Rodrick Wallace
Deborah Wallace
Division of Epidemiology
The New York State Psychiatric Institute

Magic Strategies: The Basic Biology of Multilevel, Multiscale Health Promotion

– Monograph –

May 14, 2013

DRAFT

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

Preface

A survey of the cultural psychology and related literatures suggests that Western biomedicine's fascination with atomistic, individual-oriented, interventions is a cultural artifact that may have little consonance with complex, subtle, multiscale, multilevel, social, ecological, or biological realities. Other cultural traditions may, in fact, view atomistic strategies as inherently unreal. A contrary perspective – similar to that of health promotion – implies that the most effective medical or public health interventions must be analogously patterned across scale and level of organization: 'magic strategies' will almost always be synergistically, and often emergently, more effective than 'magic bullets'. The result can be formally derived in a relatively straightforward manner using an adaptation of the Black-Scholes econometric model applied to the metabolic cost of bioregulation under uncertainty. Multifactorial interventions focused at the human 'keystone' ecosystem level of mesoscale social and geographic groupings may be particularly effective.

The analysis indicates that there is unlikely to be much in the way of 'simple' chronic disease. That is, serious comorbidity is usually inevitable, and may often be a consequence of therapeutic intervention itself. Study suggests that pairing of medical and prevention strategies with appropriate mesoscale neighborhood/social network interventions would:

(1) Damp down unwanted treatment side effects.

(2) Make the therapeutic alliance between practitioner and patient more effective.

(3) Improve patient compliance.

(4) Enhance placebo effect.

(5) In the context of real stress reduction, synergistically improve the actual biological impacts of medical interventions or prevention strategies.

Much of this is well-known and has been repeatedly described across a vast array of public health and health policy literatures, but the results will be developed here from first principles, involving the interaction of cognitive and environmental phenomena across both scale and levels of organization, echoing something of the pioneering insights of Maturana and Varela. With some added complexity, the analysis can be extended to developmental trajectories, in a large sense, through a kind

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

of catalysis induced by external, epigenetic, or genetic information sources (e.g., Wallace and Wallace, 2013).

One of the principal outcomes of this approach is a new class of 'dynamic regression models' based on the disjunction between regulatory intent and effect, via the Rate Distortion Theorem. These are models that can be fitted to data at various scales and levels of organization and, as with all such, the science ultimately lies not in the statistics themselves, but in their use. This may be most simply as benchmarks against which to compare observational or experimental data; often the essential findings are in the residuals from the models. More generally, however, such models are used for scientific inference by comparing similar systems under different, or different systems under similar, conditions.

The work is generally written at an advanced undergraduate level, with special topics introduced as needed. Some familiarity with the standard econometric use of stochastic differential equations is assumed, in particular the Ito chain rule.

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

Contents

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

Chapter 1
The Atomistic Fallacy in Health and Illness

1.1 Health promotion

A metareview by Jackson et al. (2007) identifies a number of factors essential to successful health promotion strategies that go beyond individual-oriented medical treatment:

1. Investment in building healthy public policy is a key strategy

Relevant public actions include investment in government and social policy, the creation of legislation and regulations and intersectoral and interorganizational partnerships and collaboration. In some cases healthy public policy was the strategy for which the most evidence of effectiveness exists: e.g., legislation for road safety and social policy for income security and poverty reduction.

2. Supportive environments need to be created at all levels

Such efforts include a variety of actions that represent supportive conditions at the structural (policy), social (including community) and individual levels. Key activities might include providing instrumental supports such as food vouchers or supplements, group support, nutritional education, counseling and home visits. Supportive environments are required for success at all levels of health promotion strategies.

3. Effectiveness of community action is unclear and requires further evidence

Although the impact of such actions in terms of behavior change has ranged from modest to disappointing, they have achieved success in terms of community and systems change.

4. Personal skills development must be combined with other strategies for effectiveness

Health education and related strategies were ineffective if implemented in isolation from other strategies that create structural-level conditions to support health and increase access to goods, products, and services. Intervention must address not only the health issues, but also the social and economic conditions that lead to risk behaviors.

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

5. Interventions employing multiple strategies and actions at multiple levels and sectors are most effective

The most effective interventions employ multiple health promotion strategies, operate at multiple levels (often including all of the structural, social group and personal levels), work in partnership across sectors and include a combination of integrated actions to support each strategy. Noncommunicable disease interventions in particular must employ multiple strategies and actions at multiple levels. Schools, workplaces and municipalities were found to be effective settings for many interventions because they provide opportunities to effectively reach large numbers of people with sustained interventions.

Among the important conclusions Jackson et al. reached was the observation that health promotion interventions are only effective when relevant to the context in which they are being used, including awareness of the social, cultural, economic and political contexts. The goals, strategies and actions of any intervention must be relevant and appropriate to the people they aim to reach and the systems they aim to work within.

Here, we will outline a 'basic biology' argument in support of these observations, understanding that for human biology, an utterly essential environmental context involves relations with other humans and the embedding power relations between groups. We begin with an examination of the life-course trajectory of aging.

1.2 Chronic bioregulatory activation

Theories of aging abound (e.g., Lorenzini et al., 2011). One of the most popular is disposable soma theory (Kirkwood, 1977) which proposes an allocation of energy leading to a trade-off between increased lifespan and increased fertility. The trade-off manifests itself as a reduction in the ability to maintain somatic cells when energy is directed toward reproductive fitness.

A quasi-programmed theory has been proposed, in which aging is an unintended consequence of a continuing developmental program, resulting in a defined lifespan (Blagosklonny, 2010).

The free radical theory of aging is based on the fact that oxidative processes are essential to life, yet the consequent and subsequent generation of free radical damage is inadequately controlled, leading to accumulated damage causing dysfunctions characteristic of aging (Harman, 1956).

More recently, psychosocial stress and its physiological correlates have been implicated in premature aging. Epel et al. (2004) describe accelerated telomere shortening in response to life stress. They found that psychological stress, both perceived stress and the chronicity of stress, is associated with higher oxidative stress, lower telomerase activity, and shorter telomere length, which are known determinants of cell senescence and longevity. High stress women were found to have telomeres shorter on average by the equivalent of one decade in comparison to low stress women.

Geronimus et al. (2004), focusing on the USA, describe how 'racial'/ethnic differences in chronic morbidity and excess mortality are pronounced by middle age. Evidence of early health deterioration among Blacks and racial differences in health are evident at all socioeconomic levels. They invoke a 'weathering' hypothesis positing that Blacks experience early health deterioration as a consequence of the cumulative impact of repeated experience with social or economic adversity and political marginalization.

Following Lorenzini et al., a very broad characterization of the phenotypic changes of aging is that they represent a reduced capacity to maintain homeostasis, resulting in reduced functional capacity, increased vulnerability to multiple diseases, and a reduction in the ability to respond to stress, injury, or other perturbations.

With particular regard to homeostasis, the involvement of activated bioregulation in the etiology of chronic disease has long been recognized. Bosma-den Boer et al. (2012) argue that the number of people suffering from chronic diseases such as cardiovascular disease, diabetes, respiratory diseases, mental disorders, autoimmune diseases and cancers has increased dramatically over the last three decades. The increasing rates of these chronic systemic illnesses suggest that inflammation, caused by excessive and inappropriate innate immune system activity, is unable to respond appropriately to danger signals that are new in the context of evolution. This leads, in their view, to unresolved or chronic inflammatory activation in the body.

Kolb et al. (2010) specifically study diabetes, and Miller et al. (2009) depression, from this perspective.

Cohen et al. (2012) examine the role of chronic stress in hypothalamic-pituitary-adrenocortical axis (HPA) disorders from a similar viewpoint. Chronic psychological stress is associated with increased risk for depression, cardiovascular disease, diabetes, autoimmune diseases, upper respiratory infections, and poorer wound healing, via HPA axis dysregulation (Cohen et al., 2007; McEwen, 1998).

Crowson et al. (2010) provide a similar analysis, finding that inflammation and immune dysregulation are strongly implicated in the premature aging of rheumatoid arthritis (RA) patients. Premature aging due to senescence of multiple systems, such as the immune, endocrine, cardiovascular, muscular, and nervous systems, represents an attractive biologic model that may, in part, they claim, explain the excess mortality observed in RA and other chronic diseases.

As described below and elsewhere (e.g., Wallace and Wallace, 2013; Wallace, 2012), immune and HPA function are examples of (broadly) cognitive physiological and other processes that characterize, and are linked across, all scales and levels of organization of the living state. Here, we will examine the chronic activation of such systems at low levels of incoming signals as a generalized inflammation, a form of self-attack, leading to a certain spectrum of diseases, using an information-theoretic variant of an econometric model that, in particular, allows exploration of the ability to respond to perturbation in the context of unpredictability.

The necessarily multilevel and multiscale phenotypes of pathology uncovered will suggest that therapy and prevention will be most effective when also focused across scales and levels of organization.

Holling (1992) explores the central role of 'keystone' levels and scales in ecosystem studies, that is, those at which perturbation will particularly resonate to both smaller/lower and larger/higher levels. He argues that ecosystems are controlled and organized by a small number of key plant, animal, and biotic processes that structure the landscape at different scales. Within any one ecosystem, the periodicities and architectural attributes of the critical structuring processes will establish a nested set of periodicities and spatial features that become attractors for other variables. The degree to which small, fast events influence larger, slower ones is critically dependent upon mesoscale disturbance processes.

In sum, Holling finds that the landscape is structured hierarchically by a small number of driving processes into a similarly small number of levels, each characterized by a distinct scale of 'architectural' texture and of temporal speed and variables.

More recently, this mechanism was rediscovered in public health by Glass and McAtee (2006), expressed in terms of risk regulators acting at particular scales and levels of organization. As they put it, many studies illustrate the limits of well-intentioned interventions that treat individual health behaviors as separate from social context and from biological influences. They then explore extending the stream of causation to nested levels of biology and social organization.

It is clear from much social science that particular keystone levels for humans are the geographic neighborhood of work and residence, and the embedded social networks associated with them (e.g., Wallace and Wallace, 2013). This suggests that multilevel, multiscale strategies that address more than one level of organization are likely to have far more therapeutic effect than magic bullet 'ceutical' interventions limited to molecular, cellular, organ, or individual levels of structure.

1.3 Western cultural atomism

Why does the very idea that magic bullets might be less effective than more comprehensive multilevel strategies seem so inherently alien in the context of Western biomedicine? Why, in the face of the inverse Moore's Law that has driven the catastrophic collapse of pharmaceutical industry productivity (e.g., Wallace, and Wallace, 2013), has the general response been one of Translational Medicine, i.e., more-of-the-same-but-better? Susser (1973), in his famous book *Causal Thinking in the Health Sciences*, some time ago explored the inadequacies of atomistic thinking in the study of health and illness. As Kaufman and Poole (2000) note, however, little has really changed in the basic ideology of the field, arguing that although a recent resurgence of interest in social context has revivified many of the points made by Susser in 1973, the formalization of this ecologic perspective unfortunately advanced little in the subsequent quarter-century. The progress toward more refined and systematic articulation of causal logic in the epidemiological and statistical literature in recent decades has, in their view, been characterized by an explicit conceptual foundation in atomistic interventions. The emergent properties of causal sys-

tems, as distinct from the consideration of multiple discrete actions, remains largely undescribed in any formal sense in the epidemiological literature.

Even such a supposedly multifactorial approach as network-based systems biology (e.g., Pujol et al., 2009; Boran and Iyengar, 2010; Dudley et al., 2010; Arrell and Terzic, 2010) is focused primarily on drug development for individual-level treatment, with the 'system' outlined in a major review article (Zhao and Iyengar, 2012, figure 1) as:

> Atomic/molecular interactions → Cellular/tissue-level networking and physiology → Organ-level networking and physiology → Whole-body outcomes.

Similar conceptual failures, in fact, plague economics and evolutionary theory. That is, the search for magic bullets – atomized causality – is ubiquitous in Western thought. This is, however, a social construct – a conceptual artifact – not shared by other cultures, and the resulting dissonance may singularly affect the success or failure of collaborations with partners having East Asian acculturation.

Why?

Tony Lawson's (2006) examination of heterodox economics serves as a counter-intuitive starting point. It focuses, first, on characterizing the essential features of the mainstream tradition in Western economic theory as involving explicitly physics-like, deductive mathematical models of social phenomena that inherently require an atomistic perspective on individual, isolated economic actors, a methodology subject to scathing commentary at the highest levels (e.g., Leontief, 1982). Lawson (2006) characterizes the need for isolated atomism in mainstream theory as arising from mathematical considerations, in that deductivist theorizing of the sort pursued in modern economics ultimately has to be couched in terms of such 'atoms' just to ensure that under conditions x the same (predictable or deducible) outcome y always follows. The point then, from his perspective, is that the ontological presuppositions of the insistence on mathematical modeling include the restriction that the social domain is everywhere constituted by sets of isolated atoms.

A converse interpretation, however, is also possible: that cultural assumptions of atomicity can drive the particular forms of mathematical models.

Lawson (2006) describes various heterodox economic approaches – post Keynsianism, (old) institutionalism, feminist, social, Marxian, Austrian and social economics, among others – as representing something of a generalized social science in which the dominant emphases of the separate heterodox traditions are just manifestations of categories of social reality that conflict with the assumption that social life is everywhere composed of isolated atoms.

More recently, criticism has emerged of gene-based replicator dynamics versions of evolutionary theory that suffer similar atomistic model constrictions (e.g., Lewontin, 2000, 2010). Much of the debate in evolutionary theory has revolved around the 'basic' target of selection, with the Modern Evolutionary Synthesis heavily invested in the atomistic, gradualist theory of mathematical population genetics (e.g., Ewens, 2004). Heterodox, non-atomistic, heavily contextual, evolutionary theories have emerged that materially challenge and extend that Synthesis (e.g., Gould, 2002, Odling-Smee et al., 2003, Wallace, 2010).

