

## How organisms do the right thing: The attractor hypothesis

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Neo-Darwinian theory is highly successful at explaining the emergence of adaptive traits over successive generations. However, there are reasons to doubt its efficacy in explaining the observed, impressively detailed adaptive responses of organisms to day-to-day changes in their surroundings. Also, the theory lacks a clear mechanism to account for both plasticity and canalization. In effect, there is a growing sentiment that the neo-Darwinian paradigm is incomplete, that something more than genetic structure, mutation, genetic drift, and the action of natural selection is required to explain organismal behavior. In this paper we extend the view of organisms as complex self-organizing entities by arguing that basic physical laws, coupled with the acquisitive nature of organisms, makes adaptation all but tautological. That is, much adaptation is an unavoidable emergent property of organisms' complexity and, to some a significant degree, occurs quite independently of genomic changes wrought by natural selection. For reasons that will become obvious, we refer to this assertion as the attractor hypothesis. The arguments also clarify the concept of "adaptation." Adaptation across generations, by natural selection, equates to the (game theoretic) maximization of fitness (the success with which one individual produces more individuals), while self-organizing based adaptation, within generations, equates to energetic efficiency and the matching of intake and biosynthesis to need. Finally, we discuss implications of the attractor hypothesis for a wide variety of genetical and physiological phenomena, including genetic architecture, directed mutation, genetic imprinting, paramutation, hormesis, plasticity, optimality theory, genotype-phenotype linkage and punctuated equilibrium, and present suggestions for tests of the hypothesis. © 1998 American Institute of Physics. [S1054-1500(98)00802-7]

**For years, evolutionists and others have raised concerns that natural selection could not possibly account for the degree of adaptive fine-tuning that is routinely observed in nature. These concerns have led to hot debates and no small degree of rancor between biologists whose work presumes "optimal" behavior, and those who insist no mechanism exists whereby such optimality might evolve. This paper points out that organisms, as complex structures, tend to self-organize in adaptive ways quite independent of the underlying genome. The hypothesis suggested in this work, then, goes a considerable way towards resolving concerns over the sufficiency of natural selection.**

### I. INTRODUCTION

Faced with day-to-day changes in their environment, organisms have the remarkable ability to adjust their physiology and behavior appropriately.<sup>1</sup> A faith in the appropriateness of such responses underlies much of biology, provides

the basis for the predictive discipline of sociobiology and, in the biochemical arena, has led Zubay<sup>2</sup> to speak of the "almost miraculous" adjustment of reaction rates "over broad ranges so that energy and intermediates will always be available to meet a given need." Though there is some disagreement as to the precision with which organisms adjust, there is no disputing the fact that they respond appropriately to environmental changes or insults over a wide variety of scales. How do they do it?

Traditionally, biologists attribute such responses to the workings of natural selection, an attribution solidly based in theory and supported by thousands of experiments demonstrating the power of natural selection to discriminate among phenotypes. We have no quarrel with this view as it relates to adjustments across generations, but we question whether it can fully account for responses to stimuli within a single generation.

Consider a male redwing blackbird faced with the choice of accepting or rejecting an encountered food item. An appropriate response requires consideration of the item's identity and nutrient value, the energetic cost of pursuing it, the

abundance and pursuit costs of other potential food items, short-term past ingestion history, the possible presence and proximity of aerial and ground predators, and the presence and proximity of male competitors. The sociobiological literature is full of examples suggesting appropriate behavior in such cases. But is it reasonable to believe that intergenerational genetic changes alone can code for an ability to balance so many competing considerations? Or do we conclude that perhaps the genes need a little help?<sup>3</sup> If so, we must presume that genes code less for specific responses than for plasticity. But this begs the question: by what mechanism is plasticity utilized to do the “right thing?” This concern was voiced by Waddington<sup>4</sup> as far back as the 1950s. Waddington also expressed doubts that specifically directed genetic instructions were compatible with the fact that a particular genotype might correspond to several phenotypes or that “phenotypically almost identical (individuals) could contain wildly different genotypes.” Finally, he noted that no adaptive-genetic mechanism had been proposed to account simultaneously both for plasticity and the rigidity of canalization.<sup>5</sup> These concerns remain with us today.<sup>6,7</sup>

In this paper we argue that the nature of living organisms, as complex, acquisitive systems, leads inevitably to appropriate organismal responses to the external world quite independently of genetic changes arising from natural selection. For reasons that will become clear, we refer to this assertion as the “attractor hypothesis.” A rigorous definition of “appropriate” adjustment emerges from our arguments. We follow with a discussion of consequences for neo-Darwinian theory, physiology and behavior, macroevolution, and other areas of interest. Finally, we suggest ways in which the theory presented might be tested.

