universality class', one of whose tuning gives behavior much like that of α in this simple example.

We iterate the phase transition argument on this calculation to obtain our version of the mutator, focusing on 'paths' of universality classes.

The adaptive mutator and cognitive mutation control

Suppose the renormalization properties of a biological or social language-on-a network system at some 'time' k are characterized by a set of parameters $A_k \equiv \alpha_1^k, ..., \alpha_m^k$. Fixed parameter values define a particular universality class for the renormalization. We suppose that, over a sequence of 'times', the universality class properties can be characterized by a path $x_n = A_0, A_1, ..., A_{n-1}$ having significant serial correlations which, in fact, permit definition of an adiabatically piecewise memoryless ergodic information source associated with the paths x_n. We call that source $\mathbf{X}$.

We further suppose, in the usual manner [56, 57], that external selection pressure is also highly structured, and forms another information source $\mathbf{Y}$ which interacts not only with the system of interest globally, but specifically with its universality class properties as characterized by $\mathbf{X}$. $\mathbf{Y}$ is necessarily associated with a set of paths y_n.

We pair the two sets of paths into a joint path, $z_n \equiv (x_n, y_y)$ and invoke an inverse coupling parameter, K, between the information sources and their paths. This leads, by the arguments above, to phase transition punctuation of $I[K]$, the mutual information between $\mathbf{X}$ and $\mathbf{Y}$, under either the Joint Asymptotic Equipartition Theorem or under limitation by a distortion measure, through the Rate Distortion Theorem [14]. Again, see [56, 57] for more

details of the argument. The essential point is that $I[K]$ is a splitting criterion under these theorems, and thus partakes of the homology with free energy density we have invoked above.

Activation of universality class tuning, our version of the mutator, then becomes itself a punctuated event in response to increasing linkage between organism and externally imposed selection or other pressure.

To reiterate slightly, Thaler [48] has suggested that the mutagenic effects associated with a cell sensing its environment and history could be as exquisitely regulated as transcription. Our invocation of the Rate Distortion or Joint Asymptotic Equipartition Theorems in address of the mutator necessarily means that mutational variation comes to significantly reflect the grammar, syntax, and higher order structures of the embedding processes. This involves far more than a simple 'colored noise' – stochastic excursions about a deterministic 'spine' – and most certainly implies the need for exquisite regulation. We have thus provided a deep information theory argument for Thaler's speculation.

In the same paper Thaler further argues that the immune system provides an example of a biological system which ignores conceptual boundaries between development and evolution. Elsewhere [53, 56] we explore the immune system from I.R. Cohen's information theory perspective on immune cognition. While evolutionary phenomena are not cognitive in the sense of the immune system, they may still significantly interact with development. The very reproductive mechanisms of a cell, organism, or organization may become closely coupled with structured external selection pressure in a manner recognizably analogous to 'ordinary' punctuated evolution.

Thaler [48] specifically examines the meaning of the mutator for the biology of cancer, which, like the immune system it defies, is seen as involving both development and evolution. In our version of the mechanism, the sudden phase transition-like change in the mutual information $I[K]$ at K_C might represent an initiating event, while subsequent closely linked paths that lead to malignancy could be considered a series of promoting phase transitions. In reality, there would seem to be a single, undifferentiated, interlinked process representing the staged failure of a cellular cognitive control strategy which can itself become convoluted with systems of structured external stressors affecting the mutator. We expand on this point:

Various authors have argued for 'non-reductionist' approaches to tumorigenesis (e.g.[6, 50]), including psychosocial stressors as inherent to the process [21]. What is clear is that, once a mutation has occurred, multiple systems

must fail for tumorigenesis to proceed. It is well known that processes of DNA repair (e.g. [40, 46]), programmed cell death – apoptosis – (e.g. [19]), and immune surveillance (e.g. [26, 47]) all act to redress cell mutation. The immune system is known to be cognitive, and equipped with an array of possible remediations [3, 12]. It is, then, possible to infer a larger, jointly-acting 'mutation control' process incorporating these and other cellular, systemic, and social mechanisms. This clearly must involve comparison of developing cells with some internal model of what constitutes a 'normal' pattern, followed by a choice of response: none, repair, programmed cell death, or full-blown immune attack. The comparison with an internal picture of the world, with a subsequent choice from a response repertoire, is, as [15, 31] point out, the essence of cognition.

We are, then, led to propose, in the sense of [56, 57] that a mutual information may be defined characterizing the interaction of a structured system of external selection pressures with the 'language' of cellular cognition effecting mutation control. Under the Joint Asymptotic Equipartition or Rate Distortion Theorems, that mutual information constitutes a splitting criterion for pairwise linked paths which may itself be punctuated and subject to sudden phase transitions.