Economics and evolutionary theory, however, are not the only biological/social sciences to come under the same gun. The cultural psychologist S. Heine (2001) finds that the extreme nature of American individualism suggests that a psychology based on late 20th century American research not only stands the risk of developing models that are particular to that culture, but of developing an understanding of the self that is peculiar in the context of the world's cultures.

The explanation for this pattern goes deeper than ideology, into the very bones of Western culture: Nisbett et al. (2001), following in a long line of research (Markus and Kitayama, 1991, and the summary by Heine, 2001), review an extensive literature on empirical studies of basic cognitive differences between individuals raised in what they call 'East Asian' and 'Western' cultural heritages, which they characterize, respectively, as 'holistic' and 'analytic'. They argue:

1. Social organization directs attention to some aspects of the perceptual field at the expense of others.
2. What is attended to influences metaphysics.
3. Metaphysics guides tacit epistemology, that is, beliefs about the nature of the world and causality.
4. Epistemology dictates the development and application of some cognitive processes at the expense of others.
5. Social organization can directly affect the plausibility of metaphysical assumptions, such as whether causality should be regarded as residing in the field vs. in the object.
6. Social organization and social practice can directly influence the development and use of cognitive processes such as dialectical vs. logical ones.

Nisbett et al. (2001) conclude that tools of thought embody a culture's intellectual history, that tools have theories built into them, and that users accept these theories, albeit unknowingly, when they use these tools.

Masuda and Nisbett (2006) find research on perception and cognition suggesting that whereas East Asians view the world holistically, attending to the entire field and relations among objects, Westerners view the world analytically, focusing on the attributes of salient objects. Compared to Americans, East Asians were more sensitive to contextual changes than to focal object changes, These results suggest that there can be cultural variation in what may seem to be basic perceptual processes.

Nisbett and Miyamoto (2005) similarly found evidence that perceptual processes are influenced by culture. Westerners tend to engage in context-independent and analytic perceptual processes by focusing on a salient object independently of its context, whereas Asians tend to engage in context-dependent and holistic perceptual processes by attending to the relationship between the object and the context in which the object is located. There is, in their view, a dynamic relationship between the cultural context and perceptual processes which can no longer be regarded as universal across all people at all times.

Wallace (2007) argues that a necessary conditions mathematical treatment of Baars's global workspace consciousness model, analogous to Dretske's communication theory analysis of high level mental function, can be used to explore the effects of embedding cultural heritage on inattentional blindness. Culture should express

itself in this basic psychophysical phenomenon across a great variety of sensory modalities because conscious attention must conform to constraints generated by cultural context.

We will show below that a class of statistical and analytic models useful in the study of 'biocognitive' pattern and process can be developed that is not mathematically constrained to an underlying atomistic cultural viewpoint.

In sum, profound, culturally-based, atomistic ideological constraints abound across a plethora of Western scientific disciplines, including contemporary biomedicine. Engaging other cultural sensibilities not so constrained, particularly on matters of health and illness, will almost surely require adoption of a magic strategy perspective. This is, first, because such strategies are likely to work better in the long run than atomistic interventions, and second, because East Asian and other potential markets may respond better to such approaches than to being force-fed what is widely understood (by them) to be a Western cultural conceit.

The next chapter reexamines and reinterprets a nested set of biological and other broadly inflammatory modules from a perspective that will permit construction of necessary conditions dynamic statistical models providing new perspectives on multiscale, multilevel health interventions. It characterizes both individual cognitive processes and punctuated correlations of them that recruit sets of cognitive modules into a larger whole acting across scale or level of organization. The various examples are, however, much in the spirit of Maturana and Varela (1980, 1992) who long ago understood the central role that cognition must play in biological phenomena. It is the improper activation of individual cognitive modules and their larger working coalitions that will be a central focus of this exploration.

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

Chapter 2
Cognitive Modules and Broadcasts

Cognitive phenomena operate at all levels of organization in the living state, and this observation has even been taken as defining life itself (e.g., Maturana, 1970). Here we explore some such that are particularly characteristic of the human animal, of its elaborate social and cultural constructs, and of their interaction and interpenetration.

2.1 Immune system

Atlan and Cohen (1998) have proposed an information-theoretic – and implicitly global broadcast – cognitive model of immune function and process, a paradigm incorporating cognitive pattern recognition-and-response behaviors that are certainly analogous to, but much slower than, those of the later-evolved central nervous system.

From the Atlan/Cohen 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 reformulated the 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 observed 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

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

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, and does so in a dynamic manner across many tissues, sometimes generating large-scale global broadcasts of immune activation.

2.2 Tumor control

Nunney (1999) has explored cancer occurrence as a function of animal size, suggesting that in larger animals, whose lifespan grows as about the 4/10 power of their cell count, prevention of cancer in rapidly proliferating tissues becomes more difficult in proportion to size. Cancer control requires the development of additional mechanisms and systems to address tumorigenesis as body size increases – a synergistic effect of cell number and organism longevity. Nunney concludes that this pattern may represent a real barrier to the evolution of large, long-lived animals and predicts that those that do evolve have recruited additional controls over those of smaller animals to prevent cancer.

In particular, different tissues may have evolved markedly different tumor control strategies. All of these, however, are likely to be energetically expensive, permeated with different complex signaling strategies, and subject to a multiplicity of reactions to signals, including those related to psychosocial stress. Forlenza and Baum (2000) explore the effects of stress on the full spectrum of tumor control, ranging from DNA damage and control, to apoptosis, immune surveillance, and mutation rate. Wallace et al. (2003) argue that this elaborate tumor control strategy, in large animals, must be at least as cognitive as the immune system itself, one of its prin-

cipal components: some comparison must be made with an internal picture of a healthy cell, and a choice made as to response, i.e., none, attempt DNA repair, trigger programmed cell death, engage in full-blown immune attack. This is, from the Atlan/Cohen perspective, the essence of cognition, and clearly involves the recruitment of a comprehensive set of cognitive subprocesses into a larger, highly tunable, dynamic structure. across a variety of different tissue subtypes.

2.3 Protein folding regulation

High rates of protein folding and aggregation diseases, in conjunction with observations of the elaborate cellular folding regulatory apparatus associated with the endoplasmic reticulum and other cellular structures that compare produced to expected protein forms (e.g., Scheuner and Kaufman, 2008; Dobson, 2003), presents a clear and powerful logical challenge to simple physical 'folding funnel' free energy models of protein folding, as compelling as these are *in vitro* or *in silico*. This suggests that a more biologically-based model is needed for understanding the life course trajectory of protein folding, a model analogous to Atlan and Cohen's (1998) cognitive paradigm for the immune system. That is, the intractable set of disorders related to protein aggregation and misfolding belies simple mechanistic approaches, although free energy landscape pictures (Anfinsen, 1973; Dill et al., 2007) surely capture part of the process. The diseases range from prion illnesses like Creutzfeld-Jakob disease, in addition to amyloid-related dysfunctions like Alzheimer's, Huntington's and Parkinson's diseases, and type 2 diabetes. Misfolding disorders include emphysema and cystic fibrosis.

The role of epigenetic and environmental factors in type 2 diabetes has long been known (e.g., Zhang et al., 2009; Wallach and Rey, 2009). Haataja et al. (2008), for example, conclude that the islet in type 2 diabetes shows much in common with neuropathology in neurodegenerative diseases where interest is now focused on protein misfolding and aggregation and the diseases are now often referred to as unfolded protein diseases.

Scheuner and Kaufman (2008) likewise examine the unfolded protein response in β cell failure and diabetes and raise fundamental questions regarding the adequacy of simple energy landscape models of protein folding. They find that, in eukaryotic cells, protein synthesis and secretion are precisely coupled with the capacity of the endoplasmic reticulum (ER) to fold, process, and traffic proteins to the cell surface. These processes are coupled through several signal transduction pathways collectively known as the unfolded protein response that functions to reduce the amount of nascent protein that enters the ER lumen, to increase the ER capacity to fold protein through transcriptional up-regulation of ER chaperones and folding catalysts, and to induce degradation of misfolded and aggregated protein.

Many of these processes and mechanisms seem no less examples of chemical cognition than the immune/inflammatory responses that Atlan and Cohen (1998) de-

scribe in terms of an explicit cognitive paradigm, or that characterizes well-studied neural processes.

2.4 Intrinsically disordered protein logic gates

Intrinsically disordered proteins (IDP) account for some 30 % of all protein species, and perhaps half of all proteins contain significant sections that are intrinsically disordered. These species and sections appear to carry out far more functional moonlighting than do highly structured proteins. Application of nonrigid molecule theory to IDP interaction dynamics gives this result directly (Wallace, 2011, 2012b), in that mirror image subgroup/subgroupoid tiling matching of a fuzzy molecular lock-and-key can be much richer for IDP since the number of possible symmetries can grow exponentially with molecule length, while tiling matching for three dimensional structured proteins is relatively limited. An information catalysis model implies that this mechanism can produce a large and subtle set of biological logic gates whose properties go far beyond digital AND, OR, XOR, etc., behaviors.

2.5 The glycome and glycan/lectin interaction

Following Wallace (2012b), application of Tlusty's rate distortion index theorem argument (Tlusty, 2007) to the glycome, the glycan 'kelp bed' that coats the cell surface, and through interaction with lectin proteins, carries the major share of biological information, produces a *reductio ad absurdum* of almost infinite 'code' complexity. Clearly, a complicated form of chemical cognition imposes constraints carried by external information on what would be a grotesquely large 'glycan code error network'. The machinery that manufactures glycan kelp fronds must itself be regulated by other levels of chemical cognition to ensure that what is produced matches what was scheduled for production. More generally, the information transmission involving interaction between glycan and lectin instantiates complex logic gate structures that themselves carry out higher order cognitive processes at the intercellular level (e.g., Wallace and Wallace, 2013, Ch. 8).

2.6 Wound healing

Following closely Mindwood et al. (2004), mammalian tissue repair is a series of overlapping events that begins immediately after wounding. Platelet aggregation forms a hemostatic plug and blood coagulation forms the provisional matrix. This dense cross-linked network of fibrin and fibronectin from blood acts to prevent excessive blood loss. Platelets release growth factors and adhesive proteins that stim-

ulate the inflammatory response, entraining immune function, and inducing cell migration into the wound using the provisional matrix as a substrate. Wound cleaning is done by neutrophils, solubilizing debris, and monocytes that differentiate into macrophages and phagocytose debris. The macrophages release growth factors and cytokines that activate subsequent events. For cutaneous woulds, keratinocytes migrate across the area to reestablish the epithelial barrier. Fibroblasts then enter the wound to replace the provisional matrix with granulation tissue composed of fibronectin and collagen. As endothelial cells revascularize the damaged area, fibroblasts differentiate into myofibroblasts and contract the matrix to bring the margins of the wound together. The resident cells then undergo apoptosis, leaving collagen-rich scar tissue that is slowly remodeled in the following months. Wound healing, then, provides an ancient example of a global broadcast that recruits a set of cognitive processes, in the Atlan/Cohen sense. The mechanism, which may vary across taxa, is inherently tunable, addressing the signal of 'excessive distortion' represented by a wound.

2.7 Gene expression

A cognitive paradigm for gene expression has emerged, a model in which contextual factors determine the behavior of what must be characterized as a reactive system, not at all a deterministic – or even simple stochastic – mechanical process (Cohen, 2006; Cohen and Harel, 2007; Wallace and Wallace, 2008, 2009, 2010).

O'Nuallain (2008) puts gene expression directly in the realm of complex linguistic behavior, for which context imposes meaning. He claims that the analogy between gene expression and language production is useful both as a fruitful research paradigm and also, given the relative lack of success of natural language processing by computer, as a cautionary tale for molecular biology. A relatively simple model of cognitive process as an information source permits use of Dretske's (1994) insight that any cognitive phenomenon must be constrained by the limit theorems of information theory, in the same sense that sums of stochastic variables are constrained by the Central Limit Theorem. This perspective permits a new formal approach to gene expression and its dysfunctions, in particular suggesting new and powerful statistical tools for data analysis that could contribute to exploring both ontology and its pathologies. Wallace and Wallace (2009, 2010) apply the perspective to chronic disease.

This approach is consistent with the broad context of epigenetics and epigenetic epidemiology (Jablonka and Lamb, 1995, 1998; Backdahl et al. 2009; Turner, 2000; Jaenish and Bird, 2003; Jablonka, 2004).

Foley et al. (2009) argue that epimutation is estimated to be 100 times more frequent than genetic mutation and may occur randomly or in response to the environment. Periods of rapid cell division and epigenetic remodeling are likely to be most sensitive to stochastic or environmentally mediated epimutation. Disruption of epigenetic profile is a feature of most cancers and is speculated to play a

role in the etiology of other complex diseases including asthma, allergy, obesity, type 2 diabetes, coronary heart disease, autism spectrum and bipolar disorders, and schizophrenia.

Scherrer and Jost (2007a, b) invoke information theory in their extension of the definition of the gene to include the local epigenetic machinery, a construct they term the 'genon'. Their central point is that coding information is not simply contained in the coded sequence, but is, in their terms, *provided by* the genon that accompanies it on the expression pathway and controls in which peptide it will end up. In their view, the information that counts is not about the identity of a nucleotide or an amino acid derived from it, but about the relative frequency of the transcription and generation of a particular type of coding sequence that then contributes to the determination of the types and numbers of functional products derived from the DNA coding region under consideration.

