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The ecology of suffering: developmental disorders of structured stress, emotion, and chronic inflammation

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Abstract

'Punctuated equilibrium' models of cognitive process, adapted from the Large Deviations Program of probability theory, are applied to the interaction between immune function and emotion in the context of culturally structured psychosocial stress. The analysis suggests:

(1) Chronic inflammatory diseases should be comorbid and synergistic with characteristic emotional dysfunction, and may form a collection of joint disorders most effectively treated at the individual level using multifactorial 'mind/body' strategies.

(2) Culturally constructed psychosocial stress can literally write an image of itself onto the punctuated etiology and progression of such composite disorders, beginning a trajectory to disease in utero or early childhood, and continuing throughout the life course, suggesting that, when moderated by 'social exposures', these are developmental disorders.

(3) At the community level of organization, strategies for prevention and control of the spectrum of emotional/inflammatory developmental disorders must include redress of cross-sectional and longitudinal (i.e. historical) patterns of inequality and injustice which generate structured psychosocial stress.

Evidence further suggests that within 'Westernized' or 'market economy' societies, such stress will inevitably entrain high as well as lower status subpopulations into a unified ecology of suffering.

Key words: culture, development, emotion, inflammatory disease, mathematical model, mind-body interaction, phase transition, psychosocial stress, punctuated equilibrium, renormalization

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Introduction

Disorders of chronic inflammation include coronary heart disease (Libbey et al., 2002), certain cancers (Dalgleish and O'Byrne, 2002), diabetes, asthma, and allergies (Kiecolt-Glaser et al., 2002), autoimmune disease, and such chronic infections as tuberculosis, malaria and other parasitic infestations, and HIV (e.g. Wallace and Wallace, 2002, 2003; Wallace, 2002a). These conditions account for a great portion of human morbidity and mortality, in both 'Westernized' and other societies. Some, like coronary heart disease and asthma, are already recognized as developmental disorders, beginning *in utero* or early childhood and progressing throughout the life course (e.g. Barker, 2002; Barker et al., 2002; Osmond and Barker, 2000; Godfrey and Barker, 2001; Smith et al., 1998; Smith and Ruiz, 2002; Repetti et al., 2002; Wright et al., 1998; Wallace, Wallace, and Fullilove, 2003).

Many chronic inflammatory diseases are well known to be highly structured at the community level of organization by the social and cultural constructs of 'race', 'ethnicity', and 'socioeconomic status', a circumstance which, we will show, permits profound insight into etiology. This is because, to the extent these are 'environmental' disorders, the principal environment of humans is other humans, moderated by an embedding culture which particularly characterizes the human animal. Thus culturally-sculpted 'social exposures' are likely to be important at the individual, and critical at the population, levels of organization in the expression of chronic inflammatory disease.

Here we will examine how individual emotion and immune cognition may become synergistically linked with embedding, culturally structured, psychosocial stress to produce comorbid patterns of health and illness associated with chronic inflammation. We will suggest that many such disorders either have their roots in utero, as a stressed mother communicates environmental signals across the placenta, and programs her developing child's physiology, or else are initiated during early childhood. This pattern may affect underlying susceptibility to chronic infections or parasitic infestation as well as more 'systemic' disorders.

To address these matters we adapt recent advances in understanding 'punctuated equilibrium' in evolutionary process (e.g. Wallace, 2002b; Wallace and Wallace, 1998, 1999) to the question of how embedding structured psychosocial stress affects the interaction of mind and body. We specifically seek to determine how the synergism of stress, emotion, and chronic inflammation, might be constrained by certain of the asymptotic limit theorems of probability.

We know that, regardless of the probability distribution of a particular stochastic variate, the Central Limit Theorem ensures that long sums of independent realizations of that variate will follow a Normal distribution. Analogous constraints exist on the behavior of information sources – both independent and interacting – and these are described by the limit theorems of information theory. Imposition of phase transition formalism from statistical physics, in the spirit of the Large Deviations Program of applied probability, permits concise and unified description of evolutionary and cognitive 'learning plateaus' which, in the

evolutionary case, are interpreted as evolutionary punctuation (e.g. Wallace, 2002a, b). This approach provides a 'natural' means of exploring punctuated processes in the effects of structured stress on mind-body interaction.

The model, as in the relation of the Central Limit Theorem to parametric statistical inference, is almost independent of the detailed structure of the interacting information sources inevitably associated with cognitive process, important as such structure may be in other contexts. This finesses the profound ambiguities associated with 'dynamic systems theory' and 'deterministic chaos' treatments in which the existence of 'dynamic attractors' depends on very specific kinds of differential equation models akin to those used to describe ecological population dynamics, chemical processes, or physical systems of weights-on-springs. Cognitive phenomena are neither well-stirred Erlenmeyer flasks of reacting agents, nor distorted mechanical clocks, and the application of 'dynamic systems theory' to cognition will likely be found to involve little more than hopeful metaphor.

