



Adaptive chronic infection, structured stress, and medical magic bullets: do reductionist cures select for holistic diseases?

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Abstract

With a generalized language-of-thought argument for immune cognition, we model how population-directed, structured, psychosocial stress can impose an image of itself on the coevolutionary conflict between a highly adaptive chronic infection and the immune response.

As population-level structured stress appears a fundamental part of the biology of disease, we raise the possibility that simplistic individual-oriented magic-bullet drug treatments, vaccines, and risk-reduction programs that do not address the fundamental living and working conditions which underlie disease ecology will fail to control many current epidemics. In addition, such reductionist interventions may go so far as to select for more holistic pathogens characterized by processes operating at multiple levels of biocultural organization. The complications are representative of the concerns of cultural immunology, a new field of study. © 2004 Elsevier Ireland Ltd. All rights reserved.

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1. Introduction

The first papers in this series (Wallace, 2002a; Wallace and Wallace, 2002) examined culturally-driven variation in HIV transmission and malaria pathology. 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. *Plasmodium falciparum* engages in analogous rapid clonal antigenic variation, and cyto-adherence and sequestration in the deep vascula-

ture, primary mechanisms for escaping from antibody-mediated responses of the host's immune system (e.g. (Alred, 1998)). Something much like the mutator phenotype (Thaler, 1999) or 'second order selection' (Tenallion et al., 2001), by which the mechanisms mutations come about are themselves subjected to selection, appears to generate antigenic variation in the face of immune attack for a large class of pathogens. Concomitantly, recent work by DiNola and Neuberger (2002) outlines the mechanisms by which the immune system's own antibody-producing B-cells engage in a second order fine tuning of antibody production through somatic hypermutation, allowing organisms to respond quickly and effectively to pathogens that they have been exposed to previously (Gearhart, 2002).

Many chronic infections, particularly for pathogens that cloak themselves in antigenic 'coats of many

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colors', are very often marked by distinct stages over the course of disease. HIV infections are typically marked by an initial viremia triggering an immune response that drives the virus into refugia during an extended asymptomatic period which, with the collapse of the immune system, ends in AIDS. Malaria's most evident 'stages' are expressed as explosive outbursts of rapid parasite replication which facilitate insect-mediated transmission between hosts. HIV, malaria, and a third disease, tuberculosis, account for over 5 million deaths a year worldwide and exemplify the evolutionary success of multiple-stage chronicity as a life history strategy (Ewald, 2000; Villarreal et al., 2000).

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 for chronic infection in the face of relentless immune and other selection pressures. For HIV that punctuation may arise from the direct interactions between the virus and the immune system response. In the case of malaria, it may result by means of a 'second order punctuation' through the mutator mechanism (Thaler, 1999) associated with rapid antigenic variation. Elsewhere we study clonal selection in tumorigenesis from such a 'second order' perspective (Wallace et al., 2003).

How can we characterize the interpenetration between antagonistic adaptive processes that defines disease dynamics? 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) in essence suggested something of a reverse process, in which environmental complexity represents the amount of information organisms introduce into their environment as a result of their collective actions and interactions. We propose modeling the interactions among information sources—generalized languages—provides a more faithful encapsulation of the interactive, multi-scale nature of pathogen-immune dynamics than does the common 'differential paradigm' (e.g., (Nowak and May, 2000)).

Characterizing information sources as able to reflect their own context, as Adami et al. mapped out,

Wallace (2002b) applied a rate distortion argument in the context of imposed renormalization symmetry to obtain evolutionary 'punctuated equilibrium'. Here we use the more general Joint Asymptotic Equipartition Theorem (JAEPT) 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.

Examining paths in parameter space for the renormalization properties of such transitions (i.e., 'universality class tuning' in the sense of (Albert and Barabasi, 2002)) 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 Tenallion et al. 'second order selection'.

Recognizably similar matters have long been under scrutiny: interactions between the central nervous system (CNS) and the immune system, and between 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 introduced 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 we labeled an immunocultural condensation (ICC). It is, we will argue here, the joint entity of immune, CNS, and embedding sociocultural cognition that engages in orders of 'punctuated interpenetration' with an adaptive chronic infectious challenge. Similar arguments are already in the French literature (e.g. (Combes, 2000)).

Included among the most damaging cultural inputs on immune system function are the long-term psychosocial stresses of war, oppression, and discrimination imposed by one population on another. If valid, the paradigm has fundamental consequences for concepts of human biology. While Diamond (1997) and others (Crosby, 1986; Hughes, 2001) popularized ecological explanations of human history, the paradigm presented here suggests investigation can be directed in the other direction, at the means by which human history shapes biological ontogeny.