## II. GENOTYPE AND PHENOTYPE

There exists a deeply ingrained belief that the ultimate source of biological information, the “coding system,” lies solely in the genome. But consider that quantitative genetic analysis, by virtue of being a stepwise procedure looking first at genetic influence, is bound to define genome as the primary determinant of phenotype. Generally, in fact, the genotype-phenotype linkage is not even particularly tight. A given genotype might correspond not only to a variety of response modes, but also to dramatically distinct anatomical morphs (phenocopies). Also, the genetical architecture (the additive, dominance, epistatic, environmental, and gene-environment components of a phenotype) can change dramatically with the environment in which an organism is placed.<sup>8</sup> Finally, genetic expression often changes with immediate past history (e.g., genetic imprinting, where a gene’s influence depends on its maternal or paternal history,<sup>9,10,11</sup> or paramutation, in which a gene’s influence follows from its history of homozygote or heterozygote association<sup>10,12</sup>). Phenotypes are determined not only by genes, but by the interactions of genome, cytoplasm, environment, and history, none of which alone determines the outcome.<sup>13–16</sup> Let us look more closely at these interactions.

The dynamic of an organism can be viewed as a trajectory in a phase space in which axes define (say) the organ-

ism’s concentrations of enzymes, its blood flow rate, its frequency of encounters with various species, its intensity of participation in various behavioral activities, etc. While all parts of such a system are interconnected, it is nevertheless possible to break out subsystems (represented by subsets of the phase space) that are only loosely coupled to one another.<sup>17</sup> Thus blood flow is only indirectly related to the dynamic of speaking; the process of alcohol dehydrogenase regulation is (we hope) largely unrelated to that of automobile driving. Walking and gum chewing are mostly unconnected.

Consider a minimal subsystem, that is, one that is no longer reasonably subdivisible, e.g., the glycolytic cycle. Such a system, despite its least complex status, comprises a huge number of constituent parts (substrates, enzymes, etc.) It is characterized also by a vast number of feedback loops and an input of energy, some of which is utilized to do work, the rest of which is dissipated. The dynamic of any such subsystem, providing its energy supply is not cut off, can be described as a trajectory in its corresponding phase space, a path that moves about until it encounters a region of that space where feedback processes capture it. Once it enters such a “domain of attraction” it remains there (unless shaken out by external forces), and henceforth follows a path referred to as an “attractor.” The process can be viewed, by analogy, as the capture of a tiny particle caught up in a whirlpool. Attractors in complex systems generally are cyclic (like a whirlpool), often exhibiting extraordinarily complex cycles, and occasionally chaotic behavior.<sup>18</sup> This movement into attractors, known as “self-organization,” and its consideration in biological development and adjustment to environmental changes is hardly new.<sup>7,18–20</sup> Indeed, Goodwin<sup>13</sup> (see also Goodwin<sup>20</sup>) went so far as to note that

“... development of a theory of organisms as self-organizing, transforming fields could overcome some of the inadequacies of neo-Darwinian atomism.”

But to our knowledge, the role of self-organization as an adaptive mechanism within generations (versus among generations, see Kauffman<sup>19</sup>) has not been fully explored.

A process entering an attractor that neither demands nor uses energy reaches stasis (death). But if an organism lives, its dynamic must, by definition, have reached some nonstatic attractor.

Complex systems (such as organisms) can display many attractors, and as complexity rises, the number of alternative attractors generally increases (see Goodwin<sup>20</sup>). The glycolytic cycle, for example, exhibits several attractors. And by the time the myriad loosely connected subprocesses in a whole organism are jointly considered, the number of alternative attractors must be enormous. Note that because alternate attractors are, by definition, self-sustaining, they describe alternate homeostatic modes realizable by an organism. All living organisms, given time for transient behavior, inevitably fall into one of a great many attractors/homeostatic modes.

Examples of alternate attractors abound, although their expression usually becomes known only when organisms switch among them in response to environmental changes.<sup>21</sup>

### III. ADAPTATION

Doing the “right thing” can only mean that the attractor realized by an organism is more “appropriate” than other available attractors. What do we mean by appropriate, and by what mechanism might an organism fall into the most appropriate attractor? Note first that biological systems are distinguished from the complex systems studied by chemists and physicists in an important way. The latter are forced systems, maintained by an externally imposed input of energy and/or nutrients. Biological systems are not forced; the environment does not shove food into the mouths of its denizens. Rather organisms are acquisitive systems, garnering resources to satisfy their own needs. Passive diffusion may, for some nutrients in some circumstances fulfill input and catabolic (energy) needs. But it is difficult to see how organisms utilizing this means only could compete successfully with others exhibiting effectively autocatalytic input and catabolic mechanisms (see also the discussion on autocatalysis in Sec. VII). Autoenhancement of feeding responses is not something many workers have looked for, but Takeda and Takii<sup>22</sup> found evidence that the intake of certain dietary components promotes continued feeding in fish. With respect to catabolism, note that substrates often promote their own breakdown (e.g., through the derepression of kinases in the case of glucose<sup>23</sup>). Such responses can be expected to be most effective when acting powerfully at low nutrient-precursor concentrations, less powerfully as concentrations rise. It is not surprising, therefore, that natural selection has favored allosteric regulation of reactions by substrate.<sup>24</sup>

Strong positive feedback promotes acquisition and catabolism, while prevention of runaway acceleration of processes requires negative feedback by-products and, particularly, end products. Thus we see the near ubiquity of product and particularly end product inhibition in biochemical pathways.<sup>2,23–25</sup> In fact, end product inhibition generally acts on only one, or primarily on one enzyme, usually the first expressed in a specific pathway to that end product,<sup>2,23</sup> thus promoting specificity of control. In addition, end product inhibition is generally allosteric (higher order).<sup>24</sup> It is the juxtaposition of positive (acquisitive) and negative feedback control that defines attractors and thus leads to the formation of homeostasis in biological organisms. Indeed when precursors are produced at a rate exceeding demand by the attractor, further uptake is curtailed, leading to a shut down in synthesis. This follows, by definition, from the fact that attractors are self-sustaining. Thus Zubay’s (1993)<sup>2</sup> “miraculous” balance of intake (or production) to demand is perhaps not so miraculous after all; a living system simply cannot do otherwise.

