

# CULTURE AND CANCER

Rodrick Wallace

The New York State Psychiatric Institute

Deborah Wallace

Joseph L. Mailman School of Public Health, Columbia University

Robert G. Wallace

City University of New York\*

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## Abstract

Genetic mechanisms, since they broadly involve information transmission, should be translatable into information dynamics formalism. From this perspective we reconsider the adaptive mutator, one possible means of ‘second order selection’ by which a highly structured ‘language’ of environment and development writes itself onto the variation upon which evolutionary selection and tumorigenesis operate. Our approach uses recent results in the spirit of the Large Deviations Program of applied probability that permit transfer of phase transition approaches from statistical mechanics to information theory, generating evolutionary and developmental punctuation in what we claim to be a highly natural manner.

Allowing ‘universality class tuning’ of the phase transition-analog generates a mutator by altering the rate at which an internal genetic picture of adaptive pressures comes to match them. The analysis has particular implications for understanding cancer etiology, as the collection of cellular and other mechanisms which limits tumorigenesis

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\*Address correspondence to: Rodrick Wallace, PISCS Inc., 549 W. 123 St., Suite 16F, New York, NY, 10027. Telephone (212) 865-4766, email rdwall@ix.netcom.com. Affiliations are for identification only. This material has been submitted for publication and is protected by copyright.

may be actively cognitive, and thus become linked with an embedding system of structured stress, in contrast to evolutionary process which passively reflects selection pressures in a distorted way. The punctuated interpenetration between this ‘socio-cellular’ cognition and tumorigenic clonal adaptation then accounts for the staged nature of the disease.

‘Social exposures’ are, for human populations, far more than simply incidental cofactors in the etiology of cancer, jointly affecting both rates of mutation and the failure of cognitive processes of mutation control. Evolutionary anthropologist Robert Boyd’s metaphorical aphorism that ‘culture is as much a part of human biology as the enamel on our teeth’ appears to be literally true at a very basic level.

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

## Introduction

Adami et al. (2000) 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 (Lewontin, 2000). Extending that perspective (Wallace, 2002b), 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.

Arguing by abduction from physical theory, to use Hodgson’s (1993) terminology, we adopted a version of Wilson’s (1971) classic renormalization strategy (Wallace and Wallace, 1998, 1999; Wallace, 2000, 2002a, b) to treat the dynamics of such ‘languages-on-networks’, finding their punctuated 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 (Wallace, 2002a, b). Here we use those details to extend that theory.

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. For example, Xenon, binary fluids and  $\beta$ -brass fall in one such class, while Helium 4, Iron, and Nickel fall into another (e.g. Binney, 1986).

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 be considered as well, and will be the subject of future analysis.

Universality class tuning has been observed in models of ‘real world’ networks. As Albert and Barabasi (2002) 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 will extend these results to other phenomena, in particular an information dynamics model of the adaptive mutator mechanism that has been proposed as a means for escaping local optima in fitness landscapes. We explore the model’s implications for understanding both evolutionary process and cancer etiology.

The literature on the mutator is vast and growing (see, e.g., Thaler, 1999 and Magnasco and Thaler, 1996). In sum, Thaler (1999) 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 Tenailon et al. (2001) characterize as ‘second-order selection’, write itself, in a punctuated manner, onto the very internal workings of evolutionary punctuation itself.

This has evident implications for understanding both evolutionary process and cancer tumorigenesis.

We begin with a brief review of the 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, producing a mutator.

We speculate that internal cellular mechanisms controlling cancers may be actively cognitive, in distinct contrast to evolutionary process which reflects imposed selection pressures, in the sense of Adami et al. (2000). This cognitive internal process, which includes but transcends Cohen’s (2000) immune cognition, may then itself become linked with the structured system of external selection pressures affecting the mutator, with synergistic impact on a tumorigenesis which we model as a punctuated interpenetration between a process of ‘socio-cellular’ cognition and adaptive clonal responses.

Cancer then becomes even more explicitly a complicated disease of human ecology which is likely to respond at the population level only to multifactorial, multiscale strategies including redressing patterns of past and continuing social and economic injustice. Franz Fanon (1966) has made a similar case for ‘behavioral’ and mental disorder, and we have argued that analogous mechanisms entrain immune system function (Wallace, 2002a).

### **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.

The essential homology relating information theory to statistical mechanics and nonlinear dynamics has been described elsewhere (Wallace and Wallace, 1998, 1999; Rojdestevnski and Cottam, 2000; Wallace, 2000, 2002a, b), and we truncate the discussion here.