In contrast, it seems actually possible to uncover the grammar and syntax of structured psychosocial stress, emotion, and immune function, and to express their relations in terms of empirically observed regression models relating measurable biomarkers. Our analysis will focus on the eigenstructure of those models, constrained by the ergodic and other properties of information sources.

Clearly our approach takes much from parametric statistics, and, while idiosyncratic 'nonparametric' models may be required in special cases, may well capture the essence of the most common relevant phenomena.

We are particularly interested in the effects of 'stress' on the interaction between mind and body over the life course. 'Stress', we aver, is not often random in human societies, but is itself usually a socially and culturally constructed artifact, a very highly structured, 'language', having both a grammar and a syntax, so that certain stressors are 'meaningful' in a particular context, and others are not, having little or no long-term physiological effect. We first argue that emotion and immune function are, in fact, cognitive systems each associated with a 'dual information source' which may also be expressed as a kind of language. It is the punctuated interaction of these three 'languages' which we will find critical to an understanding of how psychosocial stress affects the mind-body interaction, and, ultimately, writes a literal image of itself upon that interaction, beginning in utero or early childhood, and determining a trajectory to disease.

Immune cognition

Recently Atlan and Cohen (1998) have proposed an information-theoretic model of immune function and process, a paradigm incorporating cognitive pattern recognition-and-response behaviors analogous to those of the central nervous system.

From this perspective, the meaning of an antigen can be reduced to the type of response the antigen generates. That is, the meaning of an antigen is functionally defined by the response of the immune system. The meaning of an

antigen to the system is discernible in the type of immune response produced, not merely whether or not the antigen is perceived by the receptor repertoire. Because the meaning is defined by the type of response there is indeed a response repertoire and not only a receptor repertoire.

To account for immune interpretation Cohen (1992, 2000) has proposed a cognitive paradigm for the immune system. The immune system can respond to a given antigen in various ways, it has 'options.' Thus the particular response we observe is the outcome of internal processes of weighing and integrating information about the antigen.

In contrast to Burnet's view of the immune response as a simple reflex, it is seen to exercise cognition by the interpolation of a level of information processing between the antigen stimulus and the immune response. A cognitive immune system organizes the information borne by the antigen stimulus within a given context and creates a format suitable for internal processing; the antigen and its context are transcribed internally into the 'chemical language' of the immune system.

The cognitive paradigm suggests a language metaphor to describe immune communication by a string of chemical signals. This metaphor is apt because the human and immune languages can be seen to manifest several similarities such as syntax and abstraction. Syntax, for example, enhances both linguistic and immune meaning.

Although individual words and even letters can have their own meanings, an unconnected subject or an unconnected predicate will tend to mean less than does the sentence generated by their connection.

The immune system creates a 'language' by linking two ontogenetically different classes of molecules in a syntactical fashion. One class of molecules are the T and B cell receptors for antigens. These molecules are not inherited, but are somatically generated in each individual. The other class of molecules responsible for internal information processing is encoded in the individual's germline.

Meaning, the chosen type of immune response, is the outcome of the concrete connection between the antigen subject and the germline predicate signals.

The transcription of the antigens into processed peptides embedded in a context of germline ancillary signals constitutes the functional 'language' of the immune system. Despite the logic of clonal selection, the immune system does not respond to antigens as they are, but to abstractions of antigens-in-context.

Emotion as a cognitive process

A recent important paper by Thayer and Lane (2000) summarizes the case for what can be described as a cognitive emotional process. Emotions, in their view, are an integrative index of individual adjustment to changing environmental demands, an organismal response to an environmental event that allows rapid mobilization of multiple subsystems. Emotions are the moment-to-moment output of a continuous sequence of behavior, organized around biologically important functions. These 'lawful' sequences have been termed 'behavioral systems' by Timberlake (1994).

Emotions are self-regulatory responses that allow the efficient coordination of the organism for goal-directed behavior. Specific emotions imply specific eliciting stimuli, specific action tendencies including selective attention to relevant stimuli, and specific reinforcers. When the system works properly, it allows for flexible adaptation of the organism to changing environmental demands, so that an emotional response represents a *selection* of an appropriate response and the inhibition of other less appropriate responses from a more or less broad behavioral repertoire of possible responses. Such 'choice', we will show, leads directly to something closely analogous to the Atlan and Cohen language metaphor.