The genon, as Scherrer and Jost describe it, is precisely a localized form of global broadcast linking cognitive regulatory modules to direct gene expression in producing the great variety of tissues, organs, and their linkages that comprise a living entity.

The proper formal tools for understanding phenomena that 'provide' information – that are information sources – are the Rate Distortion Theorem and its zero error limit, the Shannon-McMillan Theorem.

2.8 HPA axis

Reiterating the Atlan/Cohen argument, the essence of cognition is comparison of a perceived external signal with an internal picture of the world, and then, upon that comparison, the choice of a response from a much larger repertoire of possible responses. Clearly, from this perspective, the HPA axis, the flight-or-fight reflex, is cognitive. Upon recognition of a new perturbation in the surrounding environment, emotional and/or conscious cognition evaluate and choose from several possible responses: no action necessary, flight, fight, helplessness (flight or fight needed, but not possible). Upon appropriate conditioning, the HPA axis is able to accelerate the decision process, much as the immune system has a more efficient response to second pathogenic challenge once the initial infection has become encoded in immune memory. Certainly hyperreactivity as a sequela of post traumatic stress disorder (PTSD) is well known. Wallace and Wallace (2010, 2013) provide detailed models.

Bjorntorp (2001) in particular examines the role of chronic HPA axis activation in abdominal and visceral obesity, a matter of great clinical and public health importance.

2.9 Blood pressure regulation

Rau and Elbert (2001) review much of the literature on blood pressure regulation, particularly the interaction between baroreceptor activation and central nervous function. We paraphrase something of their analysis. The essential point, of course, is that unregulated blood pressure would be quickly fatal in any animal with a circulatory system, a matter as physiologically fundamental as tumor control. Much work over the years has elucidated some of the mechanisms involved: increase in arterial blood pressure stimulates the arterial baroreceptors which in turn elicit the baroreceptor reflex, causing a reduction in cardiac output and in peripheral resistance, returning pressure to its original level. The reflex, however, is not actually this simple: it may be inhibited through peripheral processes, for example under conditions of high metabolic demand. In addition, higher brain structures modulate this reflex arc, for instance when threat is detected and fight or flight responses are being prepared. Thus blood pressure control cannot be a simple reflex. It is, rather, a broad and actively cognitive modular system which compares a set of incoming signals with an internal reference configuration, and then chooses an appropriate physiological level of blood pressure from a large repertoire of possible levels – a cognitive process in the Atlan/Cohen sense. The baroreceptors and the baroreceptor reflex are, from this perspective, only one set of a complex array of components making up a larger and more comprehensive cognitive blood pressure regulatory module.

2.10 Emotion

Thayer and Lane (2000) summarize 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' leads directly to something closely analogous to the Atlan and Cohen language metaphor.

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.

Gilbert (2001) suggests that a canonical form of such pathology is the excitation of modes that, in other circumstances, represent 'normal' evolutionary adaptations, a general matter to which we will return.

Panskepp (2003) has argued that emotion represents a primary form of consciousness, based in early-evolved brain structures, which has become convoluted with a later-developed global neuronal workspace. The convolution with individual consciousness appears to involve a large number of other cognitive biological and social submodules as well.

2.11 Consciousness

Sergeant and Dehaene (2004) characterize individual consciousness in terms of Bernard Baars' work, who has proposed that consciousness is associated with the interconnection of multiple areas processing a stimulus by a dynamic 'neuronal workspace' within which recurrent connections allow long-distance communication and auto-amplification of the activation. Neuronal network simulations, they claim, suggest the existence of a fluctuating dynamic threshold. If the primary activation evoked by a stimulus exceeds this threshold, reverberation takes place and stimulus information gains access, through the workspace, to a broad range of other brain areas allowing, among other processes, verbal report, voluntary manipulation, voluntary action and long-term memorization.

Below this threshold, they argue, stimulus information remains unavailable to these processes. Thus the global neuronal workspace theory predicts an all-or-nothing transition between conscious and unconscious perception. More generally, many non-linear dynamical systems with self-amplification are characterized by the presence of discontinuous transitions in internal state.

Thus Baars' global workspace model of animal consciousness sees the phenomenon as a dynamic array of unconscious cognitive modules that unite to become a global broadcast having a tunable perception threshold not unlike a theater spotlight, but whose range of attention is constrained by embedding contexts (Baars, 1988, 2005). As Baars and Franklin (2003) put it:

1. The brain can be viewed as a collection of distributed specialized networks (processors).

2. Consciousness is associated with a global workspace in the brain – a fleeting memory capacity whose focal contents are widely distributed – 'broadcast' – to many unconscious specialized networks.

3. Conversely, a global workspace can also serve to integrate many competing and cooperating input networks.

4. Some unconscious networks, called contexts, shape conscious contents, for example unconscious parietal maps modulate visual feature cells that underlie the perception of color in the ventral stream.

5. Such contexts work together jointly to constrain conscious events.

6. Motives and emotions can be viewed as goal contexts.

7. Executive functions work as hierarchies of goal contexts.

The basic mechanism emerges directly from application of the asymptotic limit theorems of information theory, once a broad range of unconscious cognitive processes is recognized as inherently involving information sources – generalized languages, as discussed below (Wallace, 2000, 2005, 2007, 2012). This permits mapping physiological unconscious cognitive modules onto an abstract network of interacting information sources, allowing a simplified mathematical attack that, in the presence of sufficient linkage – crosstalk – permits rapid, shifting, global broadcasts in response to sufficiently large impinging signals. The topology of that broadcast is tunable, depending on the spectrum of distortion measure and other limits imposed on the system of interest.

2.12 Sociocultural cognition

Humans entertain a hypersociality that embeds us all in group decisions and collective cognitive behavior within a social network, itself embedded in a historically-structured, path-dependent, shared culture. For humans, culture is utterly fundamental. Durham (1991), Richerson and Boyd (2006), Jablonka and Lamb (1995), and many others argue that genes and culture are two distinct but interacting systems of inheritance within human populations. Information of both kinds has influence, actual or potential, over behaviors, creating a real and unambiguous symmetry between genes and phenotypes on the one hand, and culture and phenotypes on the other. Genes and culture represent two parallel lines or tracks of hereditary influence on phenotypes.

The centrality of hominid evolution can be characterized as an interweaving of genetic and cultural systems. Genes came to encode for increasing hypersociality, learning, and language skills. The most successful populations displayed increasingly complex structures that better aided in buffering the local environment.

Successful human populations have a core of tool usage, sophisticated language, oral tradition, mythology, music, and decision making skills focused on relatively small family/extended family social network groupings. More complex social structures are built on the periphery of this basic object. The human species' very identity may rest on its unique evolved capacities for social mediation and cultural transmission. These are particularly expressed through the cognitive decision making of small groups facing changing patterns of threat and opportunity, processes in which we are all embedded and all participate.

The emergent cognitive behavior of organizations has long been studied under the label distributed cognition. Hollan et al. (2000) argue that unlike traditional

cognitive theories, the theory of distributed cognition extends the reach of what is considered *cognitive* beyond the individual to encompass interactions between people and with resources and materials in the environment. Distributed cognition refers to a perspective on all of cognition, rather than a particular kind of cognition. Distributed cognition looks for cognitive processes, wherever they may occur, on the basis of the functional relationships of elements that participate together in the process. A process is not cognitive simply because it happens in a brain, nor is a process noncognitive simply because it happens in the interactions between many brains. Distributed cognition describes, in their view, a system that can dynamically configure itself to bring subsystems into coordination to accomplish various functions.

Wallace and Fullilove (2008) apply a limited version of the formal approach explored below to institutions and other social structures.

Bruce et al. (2009) review in great detail the role of sociocultural stress in the etiology of a spectrum of what might well be considered generalized autoimmune disorders.

2.13 Culture and 'basic biology'

Chapter 1 described how Western and East Asian cultures affected fundamental perceptual mechanisms. What had been until recently considered basic biological phenomena proved to be greatly modulated, indeed, inverted, by cultural influence: Westerners focus on objects atomized from their context, while East Asians focus on the context itself.

Given that surprising result – at least surprising to a certain class of Western scientists, if not to anthropologists – it seems wise to suspend judgment on the role of culture in the 'basic biology' of HPA axis, blood pressure, protein folding, tumorigenesis, mental and developmental disorders, and many other pathologies, particularly in the context of stress.

Recall Heine's (2001) caution that the extreme nature of American individualism implies that a psychology based on 20th Century American research runs the risk of becoming an ideological *ignis fatuus*, a Western cultural artifact divorced from reality. This may, in fact, be an example that generalizes across the study of many broadly cognitive phenomena. In particular, the definition and dynamic impact of stress may be culturally contingent, in terms of overt manifestation, progression, and individual and collective experience.

Contrary to Western medicine's assumptions regarding 'basic biology', for much of human health and illness, one size may not fit all. Indeed, even malaria among cohabiting peoples in Burkina Faso seems much the different disease for former masters and former slaves via an immuno-cultural construct (Wallace and Wallace, 2002).

Chapter 3
Cognition, Environment, and Culture

3.1 Cognition as an information source

Humberto Maturana's classic paper, *The Biology of Cognition*, introduced a cognitive perspective on the living state, not restricted to high order 'neural' process, but as a phenomenon that must act at all levels of biological organization (Maturana, 1970; Maturana and Varela 1980, 1992). Expressing cognition as a kind of language, it is possible to construct statistical models based on the asymptotic limit theorems of information theory that instantiate many of these insights (e.g., Wallace, 2012).

As discussed above, Atlan and Cohen (1998) argue, in the context of the immune system, that cognition involves comparison of a perceived signal with an internal, learned or inherited picture of the world, and then choice of one response from a much larger repertoire of possible responses. That is, cognitive pattern recognition-and-response proceeds by an algorithmic combination of an incoming external sensory signal with an internal ongoing activity – incorporating the internalized picture of the world – and triggering an appropriate action based on a decision that the pattern of sensory activity requires a response.

Incoming sensory input is thus mixed in an unspecified but systematic manner with a pattern of internal ongoing activity to create a path of combined signals $x = (a_0, a_1, ..., a_n, ...)$. Each a_k thus represents some functional composition of the internal and the external. An application of this perspective to a standard neural network is given in Wallace (2005, p.34).

This path is fed into a highly nonlinear, but otherwise similarly unspecified, decision function, h, generating an output $h(x)$ that is an element of one of two disjoint sets B_0 and B_1 of possible system responses. Let

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

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

Assume a graded response, supposing that if

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

$$h(x) \in B_0,$$

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.

Interest focuses on paths x triggering pattern recognition-and-response: given a fixed initial state a_0, examine all possible subsequent paths x beginning with a_0 and leading to the event $h(x) \in B_1$. Thus $h(a_0, ..., a_j) \in B_0$ for all $0 \leq j < m$, but $h(a_0, ..., a_m) \in B_1$.

For each positive integer n, let $N(n)$ be the number of high probability paths of length n that begin with some particular a_0 and lead to the condition $h(x) \in B_1$. Call such paths 'meaningful', assuming that $N(n)$ will be considerably less than the number of all possible paths of length n leading from a_0 to the condition $h(x) \in B_1$.

Note that identification of the 'alphabet' of the states a_j, B_k may depend on the proper system coarse graining in the sense of symbolic dynamics (e.g., Beck and Schlogl, 1993).

Combining algorithm, the form of the function h, and the details of grammar and syntax, are all unspecified in this model. The assumption permitting inference on necessary conditions constrained by the asymptotic limit theorems of information theory is that the finite limit

$$H \equiv \lim_{n \to \infty} \frac{\log[N(n)]}{n} \tag{3.1}$$

both exists and is independent of the path x. Remember that $N(n)$ is the number of high probability paths of length n.

Call such a pattern recognition-and-response cognitive process *ergodic*. Not all cognitive processes are likely to be ergodic, implying that H, if it indeed exists at all, is path dependent, although extension to nearly ergodic processes, in a certain sense, seems possible (e.g., Wallace, 2005, pp. 31-32).

Invoking the spirit of the Shannon-McMillan Theorem, one of the basic asymptotic limit relations of information theory, it is possible to define an adiabatically, piecewise stationary, 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 satisfy the classic relations (Cover and Thomas, 2006)

$$H[\mathbf{X}] = \lim_{n\to\infty} \frac{\log[N(n)]}{n} = \lim_{n\to\infty} H(X_n|X_0,...,X_{n-1}) = \lim_{n\to\infty} \frac{H(X_0,...,X_n)}{n}. \quad (3.2)$$

This information source is defined as *dual* to the underlying ergodic cognitive process, in the sense of Wallace (2000, 2005, 2007).

'Adiabatic' means that, when the information source is parameterized according to some appropriate scheme, within continuous 'pieces', changes in parameter values take place slowly enough so that the information source remains as close to stationary and ergodic as needed to make the fundamental limit theorems work. 'Stationary' means that probabilities do not change in time, and by 'ergodic' (roughly) that cross-sectional means converge to long-time averages. Between pieces it is possible to invoke various kinds of phase change formalism, for example renormalization theory in cases where a mean field approximation holds (Wallace, 2005), or variants of random network theory where a mean number approximation is applied.

Recall that the Shannon uncertainties $H(...)$ are cross-sectional law-of-large-numbers sums of the form $-\sum_k P_k \log[P_k]$, where the P_k constitute a probability distribution. See Cover and Thomas (2006), Ash (1990), or Khinchin (1957) for the standard details.