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

$$F(K_1, \dots, K_m) = \lim_{V \rightarrow \infty} \frac{\log[Z(K_1, \dots, K_m)]}{V} \quad (1)$$

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 (Wallace, 2002b), the equivalent relation associates source uncertainty with the number of ‘meaningful’ sequences  $N(n)$  of length  $n$ , in the limit

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

‘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. Dembo and Zeitouni, 1998).

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

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

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

(2)

The  $K_j$  represent the parameters.

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. See Wallace (2002a, b) for further discussion.

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 in a ‘natural’ manner 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 which ‘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 (Granovetter, 1973), those which permit disjoint partition of the system into equivalence classes. Thus 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  $K_C$ . 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  $\chi$  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, following Wilson’s (1971) physical analog, 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 which represents the ‘richness’ of the generalized language, grows monotonically as  $f(R)$ , while the second just states that the correlation length simply scales as  $R$ .

Other, very subtle, symmetry relations – not necessarily based on the elementary physical analog we use here – may well be possible. For example McCauley, (1993, 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.

For a simple physical system,  $H$  is energy and  $f(R)$  is the power law  $f(R) = R^3$ . See Wilson (1971) or Binney et al. (1986) for details. Taking  $K$  near the ‘critical value’  $K_C$ , if  $J \rightarrow 0$ , a simple series expansion and some clever algebra (Wilson, 1971; Binney et al., 1986) gives

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

(4)

where  $\alpha$  is a positive constant. 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 (Wallace, 2002a).

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, 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 ‘language’ processes into a single, embedding hierarchical metalanguage which contains each as a linked subdialect.

This heuristic insight can be made exact using a rate distortion argument (or, more generally, using the Joint Asymptotic Equipartition Theorem). The argument goes as follows (Wallace, 2002a, b):

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  $d(y, \hat{y})$  (Cover and Thomas, 1991). 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 parametrization 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 (1998, 1999) use this kind of approach to address speciation, coevolution and group selection in a relatively unified fashion. These papers, and those of Wallace and Fullilove (1999) and Wallace (2002a), 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 which is related to a Legendre transform of information source uncertainty, in much the same way entropy is the Legendre transform of free

energy density in a physical system. The parameterized ‘instability’,  $Q[K]$ , is defined from the principal splitting criterion by the relation

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

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

(5)

where  $H[K]$  and  $I[K]$  are, respectively, information source uncertainty or mutual information in the Asymptotic Equipartition, Rate Distortion, or Joint Asymptotic Equipartition Theorems.

### 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 (Wallace 2002a, b). 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),

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

For a physical system  $\alpha$  is fixed, determined by the underlying ‘universality class’. Here we will allow  $\alpha$  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  $\alpha$  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 Wallace and Wallace (1998), Wallace and Fullilove (1999) and Wallace (2002a), 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  $\alpha$  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  $\alpha$  as the inverse coupling parameter  $K$  declines below  $K_C = 1$ . That is, *systems able to attain smaller  $\alpha$  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.

More biologically realistic renormalization strategies are given in the Appendix, producing sets of several parameters defining the ‘universality class’, one of whose tuning gives behavior much like that of  $\alpha$  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  $A_k \equiv \alpha_1^k, \dots, \alpha_m^k$ . 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  $x_n = A_0, A_1, \dots, A_{n-1}$  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 (Wallace, 2002a, b), 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,  $z_n \equiv (x_n, y_n)$  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 (Cover and Thomas, 1991). Again, see Wallace (2002a, b) 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 which 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.

Thaler (1999) 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

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 that separate development from evolution. Elsewhere (Wallace and Wallace, 2002; Wallace, 2002a) we explore the immune system at great length 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 partake of a significant interaction with development, in which the very reproductive mechanisms of a cell, organism, or organization become closely coupled with structured external selection pressure in a manner recognizably analogous to ‘ordinary’ punctuated evolution.

Thaler (1999) specifically examines the meaning of the mutator for the biology of cancer, which, like the immune system, 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. Waliszewski, Molski and Konarski, 1998; Baversotck, 2000), and even for psychosocial stressors as being inherent to the process (Forlenza and Baum, 2000). 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. Snow, 1997; Bootsma and Hoeijmakers, 1993), programmed cell death – apoptosis – (e.g. Evan and Littlewood, 1998), and immune surveillance (e.g. Herberman, 1995; Somers and Guillou, 1994) all act to redress cell mutation. The immune system is known to be cognitive, and equipped with an array of possible remediations (Atlan and Cohen, 1998; Cohen, 2000). It is, then, possible to infer a larger, jointly-acting ‘mutation control’ process incorporating these and other cellular, systemic and possibly 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 Atlan and Cohen (1998) and Cohen (2000) point out, the essence of cognition.