Damasio (1998) concludes that emotion is the most complex expression of homeostatic regulatory systems. The results of emotion serve the purpose of survival even in nonminded organisms, operating along dimensions of approach or aversion, of appetition or withdrawal. Emotions protect the subject organism by avoiding predators or scaring them away, or by leading the organism to food and sex. Emotions often operate as a basic mechanism for making decisions without the labors of reason, that is, without resorting to deliberated considerations of facts, options, outcomes, and rules of logic. In humans learning can pair emotion with facts which describe the premises of a situation, the option taken relative to solving the problems inherent in a situation, and perhaps most importantly, the outcomes of choosing a certain option, both immediately and in the future. The pairing of emotion and fact remains in memory in such a way that when the facts are considered in deliberate reasoning when a similar situation is revisited, the paired emotion or some aspect of it can be reactivated. The recall, according to Damasio, allows emotion to exert its pairwise qualification effect, either as a conscious signal or as nonconscious bias, or both, In both types of action the emotions and the machinery underlying them play an important regulatory role in the life of the organism. This higher order role for emotion is still related to the needs of survival, albeit less apparently.

Thayer and Friedman (2002) argue, from a dynamic systems perspective, that failure of what they term 'inhibitory processes' which, among other things, direct emotional responses to environmental signals, is an important aspect of psychological and other disorder. Sensitization and inhibition, they claim, 'sculpt' the behavior of an organism to meet changing environmental demands. When these inhibitory processes are dysfunctional – choice fails – pathology appears at numerous levels of system function, from the cellular to the cognitive.

Thayer and Lane (2000) also take a dynamic systems perspective on emotion and behavioral subsystems which, in the service of goal-directed behavior and in the context of a behavioral system, they see organized into coordinated assemblages that can be described by a small number of control parameters, like the factors of factor analysis, revealing the latent structure among a set of questionnaire items thereby reducing or mapping the higher dimensional item space into a lower dimensional factor space. In their view, emotions may represent preferred configurations in a larger 'state-space' of a possible behavioral repertoire of the organism. From their perspective, disorders of affect represent a condition in which the individual is unable to select the appropriate response, or to inhibit the inappropriate response, so that the response selection mechanism is

somehow corrupted.

We shall, by invoking the constraints of the asymptotic limit theorems of information theory, express very much the same qualitative pattern in terms of the algebraic structure of biomarker regression models which might actually be observable, without needing to invoke dynamic systems theory. Dynamic process is constrained by the asymptotic limit theorems of information theory 'phase transition' punctuation, and by a kind of quasi-thermodynamic 'generalized Onsager relations' which are explained more fully elsewhere (e.g. Wallace, 2002a, b).

Cognition as 'language'.

Atlan and Cohen (1998), as we have paraphrased them, argue that the essence of cognition is comparison of a perceived external signal with an internal, learned picture of the world, and then, upon that comparison, the choice of one response from a much larger repertoire of possible responses. Clearly, from this perspective, the Thayer and Lane vision of the emotional process is cognitive. Upon recognition of a new perturbation in the surrounding environment, emotional cognition evaluates and choose from several possible responses: no action necessary, or one or a few succinct emotions elicited. Upon appropriate conditioning, the emotional response is able to accelerate the decision process as to what large-scale, general response may be needed, much as the immune system has a more efficient response to second pathogenic challenge once the initial infection has become encoded in immune memory.

Following the approach of Wallace (2000, 2002a), we make a very general model of this process.

Pattern recognition-and-response, as we characterize it, proceeds by convoluting (i.e. comparing) an incoming external 'sensory' 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 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

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

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

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

(1)

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

The Shannon-McMillan Theorem provides a kind of 'law of large numbers' and permits definition of the Shannon uncertainties in terms of cross-sectional sums of the form

$$H = -\sum P_k \log[P_k],$$

where the P_k are taken from a probability distribution, so that $\sum P_k = 1$. Cover and Thomas (1991) or Ash (1990) provide algebraic details.

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. Dividing the full set of possible responses into the sets B_0 and B_1 may itself require 'higher order' cognitive decisions by other modules.

Meaningful paths – creating an inherent grammar and syntax – are defined entirely in terms of system response, as Atlan and Cohen (1998) propose.

We can apply this formalism to the stochastic neuron in a neural network: A series of inputs $y_i^j, i = 1, ...m$ from m nearby neurons at time j to the neuron of interest is convoluted with 'weights' $w_i^j, i = 1, ..., m$, using an inner product

$$a_j = \mathbf{y}^j \cdot \mathbf{w}^j \equiv \sum_{i=1}^{m} y_i^j w_i^j$$

(2)

in the context of a 'transfer function' $f(\mathbf{y}^j \cdot \mathbf{w}^j)$ such that the probability of the neuron firing and having a discrete output $z^j = 1$ is $P(z^j = 1) = f(\mathbf{y}^j \cdot \mathbf{w}^j)$.