The paradigm would appear to have practical implications as well. Interpenetrations among pathogens, the immune system's response and the embedding culture in which individuals find themselves would greatly color the success of the kinds of individual-level disease interventions largely pursued today. Reductionist interventions—drug regimens, vaccines, risk reduction programs—aimed at holistic diseases, defined by myriad processes operating at multiple scales of time and space both within and without individuals, are likely to fail. Furthermore, What successes reductionist interventions have had against reductionist diseases may very well select for holistic diseases able to dilute or deflect the effectiveness of interventions pursued at single scales alone.

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 40 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 necessary-condition regularities of punctuation and 'generalized Onsager relations', regardless of detailed mechanisms, as important as the latter may be.

Finally, just as parametric statistics are imposed, at least as a first approximation, on sometimes questionable experimental situations, relying on the robustness of the Central Limit Theorem to carry us through, we

will invoke here a similar heuristic approach for the information theory limit theorems we define.

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.

2. Cognition as language

Adams (2003) reviews in some detail the 'informational turn in philosophy', that is, the relatively recent application of communication theory formalism and concepts to the understanding of cognitive process. One of the first reasonably successful syntheses was that of Dretske (1981, 1988, 1992, 1993, 1994), whose work Adams describes as follows: "It is not uncommon to think that information is a commodity generated by things with minds. Let's say that a naturalized account puts matters the other way around, viz. it says that minds are things that come into being by purely natural causal means of exploiting the information in their environments. This is the approach of Dretske as he tried consciously to unite the cognitive sciences around the well-understood mathematical theory of communication . . ." Dretske himself (1994) writes: "Communication theory can be interpreted as telling one something important about the conditions that are needed for the transmission of information as ordinarily understood, about what it takes for the transmission of semantic information. This has tempted people . . . to exploit [information theory] in semantic and cognitive studies, and thus in the philosophy of mind.

. . . Unless there is a statistically reliable channel of communication between [a source and a receiver] . . . no signal can carry semantic information. . . [thus] the channel over which the [semantic] signal arrives [must satisfy] the appropriate statistical constraints of communication theory." Here we redirect attention from the informational content or 'meaning' of individual symbols, i.e. the province of semantics, back to the statistical properties of long trains of symbols emitted by an 'information source'. As Dretske so clearly saw, this allows scientific inference on the necessary

conditions for cognitive process, including immune cognition.

Atlan and Cohen (1998) and Cohen (2000), following a long tradition (e.g., (Grossman, 1989; Tauber, 1998)), argue that the essence of immune function is cognitive, involving 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.

Cognitive pattern recognition-and-response, as we characterize it, proceeds by using some (otherwise unspecified) algorithm to convolute 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 will, fulfilling Atlan and Cohen’s (1998) criterion of meaning-from-response, define a language’s contextual meaning entirely in terms of system output, leaving aside the question of how such a pattern recognition system is ‘trained’.

Our model is as follows.

A pattern of sensory (antigenic) input is mixed in an unspecified but systematic algorithmic manner with an internal ‘ongoing’ system activity to create a path of mixed signals $x = (a_0, a_1, \dots, a_n, \dots)$. This path is fed into a (similarly unspecified) 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

$$B_0 \equiv b_0, \dots, b_k,$$

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

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 immune event $h(x) \in B_1$. Thus $h(a_0, \dots, a_j) \in B_0$ for all $j < m$, but $h(a_0, \dots, a_m) \in B_1$.

For each positive integer n let $N(n)$ be the number of highly probable ‘grammatical’ 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 which lead to some $h(x) \in B_1$ —actual pattern recognition-and-response occurs according to some (again unspecified) set of rules which determines highly probable as opposed to improbable paths.

While convolution algorithm, form of nonlinear oscillator, and details of grammar and syntax may all be unspecified, the critical assumption in the argument—which permits inference on necessary conditions—is that the finite limit

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

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

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

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

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

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

The Shannon uncertainties $H(\dots)$ are defined in terms of cross-sectional sums of the form $-\sum_k P_k \log[P_k]$, where the P_k constitute a probability distribution.

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. However, like the use of different distortion measures in the Rate Distortion Theorem (e.g. (Cover and

Thomas, 1991)), 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 parametrize the information source uncertainty of this dual information source with respect to one or more variates, writing, e.g. $H[\mathbf{K}]$, where $\mathbf{K} \equiv (K_1, \dots, K_s)$ 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 ‘adiabatically piecewise memoryless ergodic’.

