Version 9

Chronic infection: punctuated interpenetration and pathogen virulence

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February 6, 2003

Abstract

We apply an information dynamics formalism to the Levins and Lewontin vision of biological interpenetration between a 'cognitive condensation' including immune function embedded in social and cultural structure on the one hand, and an established, highly adaptive, parasite population on the other. We iterate the argument, beginning with direct interaction between cognitive condensation and pathogen, then extend the analysis to second order 'mutator' mechanisms inherent both to immune function and to certain forms of rapid pathogen antigenic variability. The methodology, based on the Large

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Deviations Program of applied probability, produces synergistic cognitive/adaptive 'learning plateaus' that represent stages of chronic infection, and, for human populations, is able to encompass the fundamental embedding biological reality of culture omitted by other approaches. We conclude that, for 'evolution machine' pathogens like HIV and malaria, simplistic magic bullet 'medical' drug, vaccine, or behavior modification interventions which do not address the critical embedding context of overall living and working conditions may constitute selection pressures triggering adaptations in life history strategy resulting in marked increase of pathogen virulence.

Key words: adaptation, chronic infection, cognition, immune, interpenetration, mutator, phase transition, renormalization, virulence

Introduction

The first papers in this series (Wallace and Wallace, 2002; Wallace, 2002a), began our examination of culturally-driven variation in malaria pathology and rates of heterosexual HIV transmission. HIV responds to immune challenge as an evolution machine, generating copious variation and hiding from counterattack in refugia at multiple scales of space, time, and population. *P. falciparum* engages in analogous rapid clonal antigenic variation, and cyto-adherence and sequestration in the deep vasculature, primary mechanisms for escaping from antibody-mediated mechanisms of the host's immune system (e.g. Alred, 1998). Something much like the mutator mechanism, in the sense of Thaler (1999), or 'second order selection' in the sense of Tenallion et al. (2001), appears to generate antigenic variation in the face of immune attack for a large class of pathogens. On the other hand, recent work by DiNoia and Neuberger (2002) outlines the mechanisms by which the immune system's antibody-producing B-cells engage in a second-order fine tuning of antibody production through an exceedingly high rate of mutation-like transformations, a hypermutation which allows us to respond quickly and effectively to pathogens that we have encountered previously (Gearhart, 2002).

Many chronic infections, particularly those which cloak themselves in antigenic 'coats of many colors', are very often marked by distinct 'stages' over the course of the disease. For HIV this typically involves an initial viremia triggering an immune response which drives the virus into refugia during an extended asymptomatic period whose ending is characterized

by the start of a third phase, AIDS. Malaria's most evident 'stages' are expressed as explosive outbursts of rapid parasite replication which facilitate insect-mediated transmission between hosts. Such evasive pathogens presently account for a very large fraction of human deaths by infectious disease, and represent, for a broad range of organisms, the evolutionary success of multiple-stage chronicity as a life history strategy, in the particular context of rapid antigenic variation.

Here we extend the earlier theoretical analysis of Wallace (2002a), which focused on infection as a sudden 'perturbation'. We will analyze how pathogen life history stages represent a kind of evolutionary punctuation (e.g. Eldredge, 1985) for chronic infection in the face of relentless immune and other selection pressure, both directly, as is the likely case for HIV, and by means of a 'second order punctuation' through the mutator mechanism (Thaler, 1999) associated with rapid antigenic variation, as is the case with malaria. Elsewhere we study clonal selection in tumorigenesis from a similar 'second order' perspective (Wallace, Wallace, and Wallace, 2002).

Recently Adami et al. (2000) applied an information theoretic approach to conclude that genomic complexity resulting from evolutionary adaptation can be identified with the amount of information a gene sequence stores about its environment. Lewontin (2000) might be said to argue for something of a reverse process, in which environmental complexity is the amount of information organisms introduce into their environment as a result of their collective actions and interactions. We shall find this to be a persuasive perspective.