3.2 Network topology and associated symmetries

An equivalence class algebra can be constructed by choosing different origin points a_0, and defining the equivalence of two states a_m, a_n by the existence of high probability meaningful paths connecting them to the same origin point. Disjoint partition by equivalence class, analogous to orbit equivalence classes for a dynamical system, defines the vertices of a network of cognitive dual languages that interact to actually constitute the organism. Each vertex then represents a different information source dual to a cognitive process. This is not a representation of a network of interacting physical systems as such, in the sense now common to network systems biology (e.g., Arrell and Terzic, 2010). It is, rather, an abstract set of *languages* dual to the set of cognitive processes of interest, that may become linked into higher order structures.

Topology, in the 20th century, became an object of algebraic study, so-called algebraic topology, via the fundamental underlying symmetries of geometric spaces. Rotations, mirror transformations, simple ('affine') displacements, and the like, uniquely characterize topological spaces, and the networks inherent to cognitive phenomena having dual information sources also have complex underlying symmetries: Characterization via equivalence classes defines a groupoid, an extension of the idea of a symmetry group, as summarized by Brown (1987) and Weinstein (1996). Linkages across this set of languages occur via the groupoid generalization

of Landau's spontaneous symmetry breaking arguments that will be used below (Landau and Lifshitz, 2007; Pettini, 2007).

Briefly, a groupoid, G, is defined by a base set A upon which some mapping – a morphism – can be defined. Note that not all possible pairs of states (a_j, a_k) in the base set A can be connected by such a morphism. Those that can define the groupoid element, a morphism $g = (a_j, a_k)$ having the natural inverse $g^{-1} = (a_k, a_j)$. Given such a pairing, it is possible to define 'natural' end-point maps $\alpha(g) = a_j, \beta(g) = a_k$ from the set of morphisms G into A, and a formally associative product in the groupoid $g_1 g_2$ provided $\alpha(g_1 g_2) = \alpha(g_1), \beta(g_1 g_2) = \beta(g_2)$, and $\beta(g_1) = \alpha(g_2)$. Then, the product is defined, and associative, $(g_1 g_2) g_3 = g_1 (g_2 g_3)$. In addition, there are natural left and right identity elements λ_g, ρ_g such that $\lambda_g g = g = g \rho_g$.

An orbit of the groupoid G over A is an equivalence class for the relation $a_j \sim G a_k$ if and only if there is a groupoid element g with $\alpha(g) = a_j$ and $\beta(g) = a_k$. A groupoid is called transitive if it has just one orbit. The transitive groupoids are the building blocks of groupoids in that there is a natural decomposition of the base space of a general groupoid into orbits. Over each orbit there is a transitive groupoid, and the disjoint union of these transitive groupoids is the original groupoid. Conversely, the disjoint union of groupoids is itself a groupoid.

The isotropy group of $a \in X$ consists of those g in G with $\alpha(g) = a = \beta(g)$. These groups prove fundamental to classifying groupoids.

If G is any groupoid over A, the map $(\alpha, \beta) : G \to A \times A$ is a morphism from G to the pair groupoid of A. The image of (α, β) is the orbit equivalence relation $\sim G$, and the functional kernel is the union of the isotropy groups. If $f : X \to Y$ is a function, then the kernel of f, $ker(f) = [(x_1, x_2) \in X \times X : f(x_1) = f(x_2)]$ defines an equivalence relation.

Groupoids may have additional structure. For example, a groupoid G is a topological groupoid over a base space X if G and X are topological spaces and α, β and multiplication are continuous maps.

In essence, a groupoid is a category in which all morphisms have an inverse, here defined in terms of connection to a base point by a meaningful path of an information source dual to a cognitive process.

The morphism (α, β) suggests another way of looking at groupoids. A groupoid over A identifies not only which elements of A are equivalent to one another (isomorphic), but *it also parameterizes the different ways (isomorphisms) in which two elements can be equivalent*, i.e., in our context, all possible information sources dual to some cognitive process. Given the information theoretic characterization of cognition presented above, this produces a full modular cognitive network in a highly natural manner.

Groupoids will become central to extension of the theory below.

3.3 Network dynamics

It was noted above that disjoint partition of state space is possible according to sets of states that can be connected by high probability paths to the same base point, leading to a groupoid structure characterizing the underlying network topology. Groupoids generalize ideas of both symmetry and equivalence class (e.g., Brown, 1987), and ω, an index of the average crosstalk between them, can be taken as a temperature analog in a spontaneous symmetry breaking (or making) argument in Landau's sense (Landau and Lifshitz, 2007). That is, increasing ω leads to a punctuated transition to a higher groupoid symmetry representing a global broadcast.

Given a set of cognitive modules that become, as above, linked to solve a problem, the famous 'no free lunch' theorem (English, 1996; Wolpert and Macready, 1995, 1997) makes clearer how the 'cognitive' treatment of biological structures extends network theory-based systems biology (e.g., Arrell and Terzic, 2010). Wolpert and Macready have established that there exists no generally superior computational function optimizer. There is no 'free lunch' in the sense that an optimizer pays for superior performance on some functions with inferior performance on others. Gains and losses balance precisely, and all optimizers have identical average performance. That is, an optimizer has to pay for its superiority on one subset of functions with inferiority on the complementary subset.

Something much like this was, however, well-known using another description: Shannon (1959) found that there is a curious and provocative duality between the properties of an information source with a distortion measure and those of a channel. This duality is enhanced if we consider channels in which there is a cost associated with the different letters. Solving this problem corresponds, in a sense, to finding a source that is right for the channel and the desired cost. In a somewhat dual way, evaluating the rate distortion function for a source corresponds to finding a channel that is just right for the source and allowed distortion level.

From the no free lunch argument, and Shannon's insight, it is clear that different challenges facing any cognitive system – or interacting set of them – must be met by different arrangements of cooperating low level cognitive modules. It is possible to make a very abstract picture of this phenomenon based on the network of linkages between the information sources dual to the individual 'unconscious' cognitive modules (UCM). That is, the remapped network of lower level cognitive modules is reexpressed in terms of the information sources dual to the UCM. Given two distinct problems classes, there must be two different wirings of the information sources dual to the available UCM, with the network graph edges measured by the amount of information crosstalk between sets of nodes representing the dual information sources.

Clearly, the mutual information measure of cross-talk is not inherently fixed, but can continuously vary in magnitude. This suggests a parameterized renormalization: the modular network structure linked by mutual information interactions and crosstalk has a topology depending on the degree of interaction of interest.

Define an interaction parameter Ω, a real positive number, and look at geometric structures defined in terms of linkages set to zero if mutual information is less than,

and 'renormalized' to unity if greater than, Ω. Any given value of Ω will define a regime of giant components of network elements linked by mutual information greater than or equal to it.

Now invert the argument: a given topology for the giant component will, in turn, define some critical value, Ω_C, so that network elements interacting by mutual information less than that value will be unable to participate, i.e., will be locked out and not be 'consciously' perceived. Thus Ω is a tunable, syntactically-dependent, detection limit that depends critically on the instantaneous topology of the giant component of linked cognitive modules defining the global broadcast. That topology is the basic tunable syntactic filter across the underlying modular structure, and variation in Ω is only one aspect of more general topological properties described later in terms of index theorems, where far more general analytic constraints can become closely linked to the topological structure and dynamics of underlying networks, and, in fact, can stand in place of them (Hazewinkel, 2002).

3.4 Environment as an information source

Multifactorial cognitive systems interact with, affect, and are affected by, embedding environments that 'remember' interaction by various mechanisms. It is possible to reexpress environmental dynamics in terms of a grammar and syntax that represent the output of an information source – a generalized language.

For example, the turn-of-the seasons in a temperate climate, for many natural communities, looks remarkably the same year after year: the ice melts, the migrating birds return, the trees bud, the grass grows, plants and animals reproduce, high summer arrives, the foliage turns, the birds leave, frost, snow, the rivers freeze, and so on. In a social setting, interacting actors can be expected to behave within fairly well defined cultural and historical constraints, depending on context: birthday party behaviors are not the same as cocktail party behaviors in a particular social set, but both will be characteristic. Similarly, gene expression during development is highly patterned.

Suppose it possible to coarse-grain the ecosystem at time t, in the sense of symbolic dynamics (e.g., Beck and Schlogl, 1993) according to some appropriate partition of the phase space in which each division A_j represent a particular range of numbers of each possible fundamental actor in the generalized ecosystem, along with associated larger system economic or other parameters. What is of particular interest is the set of longitudinal paths, that is, ecological or social system statements of the form $x(n) = A_0, A_1, ..., A_n$ defined in terms of some natural time unit of the system. Thus n corresponds to an again appropriate characteristic time unit T, so that $t = T, 2T, ..., nT$.

To reiterate, the central interest is in the serial correlations along paths.

Let $N(n)$ be the number of possible paths of length n that are consistent with the underlying grammar and syntax of the appropriately coarsegrained eco- or social system. As above, the fundamental assumptions are that – for this chosen coarse-

graining – $N(n)$, the number of possible grammatical paths, is much smaller than the total number of paths possible, and that, in the limit of (relatively) large n, $H = \lim_{n\to\infty} \log[N(n)]/n$ both exists and is independent of path.

These conditions are the essence of a parallel with parametric statistics systems for which the assumptions are not true will require specialized 'nonparametric' approaches.

Nonetheless, not all possible ecosystem coarse-grainings are likely to work, and different such divisions, even when appropriate, might well lead to different descriptive quasi-languages for the ecosystem of interest. The example of Markov models is relevant. The essential Markov assumption is that the probability of a transition from one state at time T to another at time $T + \Delta T$ depends only on the state at T, and not at all on the history by which that state was reached. If changes within the interval of length ΔT are plastic, or path dependent, then attempts to model the system as a Markov process *within* the natural interval ΔT will fail, even though the model works quite well for phenomena separated by natural intervals.

Thus, empirical identification of relevant coarse-grainings for which this body of theory will work is clearly not trivial, and may, in fact, constitute the hard scientific core of the matter.

This is not, however, a new difficulty in natural ecosystem theory. As described, Holling (1992) explores the linkage of ecosystems across scales, finding that mesoscale structures – what might correspond to the neighborhood or a local social network in a human community – are ecological keystones in space, time, and population, and drive process and pattern at both smaller and larger scales and levels of organization.

In this spirit, Levin (1989) argues that there is no single correct scale of observation: the insights from any investigation are contingent on the choice of scales. Pattern is neither a property of the system alone nor of the observer, but of an interaction between them. Pattern exists at all levels and at all scales, and recognition of this multiplicity of scales is fundamental to describing and understanding ecosystems. In his view, there can be no inherently correct level of aggregation: we must recognize explicitly the multiplicity of scales within ecosystems, and develop a perspective that looks across scales and that builds on a multiplicity of models rather than seeking the single 'correct' one.

Given an appropriately chosen coarse-graining, define joint and conditional probabilities for different ecosystem paths, having the form

$$P(A_0, A_1, ..., A_n), P(A_n | A_0, ..., A_{n-1}),$$

such that appropriate joint and conditional Shannon uncertainties can be defined on them that satisfy equation (3.2).

Taking the definitions of Shannon uncertainties as above, and arguing backwards from the latter two parts of equation (3.2), it is indeed possible to recover the first, and divide the set of all possible ecosystem temporal paths into two subsets, one very small, containing the grammatically correct, and hence highly probable paths, that we will call 'meaningful', and a much larger set of vanishingly low probability.

Below we will show how an environmental information source can affect biocognitive regulation. This, however, first requires establishing a considerable foundation of formalism.

3.5 Physiological cognition and culture intertwined

The end of chapter 2 argued that culture and 'basic biology' can interact. This is not a new idea. The evolutionary anthropologist Robert Boyd has asserted that 'Culture is as much a part of human biology as the enamel in our teeth,' (e.g., Richerson and Boyd, 2006) and, while many other animals on Earth display some measure of culture as learned and transmitted behavior (e.g., Avital and Jablonka, 2000), nothing defines humans quite like the interpenetration of mind, self, and physiology with the 'environment' of cultural milieu.

It is not difficult to extend the model to include interaction of cognitive biological submodules with an embedding culture and with a hierarchical set of institutions within that culture, seen as a generalized transmissible language associated with a nested set of information sources (e.g., Wallace, 2013). This includes both a form of niche construction (Wallace, 2010), and distributed cognitive institutions acting on various scales (Wallace and Fullilove, 2008). This is most easily done by invoking the set of interacting information sources dual to cognitive process via network information theory (e.g., El Gamal and Kim, 2010, p.2-26): Given a basic set of such dual information sources, say $(X_1, ..., X_k)$, that can be partitioned into two ordered sets, say $X(\mathscr{J})$ and $X(\mathscr{J}')$, then the splitting criterion of the larger system becomes $H(X(\mathscr{J})|X(\mathscr{J}'))$. Generalization to three or more such ordered sets seems direct, and leads to a theory of collective consciousness in which different global workspaces act at different scales of size and time (Wallace and Fullilove, 2008).

As the anthropologists will attest, an astounding variety of culturally-driven institutions, associated forms of mind and self, and dynamics of interaction, graces the world. Typically, humans, whose overall genetic structure is more uniform than that of chimpanzee populations, do not communicate well across the many different cultural modes. Wallace and Fullilove (2008) argue that stabilizing complex systems of interacting cognitive institutions is exceedingly difficult, suggesting that the interpenetration of individual physiological dynamics with both embedding institutional and cultural structures, and their historical trajectories, can become a powerful determinant of health and illness at all levels of analysis.

In particular, the most effective interventions, from this perspective, will be multifactorial and involve components and strategies acting at the keystone level of local social networks.

Chapter 4
Dynamic Regression Models

The previous chapter introduced a basic statistical model of cognitive process using the Shannon-McMillan Theorem, which is the zero-error limit of the Rate Distortion Theorem. Here, the model is extended by that theorem to account for error, producing a comprehensive description of dynamic regulation in the context of unpredictability.