The balance of intake and production to demand applies not only to dynamics, but to spatial structure. In those parts of a cell (or a body) where an end product is utilized and therefore does not accumulate, the consequent lack of negative feedback allows continued production of the substrates and intermediate products, including enzymes, along its biosynthetic pathway. Thus continued production of the end product is promoted in those sites where it is utilized. Mucus, for example, might be produced or excreted in one spot

in response to a local need, but not in another. Processes leading to membrane folding follow the same principle.

There is another component to the definition of “appropriate” response. In a highly complex biochemical system, there may be several pathways by which a utilized end product (or alternative endproducts) can be synthesized. In such cases, the emerging dominant pathway must be that which, in the presence of the others, requires the least activation energy (a game-theoretic optimum). And if feedback shuts this dominant pathway down short of supplying adequate end product demand, the second least energy-demanding pathway should take over. Energy efficiency is maximized.

There are caveats. First, there may exist classes of response within which, but not among which the above argument applies. For example, male bullfrogs choose a strategy of dominance or of subterfuge in order to mate.<sup>26</sup> If the former leads to greater reproductive success for a given frog, that frog (presumably) adopts it, even though it (may) be more energetically expensive. The choice has been biased by natural selection. Within the chosen response class, however, we can expect the frog to follow a least effort policy. Second, negative feedback among alternative pathways may knock out a globally optimum alternative before it can emerge, leading to the evolution of a local optimum, a sub-optimal response. We suspect the emergence of local optima to be rare for two reasons, however. First, sites at adjacent points on a cell membrane, in juxtaposed cells, or in slightly displaced positions in the intercellular matrix can exhibit different dynamics, i.e., follow different attractors. By virtue of their proximity (e.g., via diffusion of compounds), such “reaction sites” exert a pull on each other, a pull that encourages convergence to one attractor or the other (see Richter<sup>27</sup>). And basic physics tells us that in coupled dynamic systems, energy flows from the most to the least energy demanding subsystem. Note further that phase locking of reaction sites eliminates the energy cost of interactive drag, thus further enhancing energy efficiency.<sup>27</sup> Second, even the most energetically efficient attractor dissipates heat, which leads to stochastic variation in diffusion and reaction rates. In effect, organismal processes are continually bombarded by small disturbances which manifest themselves as deviations from deterministic attractors in phase space. If these disruptions are very small, their impact on an organism’s overall dynamics may be negligible. As they increase in magnitude, however, the number of disrupted sites rises, and as this number grows, the number of pathways by which further spread occurs grows also; the disruption may become autocatalytic. It may, in fact, become massive and, thus, fatal. But at intermediate intensities, energy dissipation should remain mildly disruptive, enhancing the exploratory process. The result is a kinesis (akin to the simulated annealing process by which statisticians find best fits) in which the system “seeks out” the most energetically efficient attractor(s). Again, biological systems, without the need for genomic change, by virtue merely of living, do “the right thing.”

By energy efficiency, we do not necessarily mean homeostasis at least cost. Rather, the arguments above indicate choice of the most energy efficient homeostatic mode within a class of modes dictated by past natural selection. In this

context Sibly and Calow<sup>28</sup> (see also Presnov<sup>29</sup>) wrote that

evolution has apparently proceeded towards metabolic pathways that maximize the amount of ATP produced per substrate used but not necessarily to the minimization of heat production per ATP produced.

We emphasize also that settling into stable attractors is not, in itself, energetically adaptive. It is merely the alleviation of noise. But it generally results in efficiency, and in this sense can be thought of as adaptive.

There is a glaring exception to the above energetics argument. Where autocatalysis occurs, mostly in the early steps of catabolism, the “winning” pathway, all else being equal, will be that with the strongest positive feedback.<sup>30</sup> In such cases, the emergent reaction chain will not necessarily be the most energetically efficient. But the outcome, nevertheless, is not necessarily maladaptive; for a given nutrient input from the outside world, it assures the most rapid supply of energy for anabolism. For example, organisms break down glucose more efficiently than dextrose; both reactions are controlled by feedback from the ATP they produce. By virtue of positive feedback, the glucose pathway dominates when both sugars are available, but substrate scarcity forces a slowdown in glucose metabolism, permitting the autocatalytic emergence of the dextrose pathway.