We thus speculate that structured external stress can become jointly and synergistically linked both with cell mutation and with the cognitive process which attempts to redress cell mutation, enhancing the former, degrading the latter, and significantly raising the probability of successful tumorigenesis.

Elsewhere [54] we argue that the staged nature of chronic infectious diseases like malaria, HIV, and tuberculosis represents an information-dynamic punctuated version of biological interpenetration, in the sense of [33], between a cognitive 'immunocultural condensation' and an adaptive pathogen. Here we suggest that a larger system of socio-cellular cognition related to the detection and correction of mutation forms an embedding context of adaptation pressures for mutating clones of defective cells (e.g. [8]). Subsequent learning plateau-analog phase transitions of evolutionary punctuation, in the sense of [57], constitute the many stages of cancer.

Psychosocial stress and tumorigenesis

As we discuss elsewhere [56, 57], structured psychosocial stress constitutes a determining context for immune cognition or, more generally, the immunocultural condensation. Here we enlarge the perspective to processes

of cognitive cellular mutation control. We wish to analyze the way structured stress affects the interaction between cognitive mutation control (CMC) and an adaptive mutator, the principal line of defense against the CMC for a growing tumor. To do this we extend the theory to three interacting information sources.

The Rate Distortion and Joint Asymptotic Equipartition Theorems are generalizations of the Shannon-McMillan Theorem which examine the interaction of two information sources, with and without the constraint of a fixed average distortion. We conduct one more iteration, and require a generalization of the SMT in terms of the splitting criterion for triplets as opposed to single or double stranded patterns. The tool for this is at the core of what is termed *network information theory* [14, Theorem 14.2.3]. Suppose we have three (piecewise adiabatically memoryless) ergodic information sources, Y_1, Y_2 and Y_3. We assume Y_3 constitutes a critical embedding context for Y_1 and Y_2 so that, given three sequences of length n, the probability of a particular triplet of sequences is determined by *conditional probabilities with respect to* Y_3:

$$P(Y_1 = y_1, Y_2 = y_2, Y_3 = y_3) =$$

$$\Pi_{i=1}^{n} p(y_{1i}|y_{3i}) p(y_{2i}|y_{3i}) p(y_{3i}).$$

(8)

That is, Y_1 and Y_2 are, in some measure, driven by their interaction with Y_3

Then, as per our previous analyses, triplets of sequences can be divided by a splitting criterion into two sets, having high and low probabilities respectively. For large n the number of triplet sequences in the high probability set will be determined by the relation [14, p. 387]

$$N(n) \propto \exp[nI(Y_1; Y_2|Y_3)],$$

(9)

where splitting criterion is given by

$$I(Y_1; Y_2|Y_3) \equiv$$

$$H(Y_3) + H(Y_1|Y_3) + H(Y_2|Y_3) - H(Y_1, Y_2, Y_3)$$

We can then examine mixed cognitive/adaptive phase transitions analogous to learning plateaus [57] in the splitting criterion $I(Y_1, Y_2|Y_3)$, which characterizes the synergistic interaction between structured psychosocial stress, the CMC, and the tumor's adaptive mutator. These transitions delineate the various stages of tumorigenesis, which are embodied in the slowly varying 'piecewise adiabatically memoryless ergodic' phase between transitions.

Discussion and conclusions

We have applied an elaborate mathematical modeling strategy to the problem of disparities in occurrence and progression of certain cancers between powerful and marginal subgroups. As the ecologist E.C. Pielou has argued [40, p. 106], a severe methodological limit to any such approach is that mathematical models do not create new knowledge, they create new speculation, even when they appear to fit available data quite well. Their often considerable utility lies almost entirely in raising questions for subsequent empirical study, which, in a scientific context, is the only true source of new knowledge.

The speculations emerging from our model are of some interest.

We have expressed tumorigenesis in terms of a synergistic linkage of a 'language' of structured external stress with the adaptive mutator and its opposing cognitive process, mutation control.

Raised rates of cellular mutation which quite literally reflect biocultural selection pressure through Ademi's distorted mirror do not fit a cognitive paradigm: The adaptive mutator may propose, but selection disposes. However, the effect of structured stress on both the mutator and on mutation control, which itself constitutes the selection pressure facing a clone of mutated cells, connects the mechanisms. Subsequent multiple evolutionary 'learning

plateaus' [57] representing the punctuated interpenetration between mutation control and clones of mutated cells constitute the stages of disease. Such stages arise in the context of an embedding culture which, to use a Rate Distortion argument, literally writes an image of itself on all aspects of the disease.