4.1 The Rate Distortion Theorem

Many regulatory problems are inherently rate distortion problems. The implementation of a complex cognitive structure, say a sequence of control orders generated by some regulatory information source Y, having output $y^n = y_1, y_2, \ldots$ is 'digitized' in terms of the observed behavior of the regulated system, say the sequence $b^n = b_1, b_2, \ldots$. The b_i are thus the actual impact of the regulator on its target environment. Assume each b^n is then deterministically retranslated back into a reproduction of the original control signal, $b^n \rightarrow \hat{y}^n = \hat{y}_1, \hat{y}_2, \ldots$.

Define a distortion measure $d(y, \hat{y})$ that compares the original to the retranslated path. See Cover and Thomas (2006) for examples. Suppose that with each path y^n and b^n-path retranslation into the y-language, denoted $\hat{y}^n$, there are associated individual, joint, and conditional probability distributions $p(y^n), p(\hat{y}^n), p(y^n|\hat{y}^n)$.

The average distortion is given as

$$D \equiv \sum_{y^n} p(y^n) d(y^n, \hat{y}^n) \,. \tag{4.1}$$

It is possible, using these distributions, to define the information transmitted from the incoming Y to the outgoing $\hat{Y}$ process using the Shannon source uncertainty of the strings:

$$I(Y, \hat{Y}) \equiv H(Y) - H(Y|\hat{Y}) \,. \tag{4.2}$$

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

If there is no uncertainty in Y, given the retranslation $\hat{Y}$, so that $H(Y|\hat{Y}) = 0$, then no information is lost, and the regulated system is perfectly under control. In general, this will not be true.

The rate distortion function $R(D)$ for a source Y with a distortion measure $d(y,\hat{y})$ is defined as

$$R(D) = \min_{p(y,\hat{y});\sum_{(y,\hat{y})} p(y)p(y|\hat{y})d(y,\hat{y}) \leq D} I(Y,\hat{Y}). \tag{4.3}$$

Cover and Thomas (2006) provide more detail.

The minimization is over all conditional distributions $p(y|\hat{y})$ for which the joint distribution $p(y,\hat{y}) = p(y)p(y|\hat{y})$ satisfies the average distortion constraint (i.e., average distortion $\leq D$).

The Rate Distortion Theorem states that $R(D)$ is the minimum necessary rate of information transmission – essentially minimum channel capacity – that ensures the transmission does not exceed average distortion D (Cover and Thomas, 2006). The rate distortion function has been calculated for a number of systems, using Lagrange multiplier methods. Cover and Thomas (2006) show that $R(D)$ is necessarily a decreasing convex function of D, that is, always a reverse J-shaped curve. This is a critical observation, since convexity is an exceptionally powerful mathematical condition (Ellis, 1985; Rockafellar, 1970).

Recall, now, the classic relation between information source uncertainty and channel capacity (Ash, 1990; Cover and Thomas, 2006; Khinchin, 1957). First, $H[\mathbf{X}] \leq C$, where H is the uncertainty of the source X and C the channel capacity. Recall also that C is defined according to the relation $C \equiv \max_{P(X)} I(X|Y)$, where $P(X)$ is the probability distribution of the message chosen so as to maximize the rate of information transmission along a channel Y.

4.2 The channel capacity argument

The rate distortion function places limits on information source uncertainty. Thus, distortion measures can drive information system dynamics. That is, the rate distortion function itself has a homological relation to free energy in the sense of Bennett (1988) and Feynman (2000), who characterize information by the free energy needed to erase it. See Wallace (2012) for further details. In general, increasing channel capacity in a physiological regulatory structure requires increased levels of metabolic free energy. A heuristic approach is fairly simple. Given a rate of available metabolic free energy, say M, for an average distortion D, the channel capacity, a free energy measure, must be at least $R(D)$, a convex function. For a Gaussian channel with noise of mean zero and variance σ^2,

$$R(D) = \frac{1}{2}\log[\sigma^2/D], \tag{4.4}$$

under the squared distortion measure (Cover and Thomas, 2006). Using a standard Gibbs model, we can write, for the average of R and some unknown monotonic

function $F(M)$, the approximate relation

$$< R >= \frac{\int_0^\infty R \exp[-R/F(M)]dR}{\int_0^\infty \exp[-R/F(M)]dR} = F(M)\,. \tag{4.5}$$

What is the form of $M = F^{-1}(< R >)$? One suspects, in first order, a linear expression, using the first two terms of a Taylor series expansion:

$$M \approx \kappa_1 < R > +\kappa_2\,. \tag{4.6}$$

Jensen's inequality for a convex function, here

$$R(< D >) \leq < R(D) >,$$

suggests:

$$M \geq \kappa_1 R(< D >) + \kappa_2\,, \tag{4.7}$$

but, as they say, some assembly is required, and the next section introduces and applies the needed tools.

4.3 Black-Scholes

Although the Black-Scholes formalism for financial options trading (Black and Scholes, 1973) is of limited real-world use (e.g., Derman and Taleb, 2005; Haug and Taleb, 2011), the methodology remains of some interest as a conceptual model that can be generally applied to regulation. The central purpose of the approach is to explicitly account for the effects of unpredictability – noise – in a simplified analytic expression. The tool for this is a very clever use of the Ito chain rule for stochastic differential equations.

Consider the canonical example of a stock price S, whose dynamics are determined by the stochastic differential equation

$$dS_t = \mu S_t dt + b S_t dW_t\,, \tag{4.8}$$

where dW_t is ordinary white noise.

Given a known payoff function $V(S,t)$, one uses the Ito chain rule to define another SDE, in the usual manner. Now define a 'portfolio function' as the Legendre transform of V;

$$\mathscr{L} = -V + S\partial V/\partial S\,. \tag{4.9}$$

Manipulation, using the derived SDE for V, gives the result that

$$\Delta\mathscr{L} = (-\partial V/\partial t - \frac{1}{2} b^2 S^2 \partial^2 V/\partial S^2)\Delta t\,, \tag{4.10}$$

which eliminates the noise term dW_t, and incorporates the effects of noise via the Ito correction, the term in b^2. Assuming $\Delta\mathscr{L}/\Delta t \propto \mathscr{L}$ and a bit more algebra gives the classic Black-Scholes equation for V.

The question arises whether a regulatory system can be described in terms of similar hedging strategies.

The change in average distortion between regulatory intent and effect with time can be seen as representing the dynamics of the Rate Distortion Function (RDF) of a regulatory system that is distributed across an organism. Let R_t be the RDF at time t. The relation can, under conditions of both white noise and volatility, be expressed as

$$dR_t = f(t,R_t)dt + bR_t dW_t\,, \tag{4.11}$$

where b characterizes added, internal, 'regulatory' noise, beyond that inherent in the channel transmission as represented by the variance σ^2 in equation (4.4). This is a consequence of the fact that regulation takes place across the organism as a whole, adding another level of organization through which signals must be transmitted.

Let $M(R_t,t)$ represent the rate of metabolic free energy consumption (these are nonequilibrium processes) associated with R_t at time t across the organism, and expand using the Ito chain rule:

$$\begin{aligned} dM_t = [\partial M/\partial t + f(R_t,t)\partial M/\partial R + \frac{1}{2}b^2R_t^2\partial^2 M/\partial R^2]dt \\ +[bR_t\partial M/\partial R]dW_t\,. \end{aligned} \tag{4.12}$$

Again, define $\mathscr{L}$ as the Legendre transform of the free energy consumption rate M, an entropy-like measure (e.g., Wallace, 2012), having the form

$$\mathscr{L} = -M + R\partial M/\partial R\,. \tag{4.13}$$

Using the heuristic of replacing dX with ΔX in these expressions, and applying the results of equation (4.12), produces an exact analog to equation (4.10):

$$\Delta\mathscr{L} = (-\partial M/\partial t - \frac{1}{2}b^2R^2\partial^2 M/\partial R^2)\Delta t\,. \tag{4.14}$$

Again, precisely as in the Black-Scholes calculation, the terms in f and dW_t cancel out, giving a noiseless relation, or rather, one in which the effects of noise are subsumed in the Ito correction involving b. Clearly, however, the approach also invokes powerful regularity assumptions that may often be violated. Matters then revolve about model robustness in the face of such violation.

We perform a heuristic iteration as follows: $\mathscr{L}$, as the Legendre transform of the metabolic free energy rate M, is itself a kind of entropy rate index that can be expected to reach a constant level at (dynamic) equilibrium. There, $\Delta\mathscr{L}/\Delta t = \partial M/\partial t \equiv 0$, giving the final relation

$$\frac{1}{2}b^2R^2d^2M/dR^2 = 0\,. \tag{4.15}$$

Thus, at (dynamic) equilibrium:

$$M_{equlib}(R) = \kappa_1 R + \kappa_2 \,, \tag{4.16}$$

analogous to, but more precise than, equation (4.7).

More complicated models, depending on the assumed form of $\Delta\mathscr{L}/\Delta t$, are clearly possible. As above, assuming $\Delta\mathscr{L}/\Delta t \propto \mathscr{L}$, gives the Black-Scholes result.

The cost of regulation, in this model proportional to the RDF, can rapidly become very expensive, since κ_1 is expected to be large as a consequence of entropic loss. Thus, from the convexity of $R(D)$, decreasing average distortion in will consume metabolic free energy at very high rates in a kind of generalized inflammation. From the relation for $R(D)$ in a Gaussian channel, fixing average distortion D at the regulated level, and applying a 'noxious exposure' that causes σ^2 to increase, will raise demand for metabolic free energy at a rate $\propto 2\kappa_1 \log[\sigma]$, in this model. This should be an observable effect. Different observed impacts would, of course, imply other models.

4.4 Stability

The rate distortion function places limits on information source uncertainty. Thus average distortion measures D can drive information system dynamics as well as $R(D)$, via the convexity relation. That is, the rate distortion function itself has a homological relation to free energy density, in the sense of Feynman (2000) and Bennett, (1988), and one can apply Onsager arguments using D as a driving parameter.

Defining a 'Rate Distortion entropy' as the Legendre transform of equation (4.4), so that

$$S_R = R(D) - DdR(D)/dD = 1/2\log[\sigma^2/D] + 1/2\,, \tag{4.17}$$

the simplest possible nonequilibrium Onsager equation (de Groot and Mazur, 1984) is just

$$dD/dt = -\mu dS_R/dD = \mu/2D\,, \tag{4.18}$$

where t is the time and μ is a diffusion coefficient. By inspection,

$$D(t) = \sqrt{\mu t}. \tag{4.19}$$

This should be recognized as the classic solution to the diffusion equation. Such correspondence reduction to a well-known result serves as a base to argue upward in both scale and complexity.

The simplest aging model arises as

$$dD/dt = -\mu dS_R/dD - \alpha M\,, \tag{4.20}$$

where α is a scaling constant representing the translation of the rate of free energy usage, M, into system control.

This has the equilibrium solution

$$D_{equlib} = \frac{\mu}{2\alpha M}. \tag{4.21}$$

The simplest representation of aging, then, involves systematic deterioration in regulatory mechanisms, as represented by a progressive decline in the product αM.

Let $G(M)$ represent a more general monotonic increasing function of metabolic energy rate M. Then a plausible generalization of equation (4.20), in the presence of an internal regulatory noise in addition to the channel noise defined by σ^2 in equation (4.4), is

$$dD_t = (\frac{\mu}{2D_t} - G(M))dt + \frac{\beta^2}{2} D_t dW_t. \tag{4.22}$$

This has the equilibrium expectation

$$D_{equilib} = \frac{\mu}{2G(M)}, \tag{4.23}$$

representing the massive levels of metabolic free energy needed to limit distortion between the intent and effect of regulation in an organism or biological submodule: M can be expected to increase very sharply with rise in G.

Using the Ito chain rule on equation (4.22), one can calculate the variance in the distortion as $E(D_t^2) - (E(D_t))^2$.

Letting $Y_t = D_t^2$ and applying the Ito relation,

$$dY_t = [2\sqrt{Y_t}(\frac{\mu}{2\sqrt{Y_t}} - G(M)) + \frac{\beta^4}{4} Y_t]dt + \beta^2 Y_t dW_t, \tag{4.24}$$

where $\frac{\beta^4}{4} Y_t$ is the Ito correction to the time term of the SDE.

A little algebra shows that no real number solution for the expectation of $Y_t = D_t^2$ can exist unless the discriminant of the resulting quadratic equation is ≥ 0, so that

$$G(M) \geq \frac{\beta^2}{2}\sqrt{\mu}. \tag{4.25}$$

From equations (4.16) and (4.23),

$$G(M) = \frac{\mu}{2\sigma^2}\exp[2(M-\kappa_2)/\kappa_1] \geq \frac{\beta^2}{2}\sqrt{\mu}. \tag{4.26}$$

Solving for M gives the necessary condition

$$M \geq \frac{\kappa_1}{2}\log[\frac{\beta^2\sigma^2}{\sqrt{\mu}}] + \kappa_2, \tag{4.27}$$

for there to be a real second moment in D. κ_1 is, again, expected to be very large indeed. Given the context of this analysis, failure to provide adequate rates of metabolic free energy would represent the onset of a regulatory catastrophe, again associated with a generalized inflammation – very high rates of metabolic free energy consumption.

Pathogenic exposures – chemicals, infections, psychosocial stressors – can be expected to markedly increase both β and σ.