#### IV. RESPONSE TO CHANGE

Attractors are extremely sensitive to external conditions. Thus, at critical points along an environmental gradient, attractors may shift in phase space or even appear or disappear. So, with small environmental changes, an organism might shift its responses continuously. But with greater changes, or at critical points along an environmental gradient, where the occupied attractor disappears or another, more energy efficient one appears, the organism is likely to jump abruptly to a new response level. We expect, therefore, that a number of (if not most) physiological processes should be characterized by more or less discrete alternative states within each of which there is some continual variation. Thus, as *E. coli* grown on a combination of glucose and lactose run low on the more efficiently used glucose, a switch to lactose metabolism occurs involving the expression of lac operon genes formerly repressed.<sup>6</sup> Similar alternative states are widely reported in the form of physiological “set points.” Basal metabolism, for example, follows this pattern, the occupied attractor (set point) defined by exercise and dietary history. Body temperature, the set point changing in taxon-characteristic manner with disease, is another example (see Schmidt-Nielsen,<sup>1</sup> Table 5–16 in Withers<sup>31</sup>). Growth undoubtedly promotes and responds to temporal changes in development. As such, it, too, might be expected, and indeed does (at least in humans), occur in bursts separated by relatively quiescent periods.<sup>32</sup> Because of time delays around such a jump, moreover, such saltatory adaptations should exhibit hysteresis. Again, the literature is full of examples.<sup>33</sup>

Change, by differentially knocking trajectories from their domains of attraction across the body, induces drag and energy dissipation. Thus an immediate reaction to change should be a slight rise in body temperature (unless there are

corresponding changes in thermal conductivity in the organism, or unless the induced stress is a temperature drop) and a rise in oxygen consumption. This is only the immediate reaction, however. Following this transient phase, which may be very short lived, phase locking into a new attractor is likely to drop metabolism to a new level. Time lags in this adjustment may produce oscillatory responses (for a review, see Zotin<sup>34</sup>).

In addressing response to change, it is important to view an entire suite of possible alternatives. Inefficient or abnormal behavior, while less than ideal, may nevertheless represent the least of alternative evils. In addition, in assessing appropriateness of response, we must be careful to look at the whole organism. It is entirely possible that, by virtue of unshakable correlations, an adaptive response unavoidably carries with it inefficient constituent components (see Gould and Lewontin).<sup>35</sup>

The term “adapt” has evolutionary overtones. Nevertheless, for lack of a better word, we shall henceforth use it, generically, to mean “appropriately” respond. Adaptation, in this sense, therefore, occurs repeatedly in response to environmental changes over short periods of time within a generation. We can now restate the “attractor hypothesis” in a slightly different way. Adaptation can occur via movement among attractors, as an inevitable consequence of organisms’ complexity and acquisitive nature, quite independently of genomic change. As opposed to adaptation in the evolutionary sense, it refers specifically to the balancing of intake and production to demand, and to the energy efficiency with which such balancing occurs.

#### V. STRESS AND HORMESIS

The term “stress” has been variously defined, but a common thread relates to energetic efficiency. We will stay within this general interpretation, and refine it in an attempt at rigor. In keeping with the physics analogy, a stress (or stressor) is something that induces strain. Hence we define stress as an environmental change that brings about a loss in energetic efficiency. The loss itself is “strain.”

As noted above, intermediate levels of stress, enough to jolt some trajectories from their domains of attraction, but not enough to produce disruptive cascades, should enhance the kinetic “search” of the phase space. A little stress may actually lead to more rapid and more complete adaptation. Supporting this contention is a sizeable literature. The enhanced response, known as hormesis, is well documented for a wide array of chemicals (for a review see Ref. 36). It is also well studied *vis-à-vis* radiation (for plants, see Sheppard and coauthors;<sup>37</sup> for animals see Congdon, Delpa, Macklis, and Newcomb).<sup>38</sup> Were the effects of a stressor to be followed over time, the mechanism suggested here would lead one to expect first a disturbance (an excitatory response) and increased metabolism (in the event of survival) by an abatement. Such patterns are reviewed by Furst<sup>39</sup> for toxic doses of salicylates, alcohol, thiopental, many heavy metals, and barbiturates in general.

Explanations given for hormetic responses in animals usually revolve around stimulation of the immune system.

This is not inconsistent with the mechanism proposed above; indeed the immune cascade may be the quintessential example of an adaptive search for the autocatalytic path producing the fastest alleviation of need (via vanishing disruption by an antigen). Clearly, the stimulation of the immune response fails to explain hormesis in plants, while our explanation is sufficiently general to do so.

## VI. HIERARCHICAL AND PARALLEL ORGANIZATION

Susan Oyama<sup>14</sup> writes

Control of development and of behavior may be said to emerge in three senses. It emerges in interaction, defined by the mutual selectivity of interactants. Second, it emerges through hierarchical levels in the sense that entities or processes at one level interact to give rise to the entities or processes at the next, while upper-level processes can in turn be reflected in lower-level ones. Third, control emerges through time, sometimes being transferred from one process to another.

This sort of organization was recognized by Kacser in 1957,<sup>40</sup> and foreshadowed the interaction of time scales talked about by Goodwin in 1963.<sup>41</sup> It can be broken down via the communication modes by which feedback acts to define attractors and by the rates at which attractors are reached. For example, we have talked about feedback within or between adjacent reaction sites. The same arguments, with some modifications, apply across much larger distances by virtue of information carried in the circulatory and lymphatic systems. Communication also occurs via the mechanical interdependence of body parts, via the nervous system, and via interactions among individuals. Finally, communication occurs among species and between species and the physical environment.