Wallace (2002b) has applied a Rate Distortion argument in the context of imposed renormalization symmetry to obtain evolutionary 'punctuated equilibrium' (Eldredge, 1985) as a consequence of Ademi's mechanism. Here we use the more general Joint Asymptotic Equipartition Theorem to conclude that pathogenic adaptive response and coupled cognitive immune challenge will be jointly linked in chronic infection, and subject to a transient 'punctuated interpenetration' very similar to evolutionary punctuation. Multiple punctuated transitions, perhaps of mixed 'order', are seen as constituting shifts to the different stages of chronic infection. Since the joint system of host and pathogen passes through such phase transition analogs fairly rapidly, and may be stable for a relatively long time thereafter – 'piecewise adiabatic memoryless ergodic' – this is very far indeed from 'edge of chaos' arguments which rather implausibly imprison biological systems at transition. Similarly, our approach can be said to subsume 'self organized criticality' approaches

which see punctuated extinctions as generated entirely by forces internal to defined communities: biology may not be a pile of sand after all.

Examining paths in parameter space for the renormalization properties of such transitions (i.e. 'universality class tuning' in the sense of Albert and Barabasi, 2001) produces a second order punctuation in the rate at which the selection pressure of the immune system imposes a distorted image of itself onto pathogen structure. This is our version of the mutator, or what Tenallion et al. (2001) call 'second order selection'.

Recognizably similar matters have long been under scrutiny: interactions between the central nervous system (CNS) and the immune system, and between the genetic heritage and the immune system have become academically codified through journals with titles such as *Neuroimmunology* and *Immunogenetics*. Elsewhere (Wallace and Wallace, 2002) we introduce another complication by arguing that the culture in which humans are socially embedded also interacts with individual immune systems to form a composite entity that might well be labeled an *immunocultural condensation*, (ICC). It is, we will argue here, the joint entity of immune, CNS, and embedding sociocultural cognition which engages in orders of 'punctuated interpenetration' with an adaptive chronic infectious challenge. Similar arguments are already in the French literature (e.g. Combes, 2000).

Before entering the formal thicket, it is important to highlight some general considerations. First, the information theory approach we adopt is notorious for providing 'existence theorems' whose 'representation', to use physics jargon, is arduous. For example, although the Shannon Coding Theorem implied the possibility of highly efficient coding schemes as early as 1949, it took more than forty years for practical 'turbo codes' to be created. The program we propose is unlikely to be any less difficult.

Second, we are invoking information theory variants of the fundamental limit theorems of probability. These are independent of exact mechanisms, but constrain the behavior of those mechanisms. For example, although not all processes involve long sums of independent stochastic variables, those that do, regardless of the individual variable distribution, collectively 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 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.

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

We begin with a description of cognitive process, including Cohen's (2000) immune cognition, in terms of an information source, a 'language' constrained by the Shannon-McMillan or Asymptotic Equipartition Theorem, and its Rate Distortion or Joint Asymptotic Equipartition and other variants for interacting sources.

Cognition as language

Atlan and Cohen (1998) and Cohen (2000) argue that the essence of immune cognition is comparison of a perceived antigenic signal with an internal, learned picture of the world, and then, upon that comparison, the choice of one response from a large repertoire of possible responses. Following the approach of Wallace (2000, 2002a), we make a 'weak', and hence 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 pattern of sensory activity requires a response. We need not model how the pattern recognition system is 'trained', and hence we adopt a weak model, regardless of learning paradigm, which can itself be more formally described by the Rate Distortion Theorem. We will, fulfilling Atlan and Cohen's (1998) 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 (antigenic) input is convoluted (compared) with internal 'ongoing' 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. Cover and Thomas, 1991), however, it seems obvious that the underlying dynamics will all be qualitatively similar.

Meaningful paths – creating an inherent grammar and syntax – are defined entirely in terms of system response, as Atlan and Cohen (1998) propose. See Wallace (2002a) for explicit application of this formalism to the stochastic neuron.

We will eventually parametize the information source uncertainty of this dual information source with respect to one or more variates, writing, e.g. $H[\mathbf{K}]$, where $\mathbf{K} \equiv (K_1, ..., K_s)$ represents a vector in a 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 (1971).

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.