Thus the probability that the neuron does not fire at time j is just $1 - P$. In the usual terminology the m values y_i^j constitute the 'sensory activity' and the m weights w_i^j the 'ongoing activity' at time j, with $a_j = \mathbf{y}^j \cdot \mathbf{w}^j$ and the path $x \equiv a_0, a_1, ..., a_n, ...$ A little more work leads to a standard neural network model in which the network is trained by appropriately varying $\mathbf{w}$ through least squares or other error minimization feedback. This can be shown to replicate rate distortion arguments, as we can use the error definition to define a distortion function which measures the difference between the training pattern y and the network output $\hat{y}$ as a function, for example, of the inverse number of training cycles, K. As we will discuss in another context, 'learning plateau' behavior emerges naturally as a phase transition in the parameter K in the mutual information $I(Y, \hat{Y})$.

Thus we will eventually parametize the information source uncertainty of the dual information source to a cognitive pattern recognition-and-response 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). See Binney, et al. (1986) for a more complete discussion.

We will call such an information source 'adiabatically piecewise memoryless ergodic' (APME). The ergodic nature of the information sources is a generalization of the 'law of large numbers' and implies that the long-time averages we will need to calculate can, in fact, be closely approximated by averages across the probability spaces of those sources. This is no small matter.

Interacting information sources

We suppose that the behavior of the emotional or immune system can be represented by a sequence of 'states' in time, the 'path' $x \equiv x_0, x_1, ...$ Similarly, we assume an external signal of 'structured psychosocial stress' can also be represented by a path $y \equiv y_0, y_1, ...$ These paths are, however, both very highly structured and, within themselves, are serially correlated and can, in fact, be represented by 'information sources' $\mathbf{X}$ and $\mathbf{Y}$. We assume the cognitive process and external stressors interact, so that 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

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

(3)

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. As stated above, the Shannon-McMillan Theorem and its variants permit expression of the various uncertainties in terms of cross sectional sums of terms of the form

$-P_k \log[P_k]$. 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, according to the Shannon-McMillan Theorem and its 'joint' variants,

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

(4)

Generalizing the earlier language-on-a-network models of Wallace and Wallace (1998, 1999), we suppose there is a 'coupling parameter' P representing the degree of linkage between the cognitive system of interest and the structured 'language' of external signals and stressors, 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

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

(5)

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 (e.g. Wallace and Wallace, 1998, 1999; Wallace, 2000; Rojdestvensky and Cottam, 2000; Feynman, 1996) 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 cognitive mechanism and external perturbation. An extensive mathematical treatment of these ideas is presented elsewhere (e.g. Wallace, 2000, 2002a,b; Wallace et al., 2003).

Elaborate developments are possible. From a the more limited perspective of the Rate Distortion Theorem, a selective corollary of the Shannon-McMillan Theorem, we can view the onset of a punctuated interaction between the cognitive mechanism and external stressors as the literal writing of distorted image of those stressors upon cognition:

Suppose that two (piecewise, adiabatically memoryless) 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.

Extending the 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)

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

(6)

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 $I(Y_1, Y_2|Y_3)$. Note that our results are almost exactly parallel to the Eldredge/Gould model of evolutionary punctuated equilibrium (Eldredge, 1985; Gould, 2002).

The simplest model of emotion and stress

Stress, as we envision it, is not a random sequence of perturbations, and is not independent of its perception. Rather, it involves a highly correlated, grammatical, syntactical process by which an embedding psychosocial environment communicates with an individual, particularly with that individual's emotional state, typically in the context of social hierarchy. We first view the stress experienced by an individual as APME information source, interacting with a similar dual information source defined by emotional cognition.

Again, the ergodic nature of the 'language' of stress is essentially a generalization of the law of large numbers, so that long-time averages can be well approximated by cross-sectional expectations. Languages do not have simple autocorrelation patterns, in distinct contrast with the usual assumption of random perturbations by 'white noise' in the standard formulation of stochastic differential equations.