The synergistic effects of structured external stress on both mutation and the selection pressure facing mutated cell clones implies that reductionist magic bullets and 'life style' approaches will be of severely limited effect for marginalized human populations in the absence of highly proactive socioeconomic, political, and related interventions. Cancer plays a multidimensional chess across interacting levels of biological and social organization. To counter cancer, we'll need to play the same. Only in the full context of such broad 'biological control' can individual-oriented strategies contribute significant impact.

'Social exposures' are far more than incidental cofactors in tumorigenesis: adapting Boyd's aphorism, we claim that 'culture is as much a part of hormonal cancer as are oncogenes'.

Our speculations are consistent with, but suggest extension of, a growing body of research. Kiecolt-Glaser et al. [31], for example, discuss how chronic inflammation related to chronic stress has been linked with a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type II diabetes, certain cancers, and other conditions. Dalgleish and others [15, 16, 38, 41] have argued at length that chronic immune activation and inflammation are closely related to the etiology of cancer and other diseases. As Balkwill and Mantovani [4] put the matter, "If genetic damage is the 'match that lights the fire' of cancer, some types of inflammation may provide 'fuel that feeds the flames' ".

Dalgleish [15] has suggested application of non-linear mathematics to examine the role of immune response in cancer etiology, viewing different phenotypic modes of the immune system – the Th1/Th2 dichotomy – as 'attractors' for chaotic processes related to tumorigenesis, and suggests therapeutic intervention to shift from Th2 to Th1. We view such a shift in phenotype as a phase transition.

Our analysis implies a complicated and subtle biology for human cancer, one in which external cultural 'messages' become convoluted with both pathogenic clone mutation and with an opposing, and possibly organ-specific, variety of tumor control strategies. In the face of such a biology, anti-inflammants [13] and other 'magic bullet' interventions appear inadequate,

particularly for the hormonal cancers which seem to especially characterize the contrast in power relations between groups.

Although chronic inflammation, related certainly to structured psychosocial stress, is likely to be a contributor to the enhancement of pathological mutation and the degradation of corrective response, we do not believe it to be the only such trigger. The constant cross-talk between central nervous, hormonal, immune, and tumor control systems guarantees that the 'message' of culturally constructed external stress will write itself upon the full realm of individual physiology in a highly plieotropic manner, with multifactorial impact on both cell clone mutation and tumor control.

This suggests in particular that, while anti-inflammants may indeed be of benefit for individual cases, on the whole, population-level death rates from certain classes of cancer and the related disease guild of 'inflammatory' chronic diseases will continue to express an image of imposed patterns of 'pathogenic social hierarchy' and related deprivations (e.g. [34]). In particular, anti-inflammant 'magic bullet' therapies will not be effective in reducing population-level health disparities.

It is clear, however, that amelioration of 'structured patterns of stress' through legislation and public policy should be a priority if we are truly serious in addressing those disparities. Such a program would greatly benefit both powerful and marginalized groups, since cultural patterns of deprivation, discrimination, and pathogenic social hierarchy necessarily enmesh all.

Appendix: 'Biological' renormalizations

Here we provide examples of 'non-physical' renormalization schemes which may have relevance to biological or social phenomena. To reiterate, equation (3) above states that the information source and the correlation length, the degree of coherence on the underlying network, scale under renormalization clustering in chunks of size R as, after slight rearrangement,

$$H[K_R, J_R]/f(R) = H[J, K]$$

$$\chi[K_R, J_R]R = \chi(K, J),$$

with $f(1) = 1, K_1 = K, J_1 = J$.

Differentiating these two equations with respect to R, so that the right hand sides are zero, and solving for dK_R/dR and dJ_R/dR gives, after some consolidation, expressions of the form

$$dK_R/dR = u_1 d\log(f)/dR + u_2/R$$

$$dJ_R/dR = v_1 J_R d\log(f)/dR + \frac{v_2}{R} J_R.$$

(10)

The $u_i, v_i, i = 1, 2$ are functions of K_R, J_R, but not explicitly of R itself.

We expand these equations about the critical value $K_R = K_C$ and about $J_R = 0$, obtaining

$$dK_R/dR = (K_R - K_C) y d\log(f)/dR + (K_R - K_C) z/R$$

$$dJ_R/dR = w J_R d\log(f)/dR + x J_R/R.$$

(11)

The terms $y = du_1/dK_R|_{K_R=K_C}, z = du_2/dK_R|_{K_R=K_C}, w = v_1(K_C, 0), x = v_2(K_C, 0)$ are constants.