To exemplify attractors with differing time rates, and also the interaction among hierarchical levels of attractors, consider a human's response to lowered oxygen availability (a trip to higher altitude, for example). Define several sub(phase)spaces, one of which describes the domains for breathing, heart rates, and activity level. The positions of attractors in this subspace depend on environmental milieu as determined not only by air pressure outside the body but also blood volume, hemoglobin count, active status of hemoglobin-affecting genes and chest girth (among others). The most rapid response to increased altitude is a kinetic movement within this phase space toward an attractor describing increased breathing and heart rates and decreased activity. We refer to such rapid response attractors as "superficial." A second sub(phase)space describes the domains of blood volume and hemoglobin levels. The position of attractors in this subspace are influenced by breathing and heart rate, air pressure, gene status, and chest girth. As response occurs in subspace 1, and continuing after an appropriate (energetically adaptive) attractor is reached in that space, movement occurs also toward a new attractor in the second space, an attractor characterized by increased blood volume and hematocrit. Similarly, at a still slower pace, alterations in gene expression for hemoglobin type are moving

the organism toward a new attractor in a third subspace. Finally, over generations, still another subspace attractor (for increased chest girth) is favored by natural selection. Slowly reached attractors we refer to as "deep." As noted, all these subspaces define the domains of processes at least loosely interconnected to each other. Thus, acquiring the first, superficial attractor somewhat alleviates pressure for moving toward the second, and so on. As a result, with a single or infrequent exposures to an environmental change, only the first, superficial adaptation might occur...or perhaps the first and second, but not deeper adaptations. Similarly, as the deeper processes reach more efficient attractors, there is less impetus for rapid response. Thus physical conditioning lessens the heart rate response of exercise, and repeated stimuli lead to habituation.

## VII. THE GENE-ATTRACTOR INTERFACE

So far we have largely ignored the role of genes, pointing out that much adaptation can occur without genetical selection. What is the role of genes in this scheme? First, note that adaptation by attractor hopping must be considered in the context of the genome. Such adaptation depends on existing biochemistry, anatomy, etc., all of which reflect a history involving genetic (and other) change. Also, genetical selection cannot be thought of as acting only on the genome, for the genome, too, is part of the system of feedback loops. Gene products feed back to control transcription, environmental changes can alter gene expression (for example, gene expression, as indicated by allozyme analysis, varies with reproductive status and season in voles<sup>42</sup>), and behavior can alter environment (or, via movements among habitats, the experienced environment). And the role of genome as part of a much more complex whole suggests something more: The impact of random tweaking of any complex system is likely to be highly buffered and, when expressed, manifest itself in unexpected ways. Thus the effect of many genetic changes will be unpredictable (offering potential problems for genetic engineers) and extraordinarily small (see, for example, Kimura<sup>43</sup>).

Second, natural selection is qualitatively different from the adaptive processes described here in that its consequence is not necessarily increased energetic efficiency, but increased Darwinian fitness (even though the two seem likely to be highly correlated, in general). In short, natural selection does not act to push systems toward particular attractors, but toward *sets* of attractors, within which the mechanisms discussed here operate. Once this has occurred, it may act to still further narrow the options. Thus, the emergence of a specific, adaptive physiological process or a behavior pattern may actually precede its subsequent canalization by natural selection (see Waddington<sup>44</sup> for a discussion of genetic assimilation; see also Wcislo<sup>45</sup>).

Natural selection can be expected to have altered an organism's biochemistry toward a dynamic that discourages or eliminates attractors inimicable to fitness or that enhances adaptation via attractor hopping. Thus natural selection can be expected to have biased attractor choice, under breeding

season conditions, towards attractors involving reproductive behavior.

As with the case of bullfrogs cited earlier, though, within the set of reproduction-involving attractors, we should still expect kinesis toward the most energy-efficient behavior. Of course, the genetically induced bias towards certain classes of attractors depends on the existing biochemical dynamic which, in turn, depends both on genome and external conditions. As such, natural selection and the mechanism described by the attractor hypothesis act inevitably in close concert. Under some conditions, though, the genetic bias toward a particular attractor set may be breached. For example, facing extremely adverse conditions, an organism might pass up reproduction in a breeding season, thereby salvaging energy for survival.

Suppose that over the course of evolution a critical need arises that can be met (at least at the time) in only one reasonably efficient way. That is, the biochemical arsenal is such that of the various homeostatic attractors, only one stands out clearly as the efficient alternative. In such a case we should expect natural selection to act towards the elimination of all but that one attractor. This would prevent the system, even momentarily, from falling into a "wrong" response, and would result in a direct genetic determination of the associated trait. It is in such cases, where there exist no backup pathways, that deleterious mutations will have clearly defined effects (e.g., phenylketonuria or Tay-Sachs syndrome), and that knock-out gene manipulations will be successful.<sup>46</sup>

It is appropriate at this juncture to reintroduce the matter of autocatalytic reactions. The winning process in such cases is not necessarily the most energy efficient, but is the one that accomplishes a function most rapidly. We propose that where fast reaction is selectively advantageous (i.e., at the superficial level), natural selection will have favored the rise of autocatalysis; at deeper levels, where efficiency is paramount, it will have discouraged autocatalysis.