Let us suppose we cannot measure either stress or emotion directly, but can determine the concentrations of hormones, neurotransmitters, certain cytokines, and other biomarkers associated with an emotional response according to some 'natural' time frame inherent to the system, typically the circadian cycle. Suppose, in the absence of extraordinary 'meaningful' psychosocial stress, we measure a series of n concentrations at time t which we represent as an n-dimensional vector X_t. Suppose we conduct a number of experiments, and create a regression model so that we can, in the absence of perturbation, write, to first order, the concentration of biomarkers at time $t+1$ in terms of that at time t using a matrix equation of the form

$$X_{t+1} \approx < \mathbf{R} > X_t + b_0,$$

(7)

where $< \mathbf{R} >$ is the matrix of regression coefficients and b_0 a (possibly zero) vector of constant terms.

We then suppose that, in the presence of a perturbation by structured stress

$$X_{t+1} = (< \mathbf{R} > + \delta \mathbf{R}_{t+1}) X_t + b_0$$

$$\equiv < \mathbf{R} > X_t + \epsilon_{t+1},$$

(8)

where we have absorbed both b_0 and $\delta\mathbf{R}_{t+1}X_t$ into a vector ϵ_{t+1} of 'error' terms which are not necessarily small in this formulation. In addition it is important to realize that this is not a population process whose continuous analog is exponential growth. Rather what we examine is more akin to the passage of a signal – structured psychosocial stress – through a distorting physiological filter.

If the matrix of regression coefficients $< \mathbf{R} >$ is sufficiently regular, we can (Jordan block) diagonalize it using the matrix of its column eigenvectors $\mathbf{Q}$, writing

$$\mathbf{Q}X_{t+1} = (\mathbf{Q} < \mathbf{R} > \mathbf{Q}^{-1})\mathbf{Q}X_t + \mathbf{Q}\epsilon_{t+1},$$

(9)

or equivalently as

$$Y_{t+1} =< \mathbf{J} > Y_t + W_{t+1},$$

(10)

where $Y_t \equiv \mathbf{Q}X_t, W_{t+1} \equiv \mathbf{Q}\epsilon_{t+1}$, and $< \mathbf{J} >\equiv \mathbf{Q} < \mathbf{R} > \mathbf{Q}^{-1}$ is a (block) diagonal matrix in terms of the eigenvalues of $< \mathbf{R} >$.

Thus the (rate distorted) writing of structured stress onto emotional response through $\delta\mathbf{R}_{t+1}$ is reexpressed in terms of the vector W_{t+1}.

It is important to note that, in general, the eigenvectors of $< \mathbf{R} >$ are not orthogonal, suggesting the possibility that excitation of a single eigenvector will result in 'overtones' of 'mixed emotions', in our model. We will return to the importance of nonorthogonality below.

The sequence of W_{t+1} is the rate-distorted image of the information source defined by the system of external structured psychosocial stress. This formulation permits estimation of the long-term steady-state effects of that image on emotional state. The essential trick is to recognize that because everything is (APM) ergodic, we can either time or ensemble average both sides of equation (10), so that the one-period offset is absorbed in the averaging, giving an 'equilibrium' relation

$$< Y >=< \mathbf{J} >< Y > + < W >$$

or

$$< Y >= (\mathbf{I} - < \mathbf{J} >)^{-1} < W >,$$

(11)

where $\mathbf{I}$ is the $n \times n$ identity matrix.

Now we reverse the argument: Suppose that Y_k is chosen to be some fixed eigenvector of $< \mathbf{R} >$. Using the diagonalization of $< \mathbf{J} >$ in terms of its eigenvalues, we obtain the average 'emotional excitation' in terms of some eigentransformed pattern of exciting perturbations as

$$< Y_k >= \frac{1}{1 - < \lambda_k >} < W_k >$$

(12)

where $< \lambda_k >$ is the eigenvalue of $< Y_k >$, and $< W_k >$ is some appropriately transformed set of ongoing perturbations by structured psychosocial stress.

The essence of this result is that *there will be a characteristic form of perturbation by structured psychosocial stress – the W_k – which will resonantly excite a particular 'emotional eigenmode'.* Conversely, by 'tuning' the eigenmodes of $< \mathbf{R} >$, emotional output can be trained to galvanized response in the presence of particular forms of long-lasting perturbation.

This is because, if $< \mathbf{R} >$ has been appropriately determined from regression relations, then the λ_k will be a kind of multiple correlation coefficient (e.g. Wallace and Wallace, 2000), so that particular eigenpatterns of perturbation will have greatly amplified impact. If $\lambda = 0$ then perturbation has no more effect than its own magnitude. If, however, $\lambda \to 1$, then the written image of a perturbing psychosocial stressor will have very great effect. Following Ives (1995), we call a system with $\lambda \approx 0$ *resilient* since its response is no greater than the perturbation itself.

We suggest that emotional learning, is, in fact, the process of tuning response to perturbation. This is why we have written $< \mathbf{R} >$ instead of simply $\mathbf{R}$: The regression matrix is a tunable set of variables.