Introduction to the general argument

Taking this formal description of immune cognition as a starting point, Wallace (2002a) has explored host response to sudden pathogenic challenge, using a mathematical model of the generalized 'cognitive condensation' that characterizes human biology. Suppose the pathogen avoids extirpation by that response, but, changing its coat or hiding within refugia, becomes

an established invading population. The immune system is cognitive, the pathogen is adaptive.

We suppose that the host's generalized CNS and immunocultural condensation can be represented by a sequence of 'states', the 'path' $x \equiv x_0, x_1, ...$ Similarly, we assume the pathogen population can be represented by the path $y \equiv y_0, y_1, ...$ These paths are, however, both very highly structured and serially correlated and can, in fact, be represented by 'information sources' $\mathbf{X}$ and $\mathbf{Y}$. Since the host and parasite population interact, these sequences of states are not independent, but are jointly serially correlated. We can, then, define a path of sequential pairs as $z \equiv (x_0, y_0), (x_1, y_1), ...$ The essential content of the Joint Asymptotic Equipartition Theorem, one of the fundamental limit theorems of 20th Century mathematics, is that the set of joint paths z can be partitioned into a relatively small set of high probability which is termed *jointly typical*, and a much larger set of vanishingly small probability. Further, according to the JAEPT, the *splitting criterion* between high and low probability sets of pairs is the mutual information

$$I(X,Y) = H(X) - H(X|Y) = H(X) + H(Y - H(X,Y)$$

where $H(X), H(Y), H(X|Y)$ and $H(X,Y)$ are, respectively, the Shannon uncertainties of X and Y, their conditional uncertainty, and their joint uncertainty. See Cover and Thomas (1991) for mathematical details. Similar approaches to neural process have been recently adopted by Dimitrov and Miller (2001).

The high probability pairs of paths are, in this formulation, all equiprobable, and if $N(n)$ is the number of jointly typical pairs of length n, then

$$I(X,Y) = \lim_{n\to\infty} \frac{\log[N(n)]}{n}.$$

Generalizing the earlier language-on-a-network models of Wallace and Wallace (1998, 1999), we suppose there is a 'chronic coupling parameter' P representing the degree of linkage between host's ICC/CNS condensation and the parasite population, and set $K = 1/P$, following the development of those earlier studies. Then we have

$$I[K] = \lim_{n\to\infty} \frac{\log[N(K,n)]}{n}.$$

The essential 'homology' between information theory and statistical mechanics lies in the similarity of this expression with the infinite volume limit

of the free energy density. If $Z(K)$ is the statistical mechanics partition function derived from the system's Hamiltonian, then the free energy density is determined by the relation

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

F is the free energy density, V the system volume and $K = 1/T$, where T is the system temperature.

We and others argue at some length (Wallace and Wallace, 1998, 1999; Rojdestvensky and Cottam, 2000) that this is indeed a systematic mathematical homology which, we contend, permits importation of renormalization symmetry into information theory. Imposition of invariance under renormalization on the mutual information splitting criterion $I(X, Y)$ implies the existence of phase transitions analogous to learning plateaus or punctuated evolutionary equilibria in the relations between host and pathogen. An extensive mathematical development will be presented in the next section.

The physiological details of mechanism, we speculate, will be particularly captured by the definitions of coupling parameter, renormalization symmetry, and, perhaps, the distribution of the renormalization across agency, a matter we treat below.

Here, however, these changes are perhaps better described as 'punctuated interpenetration' between the challenged cognitive condensation of the host and the adaptive abilities of the pathogen.

Even more elaborate developments are possible. For example, in the next section we explore canonical patterns of transition between disease stages that emerge quite naturally. We reiterate that the details are highly dependent on the choice of renormalization symmetry, which is likely to reflect details of mechanism – the manner in which the dynamics of the forest are dependent on the detailed physiology of trees, albeit in a many-to-one manner. Renormalization properties are not likely to follow simple physical analogs, and may well be subject to characteristic distributions. The algebra is straightforward if complicated, and given later. Following Nesbitt et al. (2001), however, any 'cognitive' process is likely to show significant cultural variation, and even distribution of properties.