Many variants of the model are possible. The most natural, perhaps, is to view M as a free energy measure *per unit external perturbation*. That is, $M \equiv d\hat{M}/dK$, where $\hat{M}$ is now perceived as the rate of free energy consumption needed to meet an external perturbation of (normalized) magnitude K. Then the condition of equation (4.27), now on $\hat{M}$, becomes

$$\hat{M} \geq \int [\frac{\kappa_1}{2} \log[\frac{\beta^2\sigma^2}{\sqrt{\mu}}] + \kappa_2] dK \,. \tag{4.28}$$

Under constant conditions,

$$\hat{M} \geq [\frac{\kappa_1}{2} \log[\frac{\beta^2\sigma^2}{\sqrt{\mu}}] + \kappa_2] \Delta K \tag{4.29}$$

where ΔK is the magnitude of the perturbation. Thus the demand on free energy resources caused by perturbation can be greatly amplified, in this model, suggesting that erosion of stability by psychosocial stress or other externalities can make the system more sensitive to the impact of natural shocks, a model of premature aging.

Application of the argument to other forms of Rate Distortion Function is direct. For example, the relation for the natural channel is $R(D) \approx \sigma^2/D$, giving a condition based on the discriminant of a cubic in equation (4.25).

Equations (4.25-4.29) have fundamental implications for the dynamics, structure, and stability of interacting networks of cognitive physiological submodules as described in chapter 3. Granovetter (1973) characterizes network function in terms of 'the strength of weak ties'. Strong ties, to adapt his perspective, disjointly partition a network into identifiable submodules. Weak ties reach across such disjoint partitioning, that is, they are linkages that do not disjointly partition a network. The average probability of such weak ties, at least in a random network, defines the fraction of network nodes that will be in a 'giant component' that links the vast majority of nodes. It is well known that the occurrence of such a component is a punctuated event. That is, there is a critical value of the average probability of weak ties below which there are only individual fragments. Wallace (2012, figure 3) provides something of an introduction, in the context of interacting cognitive submodules that, here, represent the distributed cognition of the full organism.

It seems clear that the maintenance of such weak ties, allowing large-scale distributed cognition across the organism, depends critically on the 'investment' of regulatory free energy at rates M or $\hat{M}$. That is, keeping the channels of communication open in an organism under stress will require greater and greater rates of free energy expenditure, representing a generalized inflammation. In the language

of chapter 3, M is a monontonic increasing function of Ω, the tunable, syntatically-dependent detection limit that is driven by the instantaneous topology of the giant component of linked cognitive modules defining a global broadcast. Stress can be envisioned as increasing the 'slope' of that monotonicity.

More formally, M and $\hat{M}$ can be interpreted as intensity indices analogous to a generalized temperature. Identifiable cognitive submodules within the organism define equivalence classes leading to a groupoid symmetry as described in chapter 3. Groupoids can be understood as a generalization of the group symmetry concept, the simplest groupoid being a disjoint union of different groups. This leads toward something much like Landau's perspective on phase transition (e.g., Pettini, 2007; Landau and Lifshitz, 2007). The essential idea is that certain phase transitions take place in the context of a significant symmetry change, with one phase, at higher temperature, being more symmetric than the other. A symmetry is lost in the transition, what is called spontaneous symmetry breaking. The transition is usually highly punctuated. In this context, equations (4.25-4.29) can be interpreted as defining the 'critical temperature' M or $\hat{M}$ below which a complex network of interacting cognitive submodules collapses into a simpler groupoid structure of disjointly partitioned submodules. From Landau's viewpoint, the 'order parameter' that disappears at high M or $\hat{M}$ might be taken as one minus the number of (locally) active, independent submodules.

Conversely, the model implies that unwarranted increases in the parameters $\kappa_1, \kappa_2, \beta$ and σ, or a decline in μ, can trigger sudden onset of large-scale physiological activation – a generalized inflammation.

This is a central point that we now enlarge upon.

4.5 Extending the model

The most obvious generalization of this approach involves a coevolutionary pair of equations representing the possibility of a feedback loop between regulation and its metabolic cost, having the general form

$$\begin{aligned} dR_t &= f_1(t,R,M)dt + g_1(t,R,M)dW_t \\ dM_t &= f_2(t,R,M)dt + g_2(t,R,M)dW_t\,. \end{aligned} \tag{4.30}$$

Regulatory mechanisms represented by the coevolutionary pattern of equation (4.30) must, following the considerations of chapter 2, actually be nested by scale and level of organization, and linked across these by crosstalk. Then

$$\begin{aligned} dR_t^i &= f_1^i(t,\mathbf{R},\mathbf{M})dt + g_1^i(t,\mathbf{R},\mathbf{M})dW_t \\ dM_t^j &= f_2^j(t,\mathbf{R},\mathbf{M})dt + g_2^j(t,\mathbf{R},\mathbf{M})dW_t\,, \end{aligned} \tag{4.31}$$

where $\mathbf{R}$ and $\mathbf{M}$ now represent vector quantities, as $\mathbf{R} = (R^1, R^2, \ldots)$, and similarly for $\mathbf{M} = (M^1, M^2, \ldots)$.

Again, application of the Ito chain rule to $[M^j]^2$ allows calculation of the variance in demand for metabolic free energy. At equilibrium – where rates of change are zero – that is given by the expression in expectations $E[M^2] - E[M]^2$. Again, under some conditions, the variance may become unstable or or grow explosively.

Several features emerge from invoking such a coevolutionary dynamic (Champagnat et al., 2006):

1. Setting the expectation of equations (4.30) or (4.31) equal to zero and solving for stationary points gives attractor states since the noise terms preclude unstable equilibria.

2. Such a system may converge to limit cycle or pseudorandom strange attractor behaviors in which the system seems to chase its tail endlessly within a limited venue – a kind of Red Queen pathology. Another pathology may involve the instability of variance in demand for metabolic free energy beyond possible physiological bounds. For Gaussian channels, increase in noise variance σ^2 can markedly increase demand for metabolic free energy, beyond availability.

3. The noise terms in equations (4.30) and (4.31) may not be white, allowing for more subtle behaviors determined by the quadratic variation in the extended version of the Ito chain rule. Indeed, changing the spectrum of noise 'color' may be a signaling modality that carries information.

4. The complete space of quasi-stable modes to which the system can converge – the set of fixed points or strange attractors of equations (4.30) or (4.31) – may itself have a topology allowing definition of open sets within it. These must have the properties (i) that the union of open sets is itself an open set, (ii) the finite intersection of open sets is open, and (iii) the complete space and the zero set are both open.

5. This topological space may have characteristic internal dynamics that are to be mapped onto physiology via the mechanisms of equation (4.31), providing a kind of change-of-variables that may give a simplified description of the system, much as spherical coordinates can be useful in addressing problems with spherical symmetry.

A version of these ideas is now standard in systems biology (e.g., Kitano, 2004).

Different quasi-stable points of this system will have widely different rates of associated metabolic cost M or $\mathbf{M}$; high values or explosive variances will inevitably be associated with a set of conditions akin to inflammation, with all that implies for early onset of chronic disease (e.g., Wallace and Wallace, 2010).

The inherent modularity of equation (4.31) suggests the possibility of Barrs-like temporary, tunable, assemblages of low level cognitive modules at all scales to address changing, temporary patterns of challenge and opportunity confronting the organism, much as described by Wallace (2012). Regulation of such linked, hierarchical broadcasts remains to be studied in detail using these methods.

Is there any analog to equations (4.27-4.29) for this system? The essential trick is to recognize that, given such constraints, the problem can be recast as one of Kuhn-Tucker optimization of the expectations at equilibrium of equation (4.31) (Nocedal and Wright, 1999), having the form

$$\begin{aligned} f_1^i(t \to \infty, \mathbf{R}, \mathbf{M}) &= 0 \\ f_2^j(t \to \infty, \mathbf{R}, \mathbf{M}) &= 0 \\ M^k \geq M_{min}^k \forall k\,. & \end{aligned} \tag{4.32}$$

Most importantly, there may be no general solution satisfying the conditions $M^k \geq M^k_{min} \forall k$, that is, no possible Pareto surface defining the limits of optimality for the interacting system.

Note that, by the network linkages inherent to the functions f^i_1, f^j_2, a single metabolic rate function M^q can influence more than just a single R^q. That is, a metabolic rate function M^q that does not violate a particular condition M^q_{min} may still resonate across the system to cause a condition $M^x < M^x_{min}$ for some x, triggering physiological stress. Conversely, if some of the limits M^q_{min} are *themselves* pathologically increased, then excitation of other regulatory processes can be triggered as a generalized pathological inflammatory response, typically a large-scale Baars-like global broadcast across a set of regulatory systems acting at a variety of scales and levels of organization.

This is a fundamental observation, since bioregulatory dysfunction in one system can then trigger generalized inflammatory response across any number of linked modes.

Note that these results are contingent on a white noise model. Again, replacement of dW_t by noise having a color spectrum that may itself carry information would significantly complicate the model, a matter requiring further formal study.

More generally, however, setting the expectation of equation (4.31) to zero generates an index theorem (Hazewinkel, 2002), in the sense of Atiyah and Singer (1963). An index theorem relates analytic results – the solutions to the equations – to an underlying set of topological structures that are eigenmodes of a complicated geometric operator whose spectrum represents the possible multiple global broadcast states of the system as characterized by different groupoid structures. This system, and its dynamics, do not really have simple classical, quantum, or electrical analogs.

Index theorems, in this context, instantiate relations between 'conserved' quantities – here, the quasi-equilibria of basins of attraction in parameter space – and underlying topological form. Chapter 3, however, described how that network was itself defined in terms of equivalence classes of meaningful paths that, in turn, defined groupoids, a significant generalization of the group symmetries more familiar to physicists.

The approach, then, in a sense – via the groupoid construction – generalizes the famous relation between group symmetries and conservation laws uncovered by E. Noether that has become the central foundation of modern physics (Byers, 1999). Thus this work proposes a kind of Noetherian statistical dynamics of cognition. The method represents the fitting of dynamic regression-like statistical models based on the asymptotic limit theorems of information theory to data, and does not presume to be a 'real' picture of the underlying systems and their time behaviors. That is, as with simple fitted regression equations, actual scientific inference is to be done by comparing the same systems under different, and different systems under the same, conditions. Statistics is not science, and one can easily imagine the necessity of 'nonparametric' or 'non-Noetherian' models of cognition.

The phase transitions inherent to global broadcasts, as indexed by M and $\hat{M}$ of Section 4.4, must be iterated when multiple, simultaneous broadcasts occur: renormalize the interlinking information sources constituting a single broadcast down

onto a single 'point' each representing a joint information source, and now examine the crosstalk between individual global broadcasts in terms of a 'higher' M-measures. That is, M or $\hat{M}$ represents crosstalk between global broadcasts in which individual submodules are multitasking, engaging in more than one broadcast at a time. Again, in a physiological context, the immune system simultaneously engages in routine tissue maintenance, pathogen surveillance and attack, and neuroimmuno dialog. Gene expression is similarly tasked with multifactorial response during development (e.g., Wallace and Wallace, 2010). This global broadcast of global broadcasts represents, in this model, the integrity of the entire system. If the (generalized) M or $\hat{M}$ of this larger structure falls below some critical value, the physiological hybrid cannot function well.

Iterating this model further generates patterns of 'social' interaction between the system of interest and its embedding environment that, for humans, involves both social structure and dynamics, culture, and the effects of historical trajectory on the embedding environment.

The index theorem approach in M, $\hat{M}$, or larger structures, however, makes clear that M and $\hat{M}$-measures are only part of the story. The networks, and networks-of-networks linking internal subsystems by crosstalk are topologically structured, not at all random, and seldom similar. The internal topology of a composite system – including the de-facto power relations between embedding social subgroups – may critically determine the ability to respond to environmental changes in a timely and effective manner. For composite systems not dominated by power relations, internal network topology will still channel the ability to respond to environment.

4.6 Intervention

Quasi-stationary modes of the coevolutionary dynamics of equations (4.30) and (4.31), and the stability/instability condition implied by equations (4.25), (4.27), and their generalizations, are subject to 'ecosystem resilience' transitions between them when driven by increasing noise or by externally imposed forcing functions – environmental, pathogenic, sociocultural or biomedical inputs – that can themselves often be described as the output of information sources (e.g., Holling, 1973; 1992).

As Champagnat et al. (2006) note, shifts between quasi-equilibria in a coevolutionary system can be addressed by a large deviations approach. The dynamics of drift away from trajectories and quasi-stable modes predicted by canonical relations like equations (4.30) and (4.31) can be investigated by considering the asymptotic of the probability of 'rare events' for the sample paths of the diffusion.

Rare events are the diffusion paths drifting far away from the direct solutions of the canonical equation. Following Champagnat et al., the probability of such rare events is governed by a large deviation principle: under influence of a critical parameter, the probability that the sample path of the diffusion is close to a given rare path ϕ decreases exponentially to 0 with rate $\mathscr{I}(\phi)$, where the 'rate function' $\mathscr{I}$ can be expressed in terms of the parameters of the diffusion.

This result can be used to study long-time behavior of the diffusion process when there are multiple attractive singularities. Under proper conditions, the most likely path followed by the diffusion when exiting a basin of attraction is the one minimizing the rate function $\mathscr{I}$ over all the appropriate trajectories.

An essential fact of large deviations theory is that the rate function $\mathscr{I}$ that Champagnat et al. invoke can be expressed as a kind of information free energy measure, that is, having the canonical form

$$\mathscr{I} = -\sum_j P_j \log(P_j) \tag{4.33}$$

for some probability distribution. This result goes under a number of names; Sanov's Theorem, Cramer's Theorem, the Gartner-Ellis Theorem, the Shannon-McMillan Theorem, and so forth (Dembo and Zeitouni, 1998).