Suppose we require that $< \lambda >$ itself be a function of the magnitude of excitation, i.e.

$$< \lambda >= f(| < W > |)$$

where $|< W >|$ is the vector length of $< W >$. We can, for example, require the amplification factor $1/(1- < \lambda >)$ to have a signal transduction form, an inverted-U-shaped curve, for example the signal-to-noise ratio of a stochastic resonance, so that

$$\frac{1}{1- < \lambda >} = \frac{1/| < W > |^2}{1 + b \exp[1/(2| < W > |)]}.$$

(13)

This places particular constraints on the behavior of the 'learned average' $< \mathbf{R} >$, and gives a pattern of initial hypersensitization, followed by anergy or 'burnout' with increasing average stress, a behavior that might well be characterized as 'pathological resilience', and may also have evolutionary significance.

The emotional retina: responding to sudden change

Suppose we can write an emotional response to a more general and short-term perturbation, not simply the effects of long-lasting structured psychosocial stress, as

$$X_{t+1}(< \mathbf{R} > + \delta \mathbf{R}_{t+1}) X_t.$$

Again we impose a (Jordan block) diagonaliation in terms of the matrix of (generally nonorthogonal) eigenvectors of $< \mathbf{R} >$, $< \mathbf{Q} >$, obtaining, for an initial state which is an eigenvector, $Y_t \equiv Y_k$,

$$Y_{t+1} = (< \mathbf{J} > + \delta \mathbf{J}_{t+1}) Y_k = \lambda_k Y_k + \delta Y_{t+1} =$$

$$\lambda_k Y_k + \sum_{j=1}^{n} a_j Y_j,$$

(14)

where $\mathbf{J}$ is a (block) diagonal matrix, $\delta \mathbf{J}_{t+1} \equiv \mathbf{Q} \delta \mathbf{R}_{t+1} \mathbf{Q}^{-1}$, and δY_{t+1} *has been expanded in terms of a spectrum of the eigenvectors of* $< \mathbf{R} >$, with

$$|a_j| \ll |\lambda_k|, |a_{j+1}| \ll |a_j|.$$

(15)

The essential point is that, provided $< \mathbf{R} >$ has been properly 'tuned', so that this condition is true, the first few terms in the spectrum of the plieotropic iteration of the eigenstate will contain almost all of the essential information about the perturbation, i.e. most of the variance. We envision this as similar to the detection of color in the optical retina, where three overlapping non-orthogonal 'eigenmodes' of response suffice to characterize a vast array of color sensations. Here, if a concise spectral expansion is possible, a very small number of (typically nonorthogonal) 'emotional eigenmodes' permit characterization of a vast range of external perturbations, and rate distortion constraints become very manageable indeed. Thus emotional responses – the spectrum of excited eigenmodes of $< \mathbf{R} >$ – if properly tuned, can be a very accurate and precise gauge of environmental perturbation.

We have recovered much of Thayer and Lane (2000) in a simple algebraic manner involving regression models of observable biomarkers, without invocation of dynamic systems theory, but at the expense of asymptotic limit theorem complications. The next step is to impose punctuated equilibrium.

Stress, emotion, and inflammation in punctuated equilibrium

Network information theory, so-called (Cover and Thomas, 1991), in which one information source, Y_3, serves as an embedding context for two others, Y_1, Y_2, leads to the 'splitting criterion' for 'meaningful' linked triplets of sequences according to equation (6) above as

$$I(Y_1; Y_2|Y_3) =$$

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

(16)

We envision the dual information sources to emotional and immune cognition as Y_1 and Y_2 and the information source corresponding to patterns of structured psychosocial stress as Y_3. We suppose it possible to parametize the coupling between the three information sources by some 'inverse temperature', K, writing

$$I(Y_1; Y_2|Y_3) = I[K],$$

(17)

with structured psychosocial stress as the embedding context.

Invocation of the mathematical homology between equations (4) and (5) permits imposition of renormalization formalism (Wallace, 2000; Wallace et al., 2003a) resulting in punctuated phase transition depending on K. Details will vary between systems, but the punctuated equilibrium pattern seems likely to be quite universal. This means that, while stress, emotion, and immune function may vary evenly (i.e. 'adiabatically') with the strength of coupling between them over a particular range of the coupling parameter, at certain 'critical points' in coupling strength, their physiological relation can change radically and suddenly, much as a phase transition in a physical system. Elsewhere (Wallace, et al., 2003a) we explore 'universality class tuning' whereby the parameters of the renormalization relations characterizing phase transition themselves become the output of an information source interacting with another. We will not pursue such complications here, although they seem of likely significance.