Representations of the general argument

1. Language-on-a-network models. Earlier work in this series addressed the problem of how a 'language', in a large sense, 'spoken' on a

network structure responds as properties of the network change. The language might be spoken, pattern recognition, or cognition. The network might be social, chemical, or neural. The properties of interest were the magnitude of 'strong' or 'weak' ties which, respectively, either disjointly partitioned the network or linked it. These would be analogous to local and mean-field couplings in physical systems.

We fix the magnitude of strong ties, but vary the index of weak ties between components, which we call P, taking $K = 1/P$. For neural networks P is just proportional to the number of training cycles, suggesting that, for interacting cognitive/adaptive systems, P may be proportional to the number of 'challenge cycles', likely indexed by human diurnal or other activity patterns, or perhaps even those of the parasite itself.

We assume the piecewise, adiabatically memoryless ergodic information source (Wallace, 2002b) 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 will, in the limit, set $J = 0$.

The implicit parameter, which we call r, is an inherent generalized 'length' characteristic of the phenomenon, on which 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 r may be defined by the degree of niche partitioning in ecosystems or separation in social structures.

For a given generalized language of interest with a well defined (piecewise adiabatically memoryless) 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 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 (1971) analysis as a starting point, we choose the renormalization relations as

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

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

(1)

with $f(1) = 1$ and $J_1 = J, K_1 = K$. The first of these equations significantly extends Wilson's treatment. It states that 'processing capacity,' as indexed by the source uncertainty of the system, representing the 'richness' of the generalized language, grows monotonically as $f(R)$, which must itself be a dimensionless function in R, since both $H[K_R, J_R]$ and $H[K, J]$ are themsleves dimensionless. Most simply, this would require that we replace R by R/R_0, where R_0 is the 'characteristic length' for the system over which renormalization procedures are reasonable, then set $R_0 \equiv 1$, i.e. measure length in units of R_0. Wilson's original analysis focused on free energy density. Under 'clumping', densities must remain the same, so that if $F[K_R, J_R]$ is the free energy of the clumped system, and $F[K, J]$ is the free energy density before clumping, then Wilson's equation (4) is $F[K, J] = R^{-3}F[K_R, J_R]$, i.e.

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

Remarkably, the renormalization equations are solvable for a broad class of functions $f(R)$, or more precisely, $f(R/R_0), R_0 \equiv 1$.

The second relation 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. This is an important subject for future research, since we suspect that biological or social systems may alter their renormalization properties in response to external pressures.

To begin, following Wilson, we take $f(R) = R^d$ for some real number $d > 0$, and restrict K to near the 'critical value' K_C. If $J \to 0$, a simple series expansion and some clever algebra (Wilson, 1971; Binney et al., 1986) gives

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

$$\chi = \frac{\chi_0}{\kappa^s}$$

(2)

where α, s are positive constants. We provide more biologically relevant examples below.

Further from the critical point matters are more complicated, appearing to involve '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, we go 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.

To reiterate somewhat, this heuristic insight can be made more exact using a rate distortion argument (or, more generally, using the Joint Asymptotic Equipartition Theorem) 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 $\mathbf{B}$.

Define some distortion measure comparing paths y to paths $\hat{y}$, $d(y, \hat{y})$ (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 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.

In the absence of a distortion measure, we can invoke the Joint Asymptotic Equipartition Theorem to obtain a similar result.

We suggest in particular that detailed biochemical and molecular coupling mechanisms will be sharply constrained through regularities of grammar and syntax imposed by limit theorems associated with phase transition.

Wallace and Wallace (1998, 1999) use this 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 parametized 'instability', $Q[K]$, is defined from the principal splitting criterion by the relation

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

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

(3)

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.

2. 'Biological' phase transitions. Equation (2) 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

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

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

with $f(1) = 1, K_1 = K, J_1 = J$, where we have slightly rearranged terms.

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

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

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

(4)

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

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

$$dJ_R/dR = wJ_R d\log(f)/dR + xJ_R/R.$$

(5)

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

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

(6)

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), assuming that for K_R near K_C, we have

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

(7)

We iterate 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 (1) to obtain an expression for $H[K, 0]$ in terms of known functions and parameter values.