### VIII. GENETIC ARCHITECTURE

Suppose two alternate forms of a gene, A and a, influence their bearer in contributing to different (perhaps overlapping) sets of attractors. Also suppose that, for a particular environment, one set (associated with A) possesses more energetically efficient alternatives. Then any organism possessing A, regardless of the form of its diploid pair, should manifest those most efficient attractors. Only aa individuals will fail to do so. Dominance is a natural consequence of the attractor hypothesis, and should vary from weak to complete depending on the degree of attractor overlap and the degree to which one attractor set exceeds the other *vis-à-vis* efficiency. Heterozygosity, *per se*, then, should not convey selective advantage except inasmuch as it provides alternate attractor choices in a spatially or temporally varying environment. To the degree heterosis is expressed, we should expect it to reflect superior energetic efficiency (which it does, at least for the loci explored by Garten *et al.*<sup>47</sup>). Note, finally, that the attractor theory offers an explanation for why dominance may change with genetic background.

Because a change in genotype does not necessarily produce new, more efficient attractors nor destroy pre-existing ones, genetic change need have no effect on phenotype. Similarly, as we have seen, a particular genotype may exhibit multiple phenotypes (adaptive responses, phenocopies). The link between genotype and phenotype may be loose, and in addition, depends on environment and history. It is, therefore, hardly surprising that genetic architecture should vary with environmental conditions.<sup>8</sup>

The above observation has possibly important implications for the appearance and mechanisms of outbreeding depression. Attractors are formed by the interactions of multiple gene loci, and the manner in which these interactions take place are environment dependent. Thus the process of adaptive attractor choice makes the gene interaction appear synergistic/cooperative. In effect, the appearance of co-adapted genes is, at least in part, a function not only of natural selection, *per se*, but of the attractor choice mechanism as described by the attractor hypothesis. To the extent disruption of coadapted gene complexes occurs, it must happen when parental genotypes are so mutually disruptive (dependent on environmental conditions) that appropriate attractors are no longer available. We should expect, then, not a gradual rise in outbreeding depression with increasing molecular (genetic) distance, but a sudden change. And as opposed to the long-term recovery process suggested by classical natural selection theory,<sup>48</sup> recovery over time should occur relatively abruptly.

### IX. DIRECTED MUTATION AND THE INHERITANCE OF ACQUIRED CHARACTERS

Deep level attractors may be sufficiently slow to persist across generations. We have indicated that a little noise (disturbance) can facilitate the search for an efficient attractor. Note now that genes and gene-products are part of the feedback loop. Thus stress-induced phase-space exploration can be expected to entail the induction and repression of genes. Therefore by the random nature of its effects on trajectories, stress should raise the variance in gene expression over reaction sites, thereby increasing the variety of gene expression in the organism as a whole. A subsequent drop in gene expression should accompany the settling of the system into new attractors that alleviate the stress, or upon cessation of the stress. These stress reactions have, in fact, been observed.<sup>49</sup>

A cascade in genetic expression is useful to the organism in at least two ways. First, it provides new attractors from which the organism can choose. Shoposhnikov<sup>49</sup> showed that the explosive increase in phenotypic variability in aphids following transplantation to unsuitable plant hosts was followed by canalization of adaptive new phenotypes at the expense of old ones, which gradually disappeared. Second, by disrupting chemical structures and repair mechanisms, stress also may bring about an increase in the (random) mutation rate.<sup>50</sup> Stahl<sup>50</sup> suggests that adaptive mutations permit the system to calm down enough that cells can replicate and divide, while deleterious mutations will not. In such a manner, the "good" mutations are selected. Starving *E. coli* cells induce formation of about 30 proteins, some novel, in several successive

waves, some of which promote survival during starvation.<sup>49,51</sup> Davis<sup>49</sup> suggests that starvation promotes damage to genes and interferes with repair so long as the starvation stress persists. When a mutation comes along that alleviates stress in offspring, however, it is the one passed on, and the process of damage and interference abates (see also Holliday and Rosenberger<sup>52</sup>). In effect, there exists a mechanism whereby stress increases the mutation rate and then screens mutations for their beneficial effects. The screening amounts to no more than classic natural selection in the case of single-celled organisms (investigated by the above authors), but in metazoan germ cells, it provides a prereproductive selection process, leading to an apparently biased rise in beneficial mutations.