These arguments are much in the direction of equations (4.30) and (4.31), and the stability/instability condition of equations (4.25-4.29) and (4.32), now seen as subject to large deviations that are themselves the product of information sources – for example, the impact of the embedding environment as described in chapter 3, or of deliberate, cognitively-determined, medical intervention. These provide driving parameters that can trigger punctuated shifts between quasi-stable modes, or between quasi-stability and instability, or, by contrast, can represent control mechanisms that can prevent or remediate such transitions, i.e., a therapeutic environment, acting at individual or mesoscale levels of organization. Thus external signals, characterized by an information source $\mathscr{I}$, can provide parameters that serve to drive the system to different quasi-equilibrium metabolic and system states in a highly punctuated manner. Some will be pathological, others may represent therapeutic counterperturbations against pathology. These latter may be long-term or permanently needed treatment strategies.

A second perspective on intervention focuses on the inevitability of crosstalk between information sources, defining a kind of information catalysis by which incoming information can direct developmental pathways, acting as either a source of pathology, or of therapy.

The information sources dual to the linked lower level cognitive modules are not independent, but are correlated, so that a joint information source can be defined having the properties

$$H(X_1,...,X_n) \leq \sum_{j=1}^{n} H(X_j)\,. \tag{4.34}$$

This is the information chain rule (e.g., Cover and Thomas, 2006), and has implications for metabolic energy consumption and regulation in biological process. Recall Feynman's (2000) description of how information and free energy have an inherent duality. Feynman, in fact, defines information precisely as the free energy needed to erase a message. The argument is surprisingly direct, and for very simple systems it is easy to design a small (idealized) machine that turns the information within a message directly into usable work – free energy. Information is a form of free energy and the construction and transmission of information within living

things – the physical instantiation of information – consumes considerable free energy, with inevitable – and massive – losses via the second law of thermodynamics.

Suppose an intensity of available metabolic free energy is associated with each defined joint and individual information source $H(X,Y), H(X), H(Y)$, e.g., rates $M_{X,Y}$, M_X,M_Y.

Again, although information is a form of free energy, there is massive entropic loss in its actual expression, so that the probability distribution of a source uncertainty H might be written in Gibbs form as

$$P[H] = \frac{\exp[-H/\kappa M]}{\int \exp[-H/\kappa M] dH}, \tag{4.35}$$

assuming κ is very, very small.

To first order, then,

$$\hat{H} = \int HP[H]dH \approx \kappa M, \tag{4.36}$$

and, using equation (4.34),

$$\begin{aligned} \hat{H}(X,Y) &\leq \hat{H}(X) + \hat{H}(Y) \\ M_{X,Y} &\leq M_X + M_Y . \end{aligned} \tag{4.37}$$

Thus, as a consequence of the information chain rule, allowing crosstalk consumes a lower rate of free energy than isolating information sources. That is, in general, it takes more free energy – higher total cost – to isolate a set of cognitive phenomena than it does to allow them to engage in crosstalk, a signal interaction that, under typical circumstances, grows as the inverse square of the separation between circuits. This is a well-known problem in electrical engineering that can consume considerable attention and other resources for proper address.

Thus, at the energy expense of supporting two information sources, i.e., X and Y together, it becomes possible to catalyze a set of joint paths defined by their joint information source. Hence, given a cognitive module (or set of them), having an associated information source $H(...)$, an external information source Y can catalyze the joint paths associated with the joint information source $H(....,Y)$ so that a particular chosen developmental pathway – in a large sense – has the lowest free energy. This path can be pathological, in the case of a pathogenic stressor, or therapeutic, in the case of a medical or sociomedical intervention.

Again, invoking the arguments of Section 3.5, catalysis can be distributed across partitioned sets of information sources.

Yet another way of looking at this mechanism is to invoke the groupoid arguments of chapter 3, in the context of spontaneous symmetry breaking. The complex fuzzy lock-and-key logic gate-like cognitive system of interest is most likely characterized in terms of an analog to nonrigid molecule symmetries (e.g., Longuet-Higgins, 1963; Balasubramanian, 1980; Wallace, 2012), here involving the wreath product of the underlying cognitive groupoids rather than groups. Most of the mosaic-like quasi-symmetry modes will be isoenergetic under normal circum-

stances. Incoming information, the output of a catalytic information source, might be instantiated by some chemical signal like adrenaline or cortosol levels, or the concentration of some other chemical species or mix of them. Then some measure of that concentration becomes an intensity index that serves as a temperature analog to trigger the usual spontaneous symmetry breaking, defining the different states of some exceedingly subtle and complicated logic structure.

Regarding therapeutic intervention, as Wallace and Wallace (2004) argue at some length, imposed real stress may seriously interfere with any treatment strategies, affecting patient-provider interaction, patient compliance, and the actual effectiveness of drug or other interventions. Conversely, appropriate counterperturbation to stress, probably at the human keystone level of neighborhood/social network, can act to improve treatment effectiveness.

Chapter 5
Discussion and Conclusions

According to the model, the metabolic cost of physiological regulation can grow at rates at least proportional to the required regulatory Rate Distortion Function, a convex function of the average distortion between regulatory intent and effect. The constants of proportionality κ_1, κ_2 in equations (4.16) and (4.27), may be very large, given the usually massive entropic losses associated with biological process. This, in conjunction with the arguments above, suggests that exposure to noxious chemical agents, infections, psychosocial stress, and so on, can act as a kind of noise, raising values of β and σ, and trigger transitions to chronic, quasi-stable, high levels of distortion and associated massive consumption of metabolic free energy – generalized inflammation leading to early onset of chronic disease. Therapeutic intervention must overcome the quasi-stability of these pathological states. Given the path-dependent nature of physiological development, a return to previous modes may be impossible, requiring ongoing treatment that may be profoundly affected by ongoing stressors.

Equations (4.27) through (4.29) provide necessary conditions for real second moments. Most simply, failure of the condition can represent onset of a punctuated physiological crisis. More subtly, however, occurrence of a complex discriminant is often associated in physical systems with limit cycle behavior, and cycles are often characteristic of the embedding ecosystem; diurnal light/temperature variations, seasonal changes in temperature and nutrient availability, and so on. An organism might, then, avoid massive free energy demands by an evolutionary embracing, as it were, of imposed cycle behavior. Examples might include daily sleep and feeding cycles or annual patterns of mating, hibernation, and estivation, deciduous loss of leaves in plants and antlers in deer, and so on. Disruption of adapted cycling – most typically the sleep cycle in humans – then, can become a source of raised free energy demand, constituting another form of generalized inflammation.

A central consequence of the crosstalk underlying equations (4.32) and (4.33) is that there is unlikely to be much in the way of 'simple' generalized inflammatory chronic disease. That is, serious comorbidity – perturbations can resonate across the full set of bioregulatory systems – are not only inevitable, but may often be an unfortunate consequence of therapeutic intervention as well. Thus, synergistic

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

pairing of medical with appropriate neighborhood/social network interventions – for humans, a keystone level of organization in Holling's (1992) sense – would be expected to (Wallace and Wallace, 2004):

(1) Damp down unwanted treatment side effects.

(2) Make the therapeutic alliance between practitioner and patient more effective.

(3) Improve patient compliance.

(4) Enhance placebo effect.

(5) In the context of real stress reduction, synergistically improve the actual biological impacts of medical interventions or prevention strategies.

Even without pathogenic events or exposures, normal aging may make it impossible to provide rates of metabolic free energy needed for routine regulation, even in the absence of noxious agencies, leading to increasing distortion in ordinary physiological activities – systematic degradation of the organism – causing the spontaneous phenotypic shifts that constitute senescence. The triggering of shifts between quasi-stable system modes by external perturbations leading to generalized inflammation may, in fact, represent premature senescence, from this perspective. Proper cross-scale interventions – magic strategies – might well slow, or even, in some measure, reverse the effects of, such mechanisms.

While, as Jackson et al. (2007) point out, improvement in living and working conditions – what they characterize as 'healthy public policy' – has the most direct impact, reaching traditionally isolated, vulnerable populations trapped in a pathogenic historical trajectory, or any population in the absence of healthy public policy, will require special focus on keystone social network and geographic mesoscales.

Chapter 6
References

Anfinsen, C., 1973, Principles that govern the folding of protein chains, Science, 181:223-230.

Arrell, D., A. Terzic, 2010, Network systems biology for drug discovery, Clinical Pharmacology and Therapeutics, 88:120-125.

Ash, R., 1990, Information Theory, Dover, New York

Atiyah, M., I. Singer, 1963, The index of elliptical operators on compact manifolds, Bulletin of the American Mathematical Society, 69:322-433.

Atlan, H., I. Cohen, 1998, Immune information, self-organization, and meaning, International Immunology, 10:711-717.

Avital, E., E. Jablonka, 2000, Animal Traditions: Behavioral Inheritance in Evolution, Cambridge University Press, New York.

Baars, B., 1988, A Cognitive Theory of Consciousness, Cambridge University Press, New York.

Baars, B., 2005, Global workspace theory of consciousness: toward a cognitive neuroscience of human experience, Progress in Brain Research, 150:45-53.

Baars, B., S. Franklin, 2003, How conscious experience and working memory interact, Trends in Cognitive Science, 7:166-172.

Backdahl, L., A. Bushell, S.Beck, 2009, Inflammatory signallilng as mediator of epigenetic modulation in tissue-specific chronic inflammation, International Journal of Biochemistry and Cell Biology, 41:176-184.

Balasubramanian, K., 1980, The symmetry groups of nonrigid molecules as generalized wreath products and their representations, Journal of Chemical Physics, 72:665-677.

Beck, C., F. Schlogl, 1995, Thermodynamics of Chaotic Systems, Cambridge University Press, New York.

Bennett, C., 1988, Logical depth and physical complexity. In The Universal Turing Machine: A Half-Century Survey, R. Herkin (ed.), pp. 227-257, Oxford University Press, New York.

Black, F., M. Scholes, 1973, The pricing of options and corporate liabilities, Journal of Political Economy, 81:637-654.

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2

Blagosklonny, M., 2010, Why the disposable soma theory cannot explain why women live longer and why we age, Aging, 2:884-887.

Bjorntorp, P., 2001, Do stress reactions cause abdominal obesity and cormorbidities? Obesity Reviews, 2:73-86.

Boran, A., R. Iyengar, 2010, Systems approaches to polypharmacology and drug discovery, Current Opinion in Drug Discovery Development, 13:297-309.

Bosma-Den Boer, M., M. Van Wetten, L. Pruimboom, 2012, Chronic inflammatory diseases are stimulated by current lifestyle: how diet, stress levels and medication prevent our body from recovering, BMC Nutrition and Metabolism, 9:32.

Brown, R., 1987, From groups to groupoids: a brief survey, Bulletin of the London Mathematical Society, 19:113-134.

Bruce, M., B. Beech, M. Sims, T. Brown, S. Wyatt, H. Taylor, D. Williams, E. Crook, 2009, Social environmental stressors, psychological factors, and kidney disease, Journal of Investigative Medicine, 57:583-589.

Byers, N., 1999, Noether's discovery of the deep connection between symmetries and conservation laws, Israel Mathematical Conference Proceedings, Vol. 12, ArXiv physics/9807044.

Champagnat, N., R. Ferriere, S. Meleard, 2006, Unifying evolutionary dynamics: from individual stochastic process to macroscopic models, Theoretical Population Biology, 69:297-321.

Cohen, I., 1992, The cognitive principle challenges clonal selection, Immunology Today, 13:441-444.

Cohen, I., 2000, Tending Adam's Garden: evolving the cognitive immune self, Academic Press, New York.

Cohen, I., 2006, Immune system computation and the immunological homunculus. In Nierstrasz, O., J. Whittle, D. harel, G. Reddio (eds.), MoDels 2006, LNCS, vol. 4199, pp. 499-512, Springer, Heidelberg.

Cohen, I., D. Harel, 2007, Explaining a complex living system: dynamics, multiscaling, and emergence, Journal of The Royal Society: Interface, 4:175-182.

Cohen, S., D. Janicki-Deverts, G. Miller, 2007, Psychological stress and disease, Journal of the American Medical Association, 298:1685-1687.

Cohen, S., D. Janicki-Deverts, W. Doyle G. Miller, E. Frank, B. Rabin, R. Turner, 2012, Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk, Proceedings of the National Academy of Sciences,
doi/10.1073/pnas.1118355109.

Cover, T., J. Thomas, 2006, Elements of Information Theory, 2nd Edition, Wiley, New York.

Crowson, C., K. Liang, T. Therneau, H. Kremers, S. Gabriel, 2010, Could accelerated aging explain excess mortality in patients with seropositive rheumatoid arthritis? Arthritis and Rheumatism, 62:378-382.

de Groot, S., P. Mazur, 1984, Non-Equilibrium Thermodynamics, Dover, New York.

Dembo, A., O. Zeitouni, 1998, Large Deviations: Techniques and Applications, Springer, New York.

Derman, E., N. Taleb, 2005, The illusions of dynamic replication, Quantitative Finance, 5:323-326.

Dill, K., S. Banu Ozkan, T. Weikl, J. Chodera, V. Voelz, 2007, The protein folding problem: when will it be solved? Current Opinion in Structural Biology, 17:342-346.

Dobson, C., 2003, Protein folding and misfolding, Nature, 426:884-890.

Dretske, F., 1994, The explanatory role of information, Philosophical Transactions of the Royal Society A, 349:59-70.

Dudley, J., E. Schadt, M. Sirota, A. Butte, E. Ashley, 2010, Drug discovery in a multidimensional world: systems, patterns, and networks, Journal of Cardiovascular Translational Research, 3:438-447.

Durham, W., 1991, Coevolution: Genes, Culture, and Human Diversity, Stanford University Press, Palo Alto.

El Gamal, A., Y. Kim, 2010, Lecture Notes on Network Information Theory, arXiv:1001.3404v4[cs.IT].