The first step gives the general result

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

(8)

Solving this for R_C and substituting into the first of equation (1) gives, as a first iteration of a far more general procedure (e.g. Shirkov and Kovalev, 2001)

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

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

(9)

which are the essential relationships.

Note that a power law of the form $f(R) = R^m, m = 3$, which is the direct physical analog, may not be biologically reasonable, since it says that 'language richness' can grow very rapidly as a function of increased network size. Such rapid growth is simply not observed.

If we take the biologically realistic example of non-integral 'fractal' exponential growth,

$$f(R) = R^\delta,$$

(10)

where $\delta > 0$ is a real number which may be quite small, we can solve equation (8) for R_C, obtaining

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

(11)

for K near K_C. Note that, for a given value of y, we might want to characterize the relation $\alpha \equiv \delta y + z =$ constant as a "tunable universality class relation" in the sense of Albert and Barabasi (2002).

Substituting this value for R_C back into equation (9) gives a somewhat more complex expression for H than equation (2), having three parameters, i.e. δ, y, z.

A more biologically interesting choice for $f(R)$ is a logarithmic curve that 'tops out', for example

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

(12)

Again $f(1) = 1$.

Using Mathematica 4.2 to solve equation (8) for R_C gives

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

(13)

where

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

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

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

It arises in the theory of random networks and in renormalization strategies for quantum field theories.

An asymptotic relation for $f(R)$ would be of particular biological interest, implying that 'language richness' increases to a limiting value with population growth, in a loose sense, and 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 (Hart and Clark, 1997; Ridley, 1996). Taking

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

(14)

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

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

(15)

where

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

(15)

These developments indicate the possibility of taking the theory significantly beyond arguments by abduction from simple physical models, although the notorious difficulty of implementing information theory existence arguments will undoubtedly persist.

3. Universality class distribution. Physical systems undergoing phase transition usually have relatively 'pure' renormalization properties, with quite different systems clumped into the same 'universality class', having fixed exponents at transition (e.g. Binney, 1986). Biological and social phenomena may be far more complicated:

If we suppose the system of interest to be a mix of subgroups with different values of some significant renormalization parameter m in the expression for $f(R, m)$, according to a distribution $\rho(m)$, then we expect the first expression in equation (1) to generalize as

$$H[K_R, J_R] =< f(R, m) > H[K, J]$$

$$\equiv H[K, J] \int f(R, m)\rho(m)dm.$$

(16)

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

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

(17)

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

$$< R^{\delta} >= R^{<\delta>} \exp[(1/2)(\log(R^{\sigma}))^2],$$

(18)

where σ^2 is the distribution variance. The renormalization properties of this function can be determined from equation (8), and is left to the reader as an exercise, best done in Mathematica 4.2.

Thus the information dynamic phase transition properties of mixed systems will not in general be simply related to those of a single subcomponent, a matter of possible empirical importance: If sets of relevant parameters defining renormalization 'universality classes' are indeed distributed, experiments observing 'pure' phase changes may be very difficult. Tuning among different possible renormalization strategies in response to external pressures would result in even greater ambiguity in recognizing and classifying information dynamic phase transitions.

We believe that important aspects of mechanism may be reflected in the combination of renormalization properties and the details of their distribution across subsystems. Elsewhere (Wallace, Wallace, Wallace, and Wallace, 2002) we examine the possible relation of the 'tuning' of renormalization parameters to the adaptive mutator.

In sum, real biological, social, or 'biopsychosocial' systems are likely to have very rich patterns of phase transition which may not display the simplistic, indeed, literally elemental, purity familiar to physicists. Overall mechanisms will, we believe, still remain significantly constrained by our theory, in the general sense of probability limit theorems.

4. Universality class tuning Next we iterate the general argument onto the process of phase transition itself, obtaining Tenallion's 'second order selection', i.e. the mutator, in a 'natural' manner.

We suppose that a structured environment, which we take itself to be an appropriately regular information source $\mathbf{Y}$ – e.g. the immune system, or more generally, for humans the immunocultural condensation (ICC) – 'engages' a modifiable system – e.g. a pathogen – 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 (2),

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

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,

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

(19)

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

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

(20)

and is singular at $K = K_C = 1$ for $0 < \alpha < 1$. Following earlier work (Wallace and Wallace, 1998, 1999; Wallace and Fullilove, 1999; 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 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.