We are, then, led to propose, in the sense of Wallace (2002a, b) 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 in a highly punctuated manner 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 (Wallace and Wallace, 2002b) 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 Lewontin (2000), between a cognitive ‘immunocultural condensation’ and an adaptive pathogen. Here we suggest that a larger system of socio-cellular cognition – including but transcending immune function – forms an embedding context of adaptation pressures for mutating clones of defective cells (e.g. Bertram, 2001). Subsequent learning plateau-analog phase transitions of evolutionary punctuation, in the sense of Wallace (2002b), constitute the many stages of cancer.

There are two matters for further study:

At one end of mutation control, ‘simple’ mechanisms of cellular DNA repair seem more akin to error correcting codes than cognitive process. At the other end, however, a hospital oncology team is very highly cognitive indeed. We are inclined to perceive a ‘cognitive gradient’ which may not be continuous. Suppose we create an index of mutational clone pathology,  $\mathcal{M}$ , and set  $\mathcal{K} = 1/\mathcal{M}$ . We parametrize the ‘richness’ of the language of cognitive mutation control as  $H[\mathcal{K}]$ , and assume it takes the usual reverse S-shaped form, rising toward an asymptotic limit with *decreasing*  $\mathcal{K}$ , i.e. increasing clone pathology. We are inclined to impose a discontinuous phase transition at some critical value  $\mathcal{K}_C$ . That is, ‘real’ cellular cognition only kicks in if

mutational clone threat exceeds some critical point.

In a similar vein, but on the other side, as it were, we might well speculate that mutational processes may likewise be involved beyond Tenaillon's (2001) 'secondary selection': we are inclined to agree with Thaler (1999) that a cell's sensing of its environment and history may be exquisitely regulated indeed, perhaps involving a graded sequence of 'higher order mutators' matching the increasingly draconian opposing processes of cognitive mutation control.

The next section explores a complication of some note.

### Some implications of 'tuning'

Physical systems undergoing phase transition usually have relatively simple renormalization properties and do not undergo 'tuning' of the exponents defining their universality classes. As McCauley (1993, p. 168) shows, however, even for relatively straightforward mathematical structures, such simplicity is not always the case: 'deterministic chaos' is afflicted with counter-intuitive renormalization relations such as

$$f(x) = \alpha^2 f(\alpha^{-1} f(\alpha^{-1} x))$$

$$f(x) = \alpha f(\alpha f(\alpha^{-2} x)).$$

(8)

The Appendix examines the algebraic avalanche which occurs when  $f(R)$  in equation (3) takes more biologically reasonable forms.

Matters can become rapidly worse:

If we suppose the system of interest to be a mix of subgroups with different values of some significant parameter  $m$  in the expression for  $f(R, m)$ , according to a distribution  $\rho(m)$ , then we expect the first expression in equation(3) to generalize as

$$\begin{aligned}
H[K_R, J_R] &= \langle f(R, m) \rangle H[K, J] \\
&\equiv \int f(R, m) \rho(m) dm H[K, J].
\end{aligned}
\tag{9}$$

If  $f(R) = 1 + m \log(R)$  then, given a typical distribution for  $m$ , we simply obtain

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

Other forms of  $f(R, m)$  having more complicated dependencies on the distributed parameter or parameters, like the power law  $R^m$ , do not produce such a simple result. Taking  $\rho(m)$  as a normal distribution, for example, gives

$$\langle R^m \rangle = R^{\langle m \rangle} \exp[(1/2)(\log(R^\sigma))^2],$$

where  $\sigma^2$  is the distribution variance. The renormalization properties of this function can be found using the calculational strategy of the Appendix.

Thus the information dynamic phase transition properties of ‘natural’ (i.e. mixed) populations will not in general be simply related to those of a single population, a matter of possible empirical importance: If sets of relevant renormalization parameters,  $A_k$ , are indeed distributed, experiments observing ‘pure’ phase changes may be very difficult. Tuning among different possible renormalization strategies would result in even greater ambiguity in recognizing and classifying information dynamic phase transitions.

In sum, biological or social language-on-network systems are likely to have very rich patterns of phase transition behavior far beyond the literally elementary purity familiar to physicists. Something very like this has already been observed for the structure of ‘real world’ networks (Albert and Barabasi, 2002), although not in the context of phase transition.

We can generalize these results somewhat. If changes in the coupling parameter  $K$  take place at a rate characterized by some time  $T$ , and the

adaptive mutator operates at a rate characterized by  $\tau \ll T$ , then the operation  $\langle \rangle$  becomes an integral over time, i.e.  $\int f(R, \tau) \rho(\tau) d\tau$ . This introduces further complications, which can perhaps be reduced if appropriate ergodic properties allow replacement of the time integral with one across states, in an appropriate sense. We will not pursue the matter here.

