Degeneracy and complexity in biological systems

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Degeneracy, the ability of elements that are structurally different to perform the same function or yield the same output, is a well known characteristic of the genetic code and immune systems. Here, we point out that degeneracy is a ubiquitous biological property and argue that it is a feature of complexity at genetic, cellular, system, and population levels. Furthermore, it is both necessary for, and an inevitable outcome of, natural selection.

There is no evidence to support the view that evolution guarantees progress. But few would argue with the notion that over large tracts of time, the complexity of biological systems has, in general, increased. Which properties of living systems undergoing natural selection can account for this fact? Is complexity related not only to variations in the environment, but also to a biological property of great consequence? We believe that, in addition to environmental effects that lead to increasing complexity during evolution, the degeneracy of biological networks in animals within competing populations also makes a major contribution to complexity. Degeneracy is the ability of elements that are structurally different to perform the same function or yield the same output. Unlike redundancy, which occurs when the same function is performed by *identical* elements, degeneracy, which involves *structurally different* elements, may yield the same or different functions depending on the context in which it is expressed. It is a prominent property of gene networks, neural networks, and evolution itself. Indeed, there is mounting evidence that degeneracy is a ubiquitous property of biological systems at all levels of organization.

In the present paper, we wish to point up this widespread occurrence of degeneracy by reviewing specific and salient examples. We argue that degeneracy is a necessary accompaniment of natural selection, mention some applications of this property to various fields, and briefly consider its relationship to complexity. Despite the fact that biological examples of degeneracy abound, the concept has not yet been fully incorporated into biological thinking. We suspect that this is because of the lack of a general evolutionary framework for the concept and the absence, until recently (1), of a theoretical analysis.

Before considering the evidence for the ubiquitousness of degeneracy, a recent laboratory example may serve to show the salience of the concept. Molecular genetic manipulation now permits constitutive knockout of selected genes through directed homologous recombination. In some cases, this results in lethality during or after development whereas in other cases, specific phenotypic effects that can be attributed to gene loss appear in progeny animals. But, in a number of cases (up to 30%), there is little or no evident phenotypic consequence despite the absence of the selected gene products (2). Some examples include mice that are unable to make such seemingly important proteins as myoglobin (3), tenascin C (4), vimentin (5), gelsolin (6), and a neurofilament subunit (7). Similarly, in a systematic screen of single gene deletions at more than 500 loci in yeast, fewer than half showed any quantitative growth defects in either rich or minimal medium (8).

Some of the most surprising and instructive demonstrations of degeneracy have been found in human beings who have lost the function of a gene that specifies a protein that was thought to play a central and indispensable role in intercellular or systemic functions. For example, albumin is the most abundant protein in the plasma of mammals, where it carries out certain well studied functions. It therefore was quite unexpected when screens for patterns of protein expression in a population of randomly chosen healthy humans turned up individuals in whom the protein was completely absent (9).

Although some have been tempted to conclude that this shows the "uselessness" of the particular protein specified by the deleted gene, there is a more reasonable hypothesis to account for the findings; namely, that the gene networks of the affected animals are degenerate, allowing widespread, compensatory adjustments. Note, however, that evolution could not (and did not) plan for such compensatory changes and that this so-called compensation is not just a matter of feedback control. Moreover, it is likely (and sometimes found) that if the affected animals were placed in different environments, definite phenotypic effects could emerge, some of which might even be lethal.

As more and more examples of degeneracy are reported, this common property of biological systems has become a topic of interest in its own right. But, somewhat like the purloined letter in Poe's famous story, although in plain view, it often has been overlooked. For example, in some of the cases to be reviewed here, the term "functional redundancy" has been applied, usually to elements at the same level, such as duplicated genes. This usage ignores one of the critical features of degeneracy: that *different structures* have similar consequences. In contrast, redundancy, considered at the structural level, refers to the function of identical elements. Furthermore, the term redundancy somewhat misleadingly suggests a property selected exclusively during evolution, either for excess capacity or for fail-safe security. We take the contrary position that degeneracy is not a property simply selected by evolution, but rather is a prerequisite for and an inescapable product of the process of natural selection itself.

The contrast between degeneracy and redundancy at the structural level is sharpened by comparing design and selection in engineering and evolution, respectively. In engineering systems, logic prevails, and, for fail-safe operation, redundancy is built into design. This is not the case for biological systems. Indeed, not the least of Darwin's achievements was to lay the argument by design to rest. But, for obvious economic reasons, design is by far the major component of most technical efforts in modern society. In general, an engineer assumes that interacting components should be as simple as possible, that there are no "unnecessary" or unplanned interactions, that there is an explicit assignment of function or causal efficacy to each part of a working mechanism, and that error correction is met by feedback, modeling, or other paradigms of control theory. Protection can be afforded by planned redundancy, but adventitious compensation for error is neither expected nor usual. Irrelevancy is avoided from the outset.