Ellis, R., 1985, Entropy, Large Deviations, and Statistical Mechanics, Springer, New York.

English, T., 1996, Evaluation of evolutionary and genetic optimizers: no free lunch. In Evolutionary Programming V: Proceedings of the Fifth Annual Conference on Evolutionary Programming, Fogel, L., P. Angeline, T. Back (eds.), pp. 163-169, MIT Press, Cambridge, MA.

Epel, E., E. Blackburn ,J. Lin, F. Dhabhar, N. Adler, J. Morrow, R. Cawthon, 2004, Proceedings of the National Academy of Sciences, 101:17312-17315.

Ewens, W., 2004, Mathematical Population Genetics, Springer, New York.

Feynman, R., 2000, Lectures on Computation, Westview Press, New York.

Foley, D.,J. Craig, R. Morley, C. Olsson, T. Dwyer, K. Smith et al., 2009, Prospects for epigenetic epidemiology, American Journal of Epidemiology, 169:389-400.

Forlenza, M., A. Baum, 2000, Psychosocial influences on cancer progression: alternative cellular and molecular mechanisms, Current Opinion in Psychiatry, 13:639-645.

Geronimus, A., M. Hicken, D. Keene, J. Bound, 2004, 'Weathering' and age patterns of allostatic load scores among Blacks and Whites in the United States, American Nournal of Public Health, 96:826-833.

Gilbert, P., 2001, Evolutionary approaches to psychopathology: the role of natural defenses, Australian and New Zeland Journal of Psychiatry, 35:17-27.

Glass, T., M. McAtee, 2006, Behavioral science at the crossroads of public health: extending horizons, envisioning the future, Social Science and Medicine, 62:1650-1671.

Gould, S., 2002, The Structure of Evolutionary Theory, Harvard University Press, Cambridge, MA.

Granovetter, M., 1973, The strength of weak ties, American Journal of Sociology, 78:1360-1380.

Haataja, L., T. Gurlo, C. Huang, P. Butler, 2008, Islet amyloid in type 2 diabetes, and the toxic oligomer hypothesis, Endocrine Reviews, 29:303-316.

Harman, D., 1956, Aging: a theory based on free radical and radiation chemistry, Journal of Gerontology, 11:298-300.

Haug, E., N. Taleb, 2011, Option traders use (very) sophisticated heuristics, never the Black-Scholes-Merton formula, Journal of Economic Behavior and Organization, 77:97-106.

Hazewinkel, M., 2002, Encyclopedia of Mathematics, 'Index Formulas', Springer, New York.

Heine, S., 2001, Self as cultural product: an examination of East Asian and North American selves, Journal of Personality, 69:881-906.

Hollan, J., J. Hutchins, D. Kirsch, 2000, Distributed cognition: toward a new foundation for human-computer interaction, ACM Transactions on Computer-Human Interaction, 7:174-196.

Holling, C., 1973, Resilience and stability of ecological systems, Annual Reviews of Ecological Systematics, 4:1-23.

Holling, C., 1992, Cross-scale morphology, geometry, and dynamics of ecosystems, Ecological Monographs, 62:447-502.

Jablonka, E., M. Lamb, 1995, Epigenetic Inheritance and Evolution: The Lamarckian Dimension, Oxford University Press, Oxford.

Jablonka, E., M. Lamb, 1998, Epigenetic inheritance in evolution, Journal of Evolutionary Biology, 11:159-183.

Jablonka, E., 2004, Epigenetic epidemiology, International Journal of Epidemiology, 33:929-935.

Jackson, S., F. Perkins, E. Khandor, L. Cordwell, S. Hamann, S. Buasai, 2007, Integrated health promotion strategies: a contribution to tackling current and future health challenges, Health Promotion International, 21(S1):75-83.

Jaenish, R., A. Bird, 2003, Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals, Nature:Genetics Supplement, 33:245-254.

Kaufman, J., C. Poole, 2000, Looking back on 'Causal Thinking in the Health Sciences', Annual Reviews of Public Health, 21:101-119.

Khinchin, A., 1957, The Mathematical Foundations of Information Theory, Dover, New York.

Kirkwood, T., 1977, Evolution of aging, Nature, 270:301-304.

Kitano, H., 2004, Biological robustness, Nature Genetics, 5:826-837.

Kolb, H., T. Mandrup-Paulsen, 2010, The global diabetes epidemic as a consequence of lifestyle-induced low-grade inflammation, Diabetologic, 53:10-20.

Landau, L., E. Lifshitz, 2007, Statistical Physics, 3rd Edition, Part I, Elsevier, New York.

Lawson, T., 2006, The nature of heterodox economics, Cambridge Journal of Economics, 30:483-505.

Leonteif, W., 1982, Letter, Science, 217:104-107.

Levin, S., 1989, Ecology in theory and application. In Applied Mathematical Ecology, Levin, S., T. Hallam, L. Gross (eds.), Biomathematical Texts 18, Springer, New York.

Lewontin, R., The Triple Helix: Gene, Organism, and Environment, Harvard University Press, Cambridge, MA.

Lewontin, R., 2010, Not so natural selection, New York Review of Books, online.

Longuet-Higgins, H., 1963, The symmetry groups of non-rigid molecules, Molecular Physics, 6:445-460.

Lorenzini, A., T. Stamato, C. Sell, 2011, The disposable soma theory revisited, Cell Cycle, 22:3853-3856.

Markus, H., S. Kityama, 1991, Culture and the slef-implications for cognition, emotion, and motivation, Psychological Review, 98:224-253.

Masuda, T., R. Nisbett, 2006, Culture and change blindness, Cognitive Science, 30:381-399.

Maturana, H., 1970, Biology of cognition, Biological Computer Laboratory, Research Report BCL 9.0, University of Illinois, Urbana.

Maturana, H., F. Varela, 1980, Autopoiesis and Cognition, Reidel Publishing Company, Dordrecht.

Maturana, H., F. Varela, 1992, The Tree of Knowledge, Shambhala Publications, Boston.

McEwen, B., T. Seeman, 1999, Protective and damaging effects of mediators of stress: Elaborating and testing the concepts of allostasis and allostatic load, Annuals of the New York Academy of Sciences, 896:30-47.

Miller, A., V. Maletic, C. Raison, 2009, Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression, Biological Psychiatry, 65:732-774.

Mindwood, K., L. Valenick Williams, J. Schwarzbauer, 2004, Tissue repair and the dynamics of the extracellular matrix, International Journal of Biochemistry and Cell Biology, 36:1031-1037.

Nisbett, R., K. Peng, C. Incheol, A. Norenzayan, 2001, Culture and systems of thought: holistic vs. analytic cognition, Psychological Review, 108:291-310.

Nisbett, R., Y. Miyamoto, 2005, The influence of culture: holistic versus analytic perception, TRENDS in Cognitive Science, 9:467-473.

Nocedal, J., S. Wright, 1999, Numerical Opitmization, Springer, New York.

Nunney, L., 1999, Lineage selection and the evolution of multistage carcinogenesis, Proceedings of the Royal Society B., 266:493-498.

Odling-Smee, F., K. Laland, M. Feldman, 2003, Niche Construction: THe Neglected Process in Evolution, Princeton University Press, Princeton, NJ.

O'Nullain, S., 2008, Code and context in gene expression, cognition, and consciousness. In Barbiere, M., (ed.), The Codes of Life: The Rules of Macroevolution, Springer, New York, pp.347-356.

Panskepp, J., 2003, At the interface of the affective, behavioral, and cognitive neurosciences: decoding the emotional feelings of the brain, Brain and Cognition, 52:4-14.

Pettini, M., 2007, Geometry and Topology in Hamiltonian Dynamics and Statistical Mechanics, Springer, New York.

Pielou, E., 1977, Mathematical Ecology, Wiley, New York.

Protter, P., 1990, Stochastic Integration and Differential Equations, Springer, New York.

Pujol, A., R. Mosca, J. Farres, P. Aloy, 2009, Unveiling the role of network and systems biology in drug discovery, Trends in Pharmacological Sciences, 31:115-123.

Rau, H., T. Elbert, 2001, Psychophysiology of arterial baroreceptors and the etiology of hypertension, Biological Psychology, 57:179-201.

Richerson, P., R. Boyd, 2006, Not By Genes Alone: How Culture Transformed Human Evolution, Chicago University Press, Chicago, IL.

Rockafellar, R., 1970, Convex Analysis, Princeton University Press, Princeton, NJ.

Scherrer, K., J. Jost, 2007a, The gene and the genon concept: a functional and information-theoretic analysis, Molecular Systems Biology, 3:87-95.

Scherrer, K., J. Jost, 2007b, Gene and genon concept: coding versus regulation, Theory in Bioscience, 126:65-113.

Scheuner, D., R. Kaufman, 2008, The unfolded protein response: a pathway that links insulin demand with β-cell failure and diabetes, Endocrine Reviews, 29:317-333.

Sergeant, C., S. Dehaene, 2004, Is consciousness a gradual phenomenon? Evidence for an all-or-none bifurcation during the attentional blink, Psychological Science, 15:720-725.

Shannon, C., 1959, Coding theorems for a discrete source with a fidelity criterion, Institute of Radio Engineers International Convention Record Vol. 7, 142-163.

Susser, M., 1973, Causal Thinking in the Health Sciences: Concepts and Strategies of Epidemiology, Oxford University Press, New York.

Thayer, J., B. Friedman, 2002, Stop that! Inhibition, sensitization, and their neurovisceral concomitants, Scandinavian Journal of Psychology, 43:123-130.

Timberlake, W., 1994, Behavior systems, associationism, and Pavlovian conditioning, Psychonomic Bulletin, Rev. 1, 405-420.

Tlusty, 2007, A model for the emergence of the genetic code as a transition in a noisy information channel, Journal of Theoretical Biology, 249:331-342.

Turner, B., 2000, Histone acetylation and an epigenetic code, Bioessays, 22:836-845.

Wallace, R., 2000, Language and coherent neural amplification in hierarchial systems, International Journal of Bifurcation and Chaos, 10:493-502.

Wallace, R., 2005, Consciousness: A Mathematical Treatment of the Global Neuronal Workspace, Springer, New York.

Wallace, R., 2007, Culture and inattentional blindness: a global workspace perspective, Journal of Theoretical Biology, 245:378-390.

Wallace, R., 2010, Expanding the modern synthesis, Comptes Rendus Biologies, 333:701-709.

Wallace, R., 2011, Multifunction moonlighting and intrinsically disordered proteins: information catalysis, non-rigid molecule symmetries and the 'logic gate' spectrum, Comptes Rendus Chimie, 14:1117-1121.

Wallace, R., 2012a, Consciousness, crosstalk, and the mereological fallacy: an evolutionary perspective, Physics of Life Reviews, 9:426-453.

Wallace, R., 2012b, Extending Tlusty's rate distortion index theorem method to the glycome: do even 'low level' biochemical phenomena require sophisticated cognitive paradigms? BioSystems, 107:145-152.

Wallace, R., 2012c, Spontaneous symmetry breaking in a non-rigid molecule approach to intrinsically disordered proteins, Molecular BioSystems, 8:374-377.

Wallace, R., 2013, A new formal approach to evolutionary processes in socioeconomic systems, Journal of Evolutionary Economics, 23:1-15.

Wallace, R., R.G. Wallace, 2002, Immune cognition and vaccine strategy: beyond genomics, Microbes and Infection, 4:521-527.

Wallace, R., D. Wallace, R.G. Wallace, 2003, Toward cultural oncology: the evolutionary information dynamics of cancer, Open Systems and Information Dynamics, 10:159-181.

Wallace, R., D. Wallace, 2004, Structured psychosocial stress and therapeutic failure, Journal of Biological Systems 12:335-369.

Wallace, R., M. Fullilove, 2008, Collective Consciousness and its Discontents, Springer, New York.

Wallace, R., D. Wallace, 2008, Punctuated equilibrium in statistical models of generalized coevolutionary resilience: how sudden ecosystem transitions can entrain both phenotype expression and Darwinian selection, Transactions on Computational Systems Biology IX, LNBI 5121:23-85.

Wallace, R., D. Wallace, 2009, Code, context, and epigenetic catalysis in gene expression, Transactions on Computational Systems Biology XI, LNBI 5750:283-334

Wallace, R., D. Wallace, 2010, Gene Expression and its Discontents: The Social Production of Chronic Disease, Springer, New York.

Wallace, R., D. Wallace, 2013, A Mathematical Approach to Multilevel, Multiscale Health Interventions: Pharmaceutical industry decline and policy, response, Imperial College Press, London.

Wallach, J., M. Rey, 2009, A socioeconomic analysis of obesity and diabetes in New York City, Public Health Research, Practice, and Policy, Centers for Disease Control and Prevention.

Weinstein, A., 1996, Groupoids: unifying internal and external symmetry, Notices of the American Mathematical Association, 43:744-752.

Wolpert, D., W. MacReady, 1995, No free lunch theorems for search, Santa Fe Institute, SFI-TR-02-010.

Wolpert, D., W. MacReady, 1997, No free lunch theorems for optimization, IEEE Transactions on Evolutionary Computation, 1:67-82.

Zhang, Q., Y. Wang, E. Huang, 2009, Changes in racial/ethnic disparities in the prevalence of type 2 diabetes by obesity level among US adults, Ethnicity and Health, 14:439-457.

Zhao, S., R. Iyengar, 2012, Systems pharmacology: network analysis to identify multiscale mechanisms of drug action, Annual Review of Pharmacology and Toxicology, 52:505-521.

PeerJ PrePrints | https://peerj.com/preprints/8v2/ | v2 received: 21 May 2013, published: 21 May 2013, doi: 10.7287/peerj.preprints.8v2