Socioculturally constructed and structured psychosocial stress, in this model having both 'grammar' and 'syntax', can be viewed as entraining emotion, immune function, and their synergistic interaction, when the coupling between stress and individual exceeds a threshold. More than one threshold appears likely, accounting in a sense for the typically staged nature of 'environmentally caused' disorders. These should be synergistic – i.e. comorbidly interacting – affective and physical, and represent the effect of stress on the linked internal decision processes of both emotion and immune function. This is a collective 'tuning failure' which, in the Rate Distortion sense, represents a literal image of the structure of imposed psychosocial stress written upon the joint expression of emotion and inflammation. Elsewhere (Wallace et al., 2003a, b, c, d, e) we explore aspects of cancer, coronary heart disease, childhood asthma, lupus, chronic infection, and obesity, from much this perspective, without, however, explicit invocation of comorbid emotional disorder.

Coronary heart disease (CHD) is already understood as a disease of development, which begins *in utero*. Work by Barker and colleagues, which we cited above, suggests that those who develop CHD grow differently from others, both in utero and during childhood. Slow growth during fetal life and infancy is followed by accelerated weight gain in childhood, setting a life history trajectory for CHD, type II diabetes, hypertension, and, of course, obesity. Barker (2002) concludes that slow fetal growth might also heighten the body's stress responses and increase vulnerability to poor living conditions later in life. Thus, in his view, CHD is a developmental disorder that originates through two widespread

biological phenomena, developmental plasticity and compensatory growth, a conclusion consistent with the work of Smith et al. (1998), who found that deprivation in childhood influences risk of mortality from CHD in adulthood, although an additive influence of adult circumstances is seen in such cases.

With regard to asthma, Wright et al. (1998) find prospective epidemiological studies showing that the newborn period is dominated by TH2 reactivity in response to allergens, and it is also evident that TH1 memory cells selectively develop shortly after birth, and persist into adulthood in non-atopic subjects. For most children who become allergic or asthmatic, the polarization of their immune systems into an atopic phenotype probably occurs during early childhood. There is evidence that parental reports of life stress are associated with subsequent onset of wheezing in children between birth and one year. It has been speculated that stress triggers hormones in the early months of life which may influence Th2 cell predominance, perhaps through a direct influence of stress hormones on the production of cytokines that are thought to modulate the direction of immune cell differentiation.

We are led to suggest that these two case histories represent a far more general phenomenon in the etiology of the larger spectrum of chronic inflammatory disorders, in the sense that structured psychosocial stress can literally write an image of itself upon the developing child, initiating trajectories to disease.

Conclusions

The mathematical ecologist E.C. Pielou (1977, p. 106) properly cautions that mathematical models of complex ecosystem phenomena can legitimately be used to raise questions for empirical study, but not to answer them. In very much that spirit, our modeling exercise suggests:

(1) Chronic inflammatory diseases should be synergistically comorbid with emotional dysfunction, forming a distinct collection of joint disorders which can be most effectively treated at the individual level using multifactorial 'mind/body' strategies.

(2) Embedding, culturally-crafted, structured psychosocial stress can literally write an image of itself onto the punctuated etiology and progression of such composite disorders. This process probably begins either in utero or early childhood for most chronic inflammatory diseases, placing them squarely in the realm of developmental disorders.

(3) At the community level of organization, strategies for prevention and control of the spectrum of emotional/inflammatory disorders must include redress of cross sectional and longitudinal (i.e. 'historical') patterns of inequity and injustice which sculpt and structure the grammar and syntax of psychosocial stress.

Within 'Westernized' or 'market economy' societies in particular, a kind of 'pathogenic social hierarchy' seems to characterize the interaction of individuals with embedding institutions. Figure 1 is taken from Singh-Manoux et al. (2003), and displays, for men and women separately, self-reported health as a function of self-reported status rank, where 1 is high and 10 low rank, among some

7,000 male and 3,400 female London-based office staff, aged 35-55 working in 20 Civil Service departments in the late 1990's. Self-reported health is a highly significant predictor of future morbidity and mortality. This is clearly the first part of a nonlinear 'S-shaped' dose-response curve which very nearly achieves the 'LD-50' level of fifty percent of the affected population.

It is unlikely that chronic diseases of emotion/inflammation can be significantly treated or prevented in the context of such a relationship (e.g. Wilkinson, 1996). Alteration of this relation by law, regulation, or negotiation would seem a prerequisite for progress, all matters involving open conflict between groups having fundamentally different interests. It is our contention, however, that a relation like figure 1 represents concentration rather than containment of a larger ecosystem pathology (e.g. Wallace and Wallace, 1997), so that those at the lower left of figure 1 would themselves benefit greatly from mitigation of the plight of those at the upper right.