One genetic effect of disturbance is the jumping of transposons (see, e.g., Campbell,<sup>53</sup> who notes that the transposon for erythromycin resistance in *Streptococcus* TN917 jumps only when a jump is needed). We know also that cells can switch genetic states using a variety of mechanisms such as methylation and demethylation. And because gene repression and derepression are deeper level processes than many other biochemical reactions, they can be expected to lag other adaptive responses. Thus it becomes feasible for stress-induced, adaptive changes in gene expression to be inherited. We know, for example, that transpositional changes can be inherited. We know also that the methylated (gene turned off) and demethylated (gene turned on) status of genes can be transmitted across generations.<sup>54</sup> Grafen,<sup>55</sup> in a letter to the editor of *Nature*, notes this fact, and it has been observed repeatedly in experiments with bacteria,<sup>56,57</sup> protozoa,<sup>57</sup> and plants;<sup>58</sup> see also the *Drosophila* bithorax experiments of Ho,<sup>59</sup> and Jablonka and Lamb.<sup>60</sup> Perhaps this is the means by which genetic imprinting and paramutation occur.

## X. IMPLICATIONS FOR EVOLUTIONARY THEORY

In the Introduction we noted Waddington's<sup>4,5</sup> concerns as to the efficacy of natural selection in fine-tuning organisms. We have addressed this concern in some detail, above. For example, spontaneous kineses toward energy-efficient attractors negate the genetic trade-off costs of evolving adaptive responses.<sup>61</sup>

By virtue of nongenetic adaptation, the production of increased diversity under stress, and the possible prescreening of mutants, natural selection need not choose among randomly generated phenotypes. The attractor hypothesis provides, instead, a ready set of preadapted alternatives (for efficient balancing of supply and demand if not for fitness, *per se*). This virtually eliminates genetic load and enhances the selection process (see also Kauffman<sup>19</sup>).

The clangorous battle between proponents of natural selection-based optimal adaptation and their opponents<sup>62</sup> has, for a number of years, generated considerable heat (with both sides subtly settling into less noise-producing attractors). By eliminating the need for gene frequency changes as the means of evolving fine-tuned adaptive responses, the attractor hypothesis effectively reconciles these two camps...with one caveat: adaptation by natural selection and adaptation by attractor choice, while in practice probably very similar, are

defined somewhat differently. The former refers to maximizing Darwinian fitness, the latter to efficient balancing of input and production to demand (both in a game-theoretic context).

The evolution of plasticity becomes a nonproblem in light of the attractor hypothesis. Adaptive plasticity is an unavoidable consequence of biological complexity.

Waddington<sup>5</sup> argued that the neo-Darwinian paradigm could not account simultaneously both for plasticity and canalization. The attractor hypothesis provides a solution to Waddington's dilemma. Processes inhabiting attractors, as noted above, resist change and, when faced with sufficient pressure, jump attractors. Those on deep attractors react only slowly, those on superficial attractors more readily. Thus canalization can be explained as the resistance to jumping deep attractors, and plasticity the ability to hop among superficial ones. Phenocopies are represented by the deepest attractors. Ho and Saunders,<sup>7</sup> though providing no mechanism, say much the same thing. An organism consists of many interlocking hierarchies of control; it can be described as a configuration of states. At critical threshold levels of inducers, the whole system can jump into another configuration.

Finally, if indeed, the adaptive process involves a temporal hierarchy of within and among-generation processes, including the inheritance of some acquired characters and the differential passage of genes as determined by attractors at the individual, social, population, community, and ecosystem levels, variation, both behavioral and morphological, can be expected often to be discrete (see, e.g., Alberch<sup>63</sup>). Evolution should be expected to occur in jumps of varied duration, small jumps within larger ones within still larger ones (See Per Bak *et al.*<sup>18</sup>, Ayala, and Gould<sup>64</sup>). In short, the pace of evolution should be fractal.<sup>65</sup> And in the same sense that adaptive sub(phase) spaces can be, to some degree, decoupled, macro- and microevolution also are, to some degree, decoupled.<sup>66</sup>

## XI. POSSIBLE TESTS OF THE HYPOTHESIS

To test the attractor hypothesis, we must identify adaptive responses that follow from the arguments here but cannot be explained via the agency of natural selection, *per se*. Unfortunately, natural selection can be expected to favor genes that work well (promote fitness) in the context of the organism and environment in which they operate. Similarly, whatever nongenetic components interact with their genome to promote well being are passed on in conjunction with the genome. Therefore, over time, a close correlation develops among the genes and all other components comprising an organism and its environment; genetic change carries with it corresponding changes in the whole organism. It is small wonder that the genotype-phenotype linkage appears tight in many cases.

Despite this linkage, several considerations permit tests of the attractor hypothesis.

(1) There are dynamical correlates of the hypothesis (characteristic cyclicities, saltatory shifts among different cyclicities, hysteretic responses, differential prominence of autocatalytic processes in slow versus rapid responses) that

have no apparent rationale under natural selection theory. Consider that alternative physiological states exhibit characteristic signatures in the form of oscillatory frequencies and patterns. Can physiological states be changed (can we shift among attractors) by driving these signatures? The attractor hypothesis says yes, and the answer would seem outside the realm of prediction by natural selection. In this context, Adachi *et al.* and Kindelskii and Petty<sup>67</sup> were able to treat pyoderma gangrenosum lesions of a young female patient by local treatment with an electric field at resonant frequency with normal neutrophil (NAD(P)H) cycling. The otherwise chaotic dynamics of the neutrophils were entrained, with concurrent remission of the abscesses.