## Conclusions

We have applied an elaborate mathematical modeling strategy, in the spirit of the Large Deviations Program of applied probability, to the adaptive mutator, and to possible linkage with a cognitive, but culturally-linked, process of socio-cellular mutation control in humans. As ecologist E.C. Pielou has argued (Pielou, 1977, p. 106), a severe limit to any such approach is that mathematical models do not create new knowledge, they create new speculation. Thus 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 we have raised are of some interest.

We have expressed tumorigenesis in terms of a synergistic linkage of a ‘language’ of structured external stress with the mutator, and with the opposing cognitive process of mutation control. Elsewhere we describe at some length the mediating role that an enveloping local cognitive socio-cultural network plays in linking an individual to an embedding system of structured stress (Wallace and Wallace, 2002; Wallace, 2002a), a matter we have not emphasized here to simplify the development.

Raised rates of cellular mutation which structurally (and quite literally) reflect selection pressure through Ademi’s distorted mirror do not fit a cognitive paradigm: The adaptive mutator may propose, but selection disposes. However, the punctuated effect of structured stress on the cognitive process of mutation control, which itself constitutes the selection pressure facing a clone of mutated cells, connects the mechanisms. Subsequent multiple evolutionary ‘learning plateaus’ (Wallace, 2002b) representing the punctuated interpenetration between socio-cellular cognition and clones of mutated cells constitute the stages of disease.

Further consideration may even find significant variation among mutators themselves; for example, markedly different renormalization or tuning strategies which may be distributed across subpopulations in a manner quite different from familiar physical models.

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 largely ineffective for marginalized human populations in the absence of proactive – and likely very intrusive – 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 ‘biological control’ can individual-oriented strategies contribute significant impact.

‘Social exposures’ may be far more than incidental cofactors for the development of human cancers: Boyd’s metaphorical aphorism that ‘culture is as much a part of human biology as the enamel on our teeth’ appears literally true at the level of very basic biological mechanisms.

A subsequent series of papers will examine hormonal cancers from these perspectives.

### 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 (Binney, 1986; Shirkov and Kovalev, 2001), 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 (14) 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  $\alpha = my + z = \text{constant}$ . Note that nothing in the development prevents  $\alpha$  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

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

(18)

where

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

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

$$\text{LambertW}(x) \exp(\text{LambertW}(x)) = x$$

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 Section III 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 (Hartl and Clark, 1997; Ridley, 1996). 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  $R \rightarrow \infty$ . Mathematica 4.2 finds

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

(20)

where

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

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

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### References

- Adami C, C. Ofria, and T. Collier, 2000, "Evolution of biological complexity", *Proceedings of the National Academy of Sciences*, **97**, 4463-4468.
- Albert R., and A. Barabasi, 2002, "Statistical mechanics of complex networks", *Reviews of Modern Physics*, **74**, 47-97.
- Atlan H. and I.R. Cohen, 1998, "Immune information, self-organization and meaning", *International Immunology*, **10**, 711-717.
- Baverstock K., 2000, "Radiation-induced genomic instability: a paradigm-breaking phenomenon and its relevance to environmentally induced cancer", *Mutation Research*, **454**, 89-109.
- Bertram J., 2001, "The molecular biology of cancer", *Molecular Aspects of Medicine*, **21**, 167-223.
- Binney J., N. Dowrick, A. Fisher, and M. Newman, 1986, *The Theory of Critical Phenomena*, Clarendon Press, Oxford.
- Bootsma D. and J. Hoeijmakers, 1993, "DNA repair: engagement with transcription", (news: comment), *Nature*, **363**, 114-115.
- Cover T., and J. Thomas, 1991, *Elements of Information Theory*, Wiley, New York.
- Dembo A., and O. Zeitouni, 1998, *Large Deviations: Techniques and Applications*, 2nd. Ed., Springer-Verlag, New York.
- Evan G., and T. Littlewood, 1998, "A matter of life and cell death", *Science*, **281**, 1317-1322.