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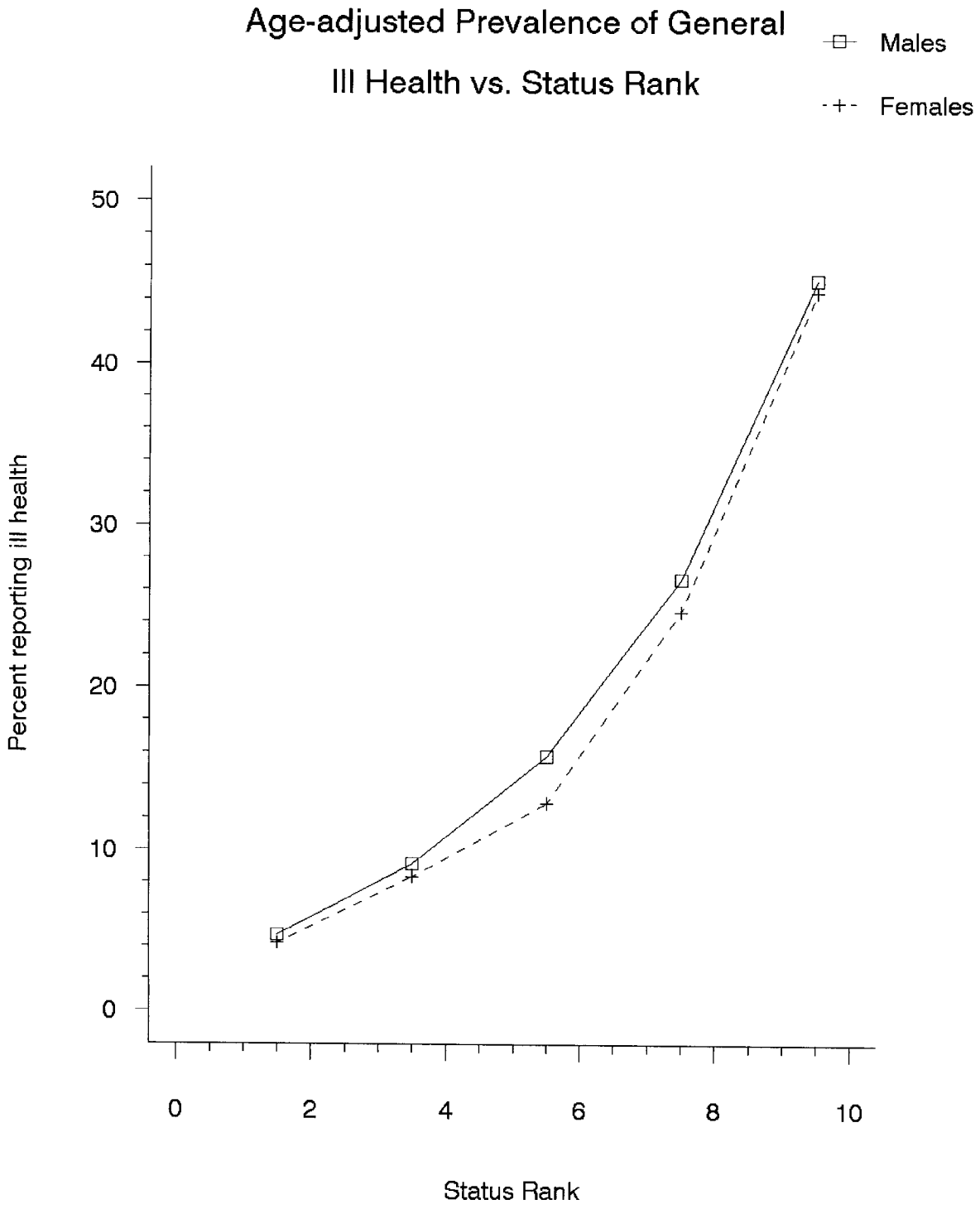
Figure Caption

Figure 1. Redisplay of data from Singh-Manoux et al. (2003). Sex-specific dose-response curves of age-adjusted prevalence of self-reported ill-health vs. self-reported status rank, Whitehall II cohort, 1997 and 1999. 1 is high and 10 is low status. Note that the curves are virtually identical, and that the upper point is very near the 'EC-50' level in this population. Self-reported health is a highly significant predictor of later mortality and morbidity.


Age-adjusted Prevalence of General
Ill Health vs. Status Rank
Males
Females
Percent reporting ill health
50
40
30
20
10
0
0
2
4
6
8
10
Status Rank