As we will show, 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.

3. The general argument

Taking a formal Dretske-style language-of-thought 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. While 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’ $x \equiv x_0, x_1, \dots$. Similarly, we assume the pathogen population can be represented

by the path $y \equiv y_0, y_1, \dots$. These paths are, however, both very highly structured and serially correlated and can, in fact, be represented by ‘information sources’ X and 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 $z \equiv (x_0, y_0), (x_1, y_1), \dots$. The essential content of the Joint Asymptotic Equipartition Theorem (JAEPT), 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 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

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

Generalizing the earlier language-on-a-network models of Wallace and Wallace (1998a,b, 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

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

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

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

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 (Rojdestvenski and Cottam, 2000; Wallace and Wallace, 1998a,b, 1999) 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 Nisbett et al. (2001), however, any ‘cognitive’ process is likely to show significant cultural variation, and even distribution of properties.

4. Representations of the general argument

4.1. 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 net-

work 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

$$H[K, J, X]$$

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

$$H[K_R, J_R, X] = f(R)H[K, J, X] \quad \chi(K_R, J_R) = \frac{\chi(K, J)}{R}, \quad (1)$$

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 themselves 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 Eq. (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 $J \rightarrow 0$, a simple series expansion and some clever algebra (Binney et al., 1986;

Wilson, 1971) gives

$$H = H_0 \kappa^\alpha \quad \chi = \frac{\chi_0}{\kappa^s} \quad (2)$$

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 Y and 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 B —strings b —and infer something about the behavior of Y from it—strings y . We suppose it possible to define a re-translation from the B -language into the Y -language through a deterministic code book, and call \hat{Y} the translated information source, as mirrored by 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 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.

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 (1998a,b, 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 parametrized ‘instability’, $Q[K]$, is defined from the principal splitting criterion by the relation

$$Q[K] = -KdH[K]/dK \quad Q[K] = -KdI[K]/dK \quad (3)$$

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

4.2. ‘Biological’ phase transitions

Eq. (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

$$\begin{aligned} dK_R/dR &= u_1 d \log(f)/dR + u_2/R \quad dJ_R/dR \\ &= v_1 J_R d \log(f)/dR + \frac{v_2}{R} J_R. \end{aligned} \quad (4)$$

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

$$\begin{aligned} dK_R/dR &= (K_R - K_C)y d \log(f)/dR \\ &\quad + (K_R - K_C)z/R \quad dJ_R/dR \\ &= w J_R d \log(f)/dR + x J_R/R. \end{aligned} \quad (5)$$

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

$$K_R = K_C + (K - K_C)R^z f(R)^y, \quad (6)$$

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

$$K_C/2 \approx K_C + (K - K_C)R^z f(R)^y. \quad (7)$$

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 that we then substitute into the first of Eq. (1) to obtain an expression for $H[K, 0]$ in terms of known functions and parameter values.

The first step gives the general result

$$f(R_C) \approx \frac{[K_C/(K_C - K)]^{1/y}}{2^{1/y} R_C^{z/y}}. \quad (8)$$

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

$$\begin{aligned} H[K, 0] &\approx \frac{H[K_C/2, 0]}{f(R_C)} = \frac{H_0}{f(R_C)} \\ \chi(K, 0) &\approx \chi(K_C/2, 0)R_C = \chi_0 R_C \end{aligned} \quad (9)$$

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,

$$f(R) = R^\delta, \tag{10}$$

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

$$R_C = \frac{[K_C/(K_C - K)]^{1/(\delta y + z)}}{2^{1/(\delta y + z)}} \tag{11}$$

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 Eq. (9) gives a somewhat more complex expression for H than Eq. (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

$$f(R) = m \log(R) + 1. \tag{12}$$

Again $f(1) = 1$.

Using Mathematica 4.2 to solve Eq. (8) for R_C gives

$$R_C = \left[\frac{Q}{\text{Lambert W}[Q \exp(z/my)]} \right]^{y/z}, \tag{13}$$

where

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

The transcendental function Lambert W(x) is defined by the relation

$$\text{Lambert W}(x) \exp(\text{Lambert W}(x)) = x.$$

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. Such a pattern is broadly consistent with calculations of the degree of allelic heterozygosity as a function of population size under a balance between genetic drift and neutral mutation ((Hartl and Clark, 1997; Ridley, 1996)). Taking

$$f(R) = \exp[m(R - 1)/R] \tag{14}$$

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

$$R_C = \frac{my/z}{\text{Lambert W}[S]} \quad \text{where} \\ S \equiv (my/z) \exp(my/z) [2^{1/y} [K_C/(K_C - K)]^{-1/y}]^{y/z}. \tag{15}$$

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.