The more biologically realistic renormalization strategies given above produce sets of several parameters defining the 'universality class', whose tuning gives behavior much like that of α in this simple example.

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

The adaptive mutator

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 (Wallace, 2002a, b), that external selection pressure is also highly structured – e.g. the cognitive immune system or, in humans, the ICC – 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 (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 (i.e. the pathogen) and externally imposed selection or other pressure (i.e. responses of the ICC).

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. While evolutionary phenomena are not cognitive in the sense of the immune system (Cohen, 2000), 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.

That is, we argue that the staged nature of chronic infectious diseases like malaria and HIV represents a punctuated version of biological interpenetration, in the sense of Lewontin (2000), between a cognitive 'immunocultural condensation' and a highly adaptive pathogen. We further suggest that this punctuated interpenetration may have both first, i.e. direct, and second order characteristics, possibly involving cross interactions between direct cognitive effects of the immune system or ICC, or more generally, of the immunocultural condensation, and the mutator systems of both that system and the adaptive pathogen.

Extending the general argument: Psychosocial stress and the pathogenic coat of many colors

As we discuss elsewhere (Wallace and Wallace, 2002; Wallace, 2002a), structured psychosocial stress constitutes a determining context for immune cognition or, more generally, the immunocultural condensation. We wish to analyze the way structured stress affects the interaction between the cognitive ICC and an adaptive mutator, the principal line of defense against the ICC for a large class of highly successful pathogens. To do this we must extend our 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* [Cover and Thomas, 1991, 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:

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

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

(21)

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

Then, in analogy with 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 [Cover and Thomas, 1992, p. 387]

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

(22)

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 (Wallace, 2002b) in the splitting criterion $I(Y_1, Y_2|Y_3)$, which characterizes the synergistic interaction between structured psychosocial stress, the ICC, and the pathogen's adaptive mutator. These transitions delineate the various stages of the chronic infection, which are embodied in the slowly varying 'piecewise adiabatically memoryless ergodic' phase between transitions. Again, our results are exactly analogous to the Eldredge/Gould model of evolutionary punctuated equilibrium.

While this argument has been focused on complex parasites like malaria which may have mutator mechanisms determining behavior of their antigentic coat of many colors, a simplified analysis can be applied directly to HIV, which, as a kind of evolution machine, seems to engage in endless, rapid, direct mutation.

Discussion: Evolution machines and magic bullets

Scientific enterprise encompasses the interaction of facts, tools, and theories, all embedded in a path-dependent political economy which seems as natural to us as air to a bird, water to a fish, or an atomic matrix to a solid state electron. Molecular biology, Central Limit Theorem statistics, and 19th

century mathematics, presently provide the reductionist tool kit most popular in the study of immune function and disease process. Many essential matters related to the embedding social, economic, and cultural matrix so fundamental to human biology are simply blindsided, and one is reminded, not very originally, of the joke about the drunk looking for his car keys under a street lamp, while having lost them down the block in a darkened parking lot, "because the light here is better".

The asymptotic limit theorems of probability beyond the Central Limit Theorem, in concert with related formalism adapted from statistical physics, would seem to provide new tools which can generate theoretical speculations of value in obtaining and interpreting empirical results about infection and immune process, particularly regarding the way in which culture is, for human populations, "as much a part of human biology as the enamel on our teeth" (Richerson and Boyd, 1995).

We have, as yet, explored relatively few possibilities: While we can model the interaction of first and second order phenomena in the context of structured stress using network information theory, it is difficult to envision interaction between second order 'tuning' processes, or the mechanics of even higher order effects: can we continue to 'tune the tuners' in a kind of idiotypic hall of mirrors? The mathematics would be straightforward, but the corresponding molecular biology would have to be subtle indeed. While unlikely in general, higher order interpenetration – mutating the mutator – may be observable in certain isolated circumstances, for example the interplay between B-cell hypermutation and a high order parasitic coat of many colors.