If an organism experiences continuing change in its environment, does it, as the hypothesis predicts, eventually display a saltatory change in some aspect of its phenotype? Does the change exhibit hysteresis, and is the switch accompanied by an decrease in energy dissipated per energy taken in?

We argued that autocatalysis can be expected to evolve more often with respect to superficial than deep processes. Is this so? For example, does food intake stimulate further ingestion (to a point) and are dietary preferences, by contrast, conservative? Does fear feed on itself while learned avoidance patterns resist change? Are rapid physiological responses more likely to be self-inducing relative to slow responses?

(2) Under the attractor hypothesis, hormesis arises when stress jolts an organism from one attractor into a more energetically efficient attractor. This suggests that organisms “stuck” in inappropriate behaviors may be cured by applying limited stress. Animals, including humans, exhibit a wide array of “bad habits” that can be acquired or lost within a generation and so do not qualify as unavoidable side effects of genetically selected traits. These range from addictions to anorexia to inappropriate motor habits in dance, other athletics, and piano playing. It is highly unlikely that the former two contribute to Darwinian fitness, and the latter is probably irrelevant to fitness. In the contexts in which they developed do these behaviors represent energy-efficient alternatives? Would a little bit of stress hasten a correction of these habits? The attractor hypothesis would answer both questions affirmatively.

On the other hand, too much stress can prevent biochemical and behavioral trajectories from settling in on *any* attractor, continually knocking them out of domains of attraction. Indeed, distortions of a trajectory in one sub(phase) space, by altering the milieu for others whose subsequent distortions feed back on the former, might set up a dynamic of attractor change that is self-sustaining. In such cases, adaptation requires a reduction in stress. In this regard, Blanchard *et al.*<sup>68</sup> have demonstrated the clinical value of relaxation training as a treatment of irritable bowel syndrome, and Deepak *et al.*<sup>69</sup> have successfully used meditation in the treatment of drug-resistant epilepsy patients. Lowering of temperature can be expected to alleviate some stress disruption and so might be used, also, to treat conditions characterized by an inability to settle into an energy-efficient attractor. In this regard Adachi *et al.*<sup>70</sup> successfully induced short-

term relief from sterile abscesses in their young pyoderma patient by local cooling to 33 °C. Associated with remission of these lesions, the metabolic behavior of local neutrophils changed from chaotic to a normal cyclic pattern.

(3) Adaptation by attractor search is related to energy efficiency, adaptation by natural selection to life-time reproductive output. Thus we can look for examples of homeostatic response that satisfy one and not the other.

(4) Natural selection-based responses to strictly novel stimuli will not necessarily be adaptive. Scharloo<sup>71</sup> wrote

adaptive phenotypic reactions only occur for variation found within the natural environment of the species.

Not so if the attractor hypothesis is correct. Perhaps we could look at the Darwinian fitness and energetics of organismal responses to novel stimuli (such as hypergravity).

(5) Under the attractor hypothesis, the tightness of the genotype-phenotype link can be expected to loosen when genetic change comes via induced mutations rather than selection. Similarly, the penetrance of genes should drop when genetic background is altered. Do these predictions match observations?

A change in environment, or an enforced change in cytoplasmic chemistry (perhaps via drug delivery), coming as it would without corresponding change in the genome, should disrupt the genotype-phenotype linkage. Does heritability of specific traits decline under stress? There is some indirect data on this latter question. Jinks *et al.*<sup>3</sup> found an increased epistatic (and thus a decreased remaining genetic component) for phenotypes in marginal as opposed to prime habitat.

The last two predictions apply only under light or moderate stress. Under intense stress, it is likely that disruption will prevent organisms from settling into any but a very few of the deepest domains of attraction. Hence, though adaptation still may occur via attractor choice, that choice is severely limited, thereby resulting in a tighter genotype-phenotype link (see Parsons<sup>72</sup>).

## XII. CONCLUSIONS

As illustrated repeatedly, above, the attractor hypothesis provides a framework within which a whole host of observations derive explanation. In general, it complements known mechanisms, including natural selection; in some cases, it comprises a more general reference for mechanisms already invoked and understood (immunological responses, for example). Our purpose in presenting it is not to displace other hypotheses (with which it does not compete in any case) but to provide a somewhat new thought orientation that may prove heuristic.

The processes described in this paper enhance adaptive fine-tuning, facilitate the evolutionary process, and expand the context within which genetic dominance, coadapted gene complexes, and alternate genetic architectures come about. They also provide possible explanations for such phenomena as genetic imprinting, paramutation, “directed mutation,” the increased expression and mutation of genes in response to stress, and hormesis. Simply by virtue of being acquisitive self-organizing systems, organisms respond to changes in

their environments by matching nutrient and energy input and biosynthesis to needed levels. In addition, the emerging response mechanisms utilized to meet those needs should tend toward either the most energy efficient or the most rapid of the available alternatives, or both. Efficiency should prevail among slow response mechanisms, while within the class of fast mechanisms, the emerging response should be that meeting the particular need most rapidly. These adaptive responses depend only on organismal complexity and the acquisitive nature of organisms, and require the intervention of natural selection only indirectly (the nature of the complexity is a consequence of history, both genetic and otherwise).

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