4.3. 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 Eq. (1) to generalize as

$$H[K_R, J_R] = \langle f(R, m) \rangle H[K, J] \\ \equiv H[K, J] \int f(R, m) \rho(m) dm. \tag{16}$$

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

$$\langle f(R) \rangle = 1 + \langle m \rangle \log(R) \tag{17}$$

where $\langle m \rangle$ is simply the mean of m over that distribution.

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

$$\langle R^\delta \rangle = R^{\langle \delta \rangle} \exp[\frac{1}{2}(\log(R^\sigma))^2], \tag{18}$$

where σ^2 is the distribution variance. The renormalization properties of this function can be determined

from Eq. (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.

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.

4.4. 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 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. The ICC begins to write itself on the pathogen’s genetic sequences or protein residues 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 Eq. (2),

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

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,

$$I[K] \approx (1 - K)^\alpha. \quad (19)$$

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

$$Q[K] \equiv -KdI[K]/dK = \alpha K(1 - K)^{\alpha-1}, \quad (20)$$

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

5. 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 $A_k \equiv \alpha_1^k, \dots, \alpha_m^k$. 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 X .

We further suppose, in the manner of 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 Y which interacts not only with the system of interest globally, but specifically with its universality class properties as characterized by X . 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 X and 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). Mutation rates become a function of the relationship between the ICC and the pathogen, above and beyond environmental insult alone.

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. Our information theory argument here converges with 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 the staged nature of chronic infectious diseases like HIV and malaria 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, involving cross interactions between direct cognitive effects of the immune system or immunocultural condensation, or, more generally, of the ICC and the mutator mechanisms of both the immune system and its pathogen targets.

We note without calculation that another path to the mutator might be through a second order interaction similar to that just above, but focused on the parameters defining the universality class distributions of Section 4.3.

6. Population stress and pathogen response

As we discuss elsewhere (Wallace, 2002a; Wallace and Wallace, 2002), structured psychosocial stress directed at populations, by policy choice or as unfore-

seen consequence, 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* :

$$P(Y_1 = y_1, Y_2 = y_2, Y_3 = y_3) = \prod_{i=1}^n p(y_{1i}|y_{3i})p(y_{2i}|y_{3i})p(y_{3i}). \quad (21)$$

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, 1991), p. 387]

$$N(n) \propto \exp[nI(Y_1; Y_2|Y_3)], \quad (22)$$

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.

We can, if necessary, extend this model to any number of interacting information sources, Y_1, Y_2, \dots, Y_s conditional on an external context Z in terms of a splitting criterion defined by

$$I(Y_1; \dots; Y_s|Z) = H(Z) + \sum_{j=1}^s H(Y_j|Z) - H(Y_1, \dots, Y_s, Z), \quad (23)$$

where the conditional Shannon uncertainties $H(Y_j|Z)$ are determined by the appropriate direct and conditional probabilities.

While this argument has been focused on complex parasites like malaria which may have mutator mechanisms determining behavior of their antigenic 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, and, at broader temporal scales, recombination.

7. Discussion and conclusions

Scientific enterprise encompasses the interaction of facts, tools, and theories, all embedded in a path-dependent political economy that seems as natural to us as air to a bird. 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 encompassing 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, "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. We think these can generate theoretical speculations of value in obtaining and interpreting empirical results about infection and immune process.

Our model explicitly invokes the possibility of synergistic interaction between the selection pressure of the immunocultural condensation (ICC) that characterizes human immune response and the variable antigenic coat of an established pathogen population, particularly in the context of embedding patterns of structured psychosocial stress which, to take a Rate Distortion perspective, can literally write an image of itself onto that interaction. The ICC, through immune hypermutation and the choice of immune response pursued, may engage in its own second order selection. What results are first, second, and possibly mixed, order interpenetrations, in which the ICC and pathogens constitute each other's selection pressure and selected structure, an interaction that may become a distorted image of enfolding patterns of socioeconomically, historically, and politically determined psychosocial stress. As the evolutionary anthropologist Robert Boyd put succinctly, Culture is as much a part of human biology as the enamel on our teeth (Richerson and Boyd, 1995), and, it follows, any effort to characterize and respond to threats to human biology need account for culture's roles.