Solving the first of these equations gives

$$K_R = K_C + (K - K_C) R^z f(R)^y,$$

(12)

again remembering that $K_1 = K, J_1 = J, f(1) = 1$.

Wilson's essential trick is to iterate on this relation, which is supposed to converge rapidly [9, 60], assuming that for K_R near K_C, we take

$$K_C/2 \approx K_C + (K - K_C)R^z f(R)^y.$$

(13)

We next proceed in two steps, first solving this for $f(R)$ in terms of known values, and then solving for R, finding a value R_C which we then substitute into the first of equations (3) to obtain an expression for $H[K, 0]$ in terms of known functions and parameter values.

The first step gives the general result

$$f(R_C) \approx \frac{[(KC/(KC - K))]^{1/y}}{2^{1/y} R_C^{z/y}}.$$

(14)

Solving this for R_C and substituting into the first of equation(3) gives

$$H[K, 0] \approx \frac{H[K_C/2, 0]}{f(R_C)} = \frac{H_0}{f(R_C)}$$

$$\chi(K, 0) \approx \chi(K_C/2, 0)R_C = \chi_0 R_C$$

(15)

which are the essential relationships.

If we take $f(R) = R^m$, where $m > 0$ may be non-integral and very small, representing the geometry of a 'fractal' network, we can solve equation (16) for R_C as

$$R_C = \frac{[KC/(KC-K)]^{1/(my+z)}}{2^{1/(my+z)}}$$

(16)

Note that, for given y, m and z could be characterized by a "universality class relation" of the form $\alpha = my + z =$ constant. Note that nothing in the development prevents α from being continuously tunable.

Substituting this value for R_C back into equation (15) gives a somewhat more complex expression for H than equation (4), having three parameters, i.e. m, y, z. Fixing m, z and K_C, some exploration shows that tuning y gives results qualitatively similar to those of equations (6) and (7). The exercise is best done in a symbolic mathematics program.

If we make the more biologically reasonable assumption of logarithmic growth, so that

$$f(R) = m \log(R) + 1,$$

(17)

with $f(1) = 1$, then plugging in to equation (14) and solving for R_C in Mathematica 4.2 gives

$$R_C = [\frac{Q}{LambertW[Q \exp(z/my)]}]^{y/z},$$

(18)

where

$$Q \equiv [(z/my)2^{-1/y}[KC/(KC-K)]^{1/y}].$$

The transcendental function LambertW(x) is defined by the relation

$$LambertW(x)\exp(LambertW(x)) = x$$

and is found in the computer algebra program Mathematica, where it is called the ProductLog. It arises in the theory of random networks and in renormalization strategies for quantum field theories.

Fixing K_C, m and z, and tuning y again gives behavior recognizably similar to the simple development of surrounding equatuin (7) above, an exercise likewise best carried out through a symbolic mathematics program.

An asymptotic relation for $f(R)$, rising toward a finite limit with increase in R, would be of particular biological interest, implying that 'language richness' increases to a limiting value with population growth, in a loose sense. Such a pattern is broadly consistent with calculations of the degree of allelic heterozygosity as a function of population size in the context of a balance between genetic drift and neutral mutation [27. 41]. Taking

$$f(R) = \exp[m(R-1)/R]$$

(19)

gives a system which begins at 1 when $R = 1$, and approaches the asymptotic limit $\exp(m)$ as $R \to \infty$. Mathematica 4.2 finds

$$R_C = \frac{my/z}{LambertW[L]},$$

(20)

where

$$L \equiv (my/z)\exp(my/z)[2^{1/y}[KC/(KC-K)]^{-1/y}]^{y/z}.$$

If we take $f(R)$ to be proportional to the approximate number of prime numbers less than R, i.e. $f(R) = mR/\log(R)$, then, using Mathematica 4.2, we obtain

$$R_C =$$

$$[\frac{-2^{-1/y}[(KC/(KC-K)]^{1/y} yLambertW[(-2^{1/y}[KC/(KC-K)]^{-1/y})[m(y+z)/y]]}{m(y+z)}]^{y/(y+z)}.$$

(21)

The exponential relation $f(R) = \exp[m(R-1)]$ gives

$$R_C =$$

$$\frac{zLambertW[\exp(my/z)[(2^{-1/y}(KC/(KC-K))^{1/y}]^{y/z}(my/z)]}{my}.$$

(22)

The reader is encouraged to complete an exercise, solving for R_C using a normally distributed $f(R) = R^m$, i.e. $< f(R) >= R^{<m>}\exp[(1/2)(\log(R^\sigma))^2]$.

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