Our model, then, explicitly invokes the possibility of synergistic interaction between the selection pressure of the ICC and the variable antigenic coat of the established invading pathogen population, particularly in the context of embedding patterns of structured psychosocial stress. The ICC, through its B-cell hypermutation, may engage in its own second order selection. Hence first, second, and possibly mixed, order interpenetration, in which ICC and pathogen each constitute both selection pressure and selected structure, an interaction in turn driven by enfolding patterns of socioeconomic stress.

To reiterate, extending the theoretical analysis of Wallace (2002a), which focused on infection as a 'perturbation', chronic infection in humans is, from our perspective, defined by orders of punctuated interpenetration between the adapting pathogen and an interactive condensation of the host's *cognitive* immune, central nervous, and embedding sociocultural systems, in the

sense of Wallace and Wallace (2002). This punctuated interpenetration is, itself, embedded in a punctuated manner within the grammar and syntax of structured stressors. Human chronic infection cannot, in particular, be simply abstracted as a matter of conflict between the pathogen and the immune system alone. Indeed, the concept of an immune system 'alone' has no meaning within our model, in stark contrast with, for example, the well-stirred Ehrlenmyer flask predator-prey population dynamics of Nowak and May (2000).

Our analysis suggests that 'mind-body interaction' and culture profoundly influence the course of chronic infection at the individual level. The inherently cognitive nature of human biology, especially the intimate role of culture, would seem to limit the utility of animal models in the study of chronic disease much beyond what is already commonly realized.

Individual and collective history, socioeconomic structure, and emotional state, may not be mere adjuncts to what is termed 'basic science' in the medical journals. Rather, they may be as much basic human biology as T-cells. 'Magic bullet' vaccine, therapeutic drug, or highly-focused medicalized 'social' interventions against HIV disease and other mutagenic parasites – approaches that inherently cannot reckon with socioeconomic, historical, and cultural determinants of health and illness – will likely be doomed as they are overwhelmed by relentless pathogen adaptation and the population specificity of immune cognition. For chronic infections like HIV and malaria in human populations, individual level or limited 'social network' intervention strategies which neglect larger embedding context, and the history of that context, embody a grossly unreal paradigm of basic human biology.

Our model, by contrast, raises the possibility of effective 'integrated pathogen management' (IPM) programs through synergistic combinations of social, ecological, and medical interventions. IPM far transcends 'medical' strategies that amount to little more than a kind of pesticide application, an approach currently being abandoned in agriculture as simply inadequate to address pathogen evolutionary strategies.

We know that certain kinds of social systems – relatively stable with fairly decent living and working conditions for most people – have, to date, escaped large-scale HIV infection, while others have succeeded in controling malaria through, for example, persistent and highly organized programs of insect vector control. For HIV, of course, we are both the intermediate vector and primary host. Recent work by one of us (R.G. Wallace, 2002) suggests that, for heavily infested societies, individual-level 'magic bullet' antiretrovi-

ral treatment of HIV, without benefit of larger IPM strategies, may constitute a selection pressure forcing evolutionary changes in HIV life history which could cause markedly increased virulence, in particular the rapid onset of the 'accelerated senecence' of early AIDS. In essence this is because pathogen reproduction during the long-lasting, but possibly epidemiologically important 'latent phase' of infection is markedly reduced by drugs. The 'weak' approach we have taken here to evolutionary process clearly implies that limited perspective magic bullet 'medicalized' social interventions – typically behavior control strategies without real improvements in the critical embedding context of living and working conditions – are closely analogous to simplistic drug treatment strategies, and could well constitute a similar selection pressure on 'evolution machine' pathogens, causing life history adaptations which we would perceive as markedly increased virulence.

Many of us, and many of our institutions, are being severely damaged or destroyed by HIV, malaria, and other highly adaptive parasites. Twentieth Century reductionist biomedicine would appear to be among the pending victims.

Acknowledgments

This research was partially supported through NIEHS Grant I-P50-ES09600-04, and benefited from earlier monies given Rodrick Wallace under an Investigator Award in Health Policy Research from the Robert Wood Johnson Foundation.

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