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 Erlenmeyer flask predator–prey population dynamics of Nowak and May (2000). The cells of the immune system comprise only the point of a long biocultural sword aimed at the throats of most infections.

Individual and collective history, socioeconomic structure, psychosocial stress and the resulting emotional states, may not be mere adjuncts to what is termed 'basic science' in the medical journals. Rather, they may be as much a part of basic human biology as T-cells. 'Magic bullet' vaccines, therapeutic drugs, or highly-focused medicalized 'social' interventions against HIV disease and other mutagenic parasites—approaches that inherently cannot reckon with socioeconomic, historical, and cultural determi-

nants of health and illness – will likely largely fail as they are overwhelmed by a combination of relentless pathogen adaptation, cross-population variation in immune cognition, and a globalized travel network that increasingly confronts host populations with myriad pathogen variants. For chronic infections like HIV and malaria, 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.

We know that some social systems have succeeded in controlling malaria through, for example, persistent and highly organized programs of insect vector control. For HIV, humans are both vector and host. The larger social context, then, plays a fundamental role in the individual- and population-level decisions that promote or decelerate the HIV epidemic (Schoepf et al., 2000; Wallace and Wallace, 1998a,b). The biological consequences of ignoring the larger context are devastating, above and beyond the awful human cost of the epidemic. Recent work by one of us (Wallace, *in press*) suggests that, alone, individual-level antiretroviral treatment of the HIV epidemic may constitute a selection pressure forcing evolutionary changes in HIV life history, including, in one albeit remote possibility, a more rapid onset of AIDS. A key result, however, is that increasing infection survivorship and decreasing the transition rate from the asymptomatic stage to AIDS, as drug regimens aim to do, may induce the greatest increase in infection population growth. Because infection survivorship is physiologically enmeshed with host survivorship the asymptomatic stage becomes under the drug regimens a demographic shield against epidemiological intervention. In other words, HIV may use processes at one level of biocultural organization to defend itself against cures directed at it at other levels. Any successful intervention, then, must display a comparable multidimensionality.

Cartesian reductionism internalizes causality by assuming the whole of any phenomenon is a sum of its parts. Despite its successes, many (Bignami, 1982; Gould, 2003; Levins and Lewontin, 1985; Levins, 1998; Mayr, 1996; Oyama et al., 2001; Van Regenmortel and Hull, 2002; Wimsatt, 1980) have pointed out the problems with the reductionist approach in the study of biological phenomena, including of disease. Reductionism's widespread ap-

plication, even on problems that do not yield to its approaches, is in part an outgrowth of social decisions about the role and nature of science.

Our work, here and cited, suggests a further complication. The consequences of reductionism's failures do not merely include mischaracterizing epidemics. The nature of study itself can affect the evolution of pathogens. The reductionist approach may very well *select for* holistic or dialectical responses on the part of pathogens. Reductionism's wholesale application, while succeeding against diseases, such as polio and smallpox, welcome developments notwithstanding, may select for diseases that are characterized by complex sociogeographies, multiple hosts, and multidimensional interactions across scale. The HIV, malaria, and tuberculosis epidemics, as we have discussed, are obvious examples of holistic pathogens. In industrial countries, heart disease, cancer, and obesity take their toll; so-called diseases of affluence the poorest and most marginalized typically suffer the worst (Wallace et al., 2003, in press). The ecology literature tells us sources of mortality compete. While pharmaceuticals, surgery, and individual-level risk reduction interventions control reductionist threats—additive sources of mortality both within individuals and populations—the pathogenic playing field appears now tilted towards holistic diseases we are largely unable to address because of the restricted scientific and medical practices pursued.

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 increasingly abandoned in agriculture as simply inadequate to address pathogen evolutionary strategies.

Prospects for studying immunocultural condensation and implementing a related IPM appear both exciting and difficult. 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 idiosyncratic hall of mirrors? The mathematics would be straightforward, but the corre-

sponding molecular biology would have to be subtle indeed. Higher order interpenetration—mutating the mutator—may be observable in certain isolated circumstances, for example in the interplay between B-cell somatic hypermutation and a pathogen's hypervariable membrane proteins. Clearly much work is needed to trace the connections among the culture-specific and cognitive nature of the immune system, pathogen adaptation, the information dynamics of their interaction, the molecular manifestations of those dynamics, and the particularities of intervention. The new field of cultural immunology awaits practitioners. A frontier beckons.

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