- Fanon F., 1966, *The Wretched of the Earth*, Grove Press, New York.
- Forlenza M. and A. Baum, 2000, “Psychosocial influences on cancer progression: alternative cellular and molecular mechanisms”, *Current Opinion in Psychiatry*, **13**, 639-645.
- Granovetter M., 1973, “The strength of weak ties”, *American Journal of Sociology*, **78**, 1360-1380.
- Hartl D. and A. Clark, 1997, *Principles of Population Genetics*, Sinaur Associates, Sunderland, MA.
- Herberman R., 1995, “Principles of tumor immunology” in Murphy G., W. Lawrence and R. Lenhard (eds.), *American Cancer Society Textbook of Clinical Oncology*, ACS, Second Edition, pp. 1-9.
- Hodgson G., 1993, *Economics and Evolution: Bringing life back into economics*, University of Michigan Press, Ann Arbor.
- Lewontin R., 2000, *The Triple Helix: Gene, Organism and Environment*, Harvard University Press, Cambridge, MA.
- Magnasco M. and D. Thaler, 1996, “Changing the pace of evolution”, *Physics Letters A*, **221**, 287-292.
- Massey D. and N. Denton, 1993, *American Apartheid*, Harvard University Press, Cambridge, MA.
- McCord C. and H. Freeman, 1990, “Excess mortality in Harlem”, *New England Journal of Medicine*, **322**, 173-177.
- Pielou E., 1977, *Mathematical Ecology*, John Wiley and Sons, New York.
- Ridley M., 1996, *Evolution*, Second Edition, Blackwell Science, Oxford, UK.
- Rojdestevenski I., and M. Cottam, 2000, “Mapping statistical physics to information theory with applications to biological systems”, *Journal of Theoretical Biology*, **202**, 43-54.
- Shirkov D., and V. Kovalev, 2001, “The Bogoliubov renormalization group and solution symmetry in mathematical physics”, *Physics Reports*, **352**, 219-249.
- Snow E., 1997, “The role of DNA repair in development”, *Reproductive Toxicology*, **11**, 353-365.
- Somers S. and P. Guillou, 1994, “Tumor strategies for escaping immune control: implications for psychoimmunotherapy”, in Lewis C., C. O’Sullivan and J. Barraclough (eds.), *The Psychoimmunology of Cancer: Mind and body in the fight for survival*, Oxford Medical Publishing, pp. 385-416.
- Tenaillon O., F. Taddei, M. Radman and I. Matic, 2001, “Second-order selection in bacterial evolution: selection acting on mutation and recombina-

nation rates in the course of adaptation”, *Research in Microbiology*, **152**, 11-16.

Thaler D., 1999, “Hereditary stability and variation in evolution and development”, *Evolution and Development*, **1**, 113-122.

Tsutsui T., H. Maizumi, J. McLachlan, and J. Barrett, 1983, “Aneuploidy induction and cell transformation by diethylstilbestrol: a possible chromosomal mechanism in carcinogenesis”, *Cancer Research*, **43**, 3814-3821.

Waliszewski P., M. Molski, and J. Konarski, 1998, “On the holistic approach in cellular and cancer biology: nonlinearity, complexity, and quasi-determinism of the dynamic cellular network”, *Journal of Surgical Oncology*, **68**, 70-78.

Wallace D., 1995, “Smaller increases in life expectancy for blacks and whites between the 1970’s and 1980’s”, *American Journal of Public Health*, **85**, 875-876.

Wallace R., 2000, “Language and coherent neural amplification in hierarchical systems: renormalization and the dual information source of a generalized spatiotemporal stochastic resonance”, *International Journal of Bifurcation and Chaos*, **10**, 493-502.

Wallace R., 2002a, “Immune cognition and vaccine strategy: pathogenic challenge and ecological resilience”, *Open Systems and Information Dynamics*, **9**, 51-83.

Wallace R., 2002b, “Adaptation, punctuation and information: a rate-distortion approach to non-cognitive ‘learning plateaus’ in evolutionary process”, *Acta Biotheoretica*, **50**, 101-116.

Wallace R. and R. Fullilove, 1999, “Why simple regression models work so well describing ‘risk behaviors’ in the USA”, *Environment and Planning A*, **32**, 719-734.

Wallace R. and R.G. Wallace, 1998, “Information theory, scaling laws and the thermodynamics of evolution”, *Journal of Theoretical Biology*, **192**, 545-559.

Wallace R. and R.G. Wallace, 1999, “Organisms, organizations and interactions: an information theoretic approach to biocultural evolution”, *BioSystems*, **51**, 101-119.

Wallace R. and R.G. Wallace, 2002a, “Immune cognition and vaccine strategy: beyond genomics”, **4**, 521-527.

Wallace R. and R.G. Wallace, 2002b, “Punctuated interpenetration and chronic disease progression”. Submitted.

Wilson, K., 1971, “Renormalization group and critical phenomena. I.

Renormalization group and the Kadanoff scaling picture", *Physical Review B*, **4**, 3174-3183.