By contrast, in evolutionary systems, where there is no design, the term "irrelevant" has no *a priori* meaning. It is possible for any change in a part to contribute to overall function, mutations can prompt compensation, stochastic interactions with the en-

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vironment can lead to strong selection, often there is no fixed assignment of exclusive responsibility for a given function, and, unlike the engineering case, interactions become increasingly complex. A theoretical analysis (1) suggests that this increase in complexity results not only from selection in rich environments (which include other species) but also from the prevalence of degeneracy.

For all of the reasons mentioned above, we suggest that in many cases the term "degeneracy" is more apt than "functional redundancy." The term has been used correctly in biology to refer to the third position of code words in the genetic code and to the ability of structurally different antibodies to bind equally well to the same antigen (10). And, of course, in quantum mechanics, it has been used to designate different but equally correct solutions of the wave equation as they apply to systems taking on several distinct energy levels or states.

Degeneracy in Cellular Systems

The genetic code relating sequences of polypeptides and polynucleotides is degenerate because there are many more triplet codons than encoded amino acid residues. Consequently, an enormous number of structurally distinct mRNA species could be translated to generate the amino acid sequence of any particular protein. This degree of structural variation can be considered to be merely the tip of the iceberg, particularly if we broaden our definition of degeneracy to include variations in polynucleotide sequences that result in functionally equivalent gene products. For example, it is now clear that at many sites along the polypeptide chain, substitution of one amino acid residue for another has little effect on overall protein conformation or function. By inference, we can assume that an astronomical number of different amino acid sequences could contribute equally to the survival of the species.

It is becoming increasingly evident, however, that this view, based on coding of the degree of possible degeneracy in biological structures, is relatively narrow. More and more, it has become evident that many biological functions cannot be assigned to cellular components in a one-to-one manner. Instead, multiple gene products contribute to almost any observed behavior or function, and every gene has the potential for pleiotropic effects.

Degeneracy can be found at every level and in most processes found in living cells (see Table 1 for some examples). A gene, to take one example, can, in general, no longer be thought of as having only a single sequence with fixed ends and length. In many cases, transcription can begin at a number of different 5′ start sites (11), or it may terminate at one of several 3′ sites (12, 13); moreover, the transcribed product may undergo different patterns of RNA splicing to yield a degenerate set of isoforms (14). The exact pattern of isoforms produced is regulated by intragenic segments called splicing enhancers; such elements in a gene for cardiac troponin have been reported to demonstrate functional redundancy (15). The RNA polymerase holoenzyme that catalyzes RNA synthesis itself appears not to be a single, well defined entity but, rather, is a degenerate population of complexes with different polypeptide chain compositions (16).

Often, a degenerate set of DNA sequence elements that determines the rate of gene transcription is located upstream, or downstream, or in coding or noncoding segments of a particular eukaryotic gene. Numerous, distinct polynucleotide motifs commonly are found within these promoter and enhancer elements, and in some instances they have been said to be "functionally redundant" (17–21). In numerous experimental systems, the protein transcription factors that bind to these sequences also have been found to act degenerately—i.e., individual regulatory factors appear to have functionally overlapping roles (22–24). In an analogous fashion, degenerate sets of specific intramolecular motifs have been shown to stabilize mRNA (25) as well as to localize its products to the appropriate cellular compartments (26–28). The intracellular localization of the protein molecules synthesized by using these mRNAs also has been shown to be determined by degenerate signals, which, in these cases, are contained within their polypeptide chains (29, 30).

The very complexity of these degenerate structures and the mechanisms operating to ensure that the products of a particular gene are expressed in specified amounts within specified compartments of certain cells of an organism would seem to support the presupposition that the gene in question must play a crucial role in the survival of the organism or species. That such a gene often can be inactivated completely without significant effect on the phenotype of the organism therefore initially was quite surprising. One reason for this already has been mentioned: certain gene products themselves form a degenerate set with overlapping functions. Even proteins having no apparent structural, physiologic, or evolutionary relationship can together

Table 1. Degeneracy at different levels of biological organization

1. Genetic code (many different nucleotide sequences encode a polypeptide)
2. Protein fold (different polypeptides can fold to be structurally and functionally equivalent)
3. Units of transcription (degenerate initiation, termination, and splicing sites give rise to functionally equivalent mRNA molecules)
4. Genes (functionally equivalent alleles, duplications, paralogs, etc., all exist)
5. Gene regulatory sequences (there are degenerate gene elements in promoters, enhancers, silencers, etc.)
6. Gene control elements (degenerate sets of transcription factors can generate similar patterns of gene expression)
7. Posttranscriptional processing (degenerate mechanisms occur in mRNA processing, translocation, translation, and degradation)
8. Protein functions (overlapping binding functions and similar catalytic specificities are seen, and ''moonlighting'' occurs)
9. Metabolism (multiple, parallel biosynthetic and catabolic pathways exist)
10. Food sources and end products (an enormous variety of diets are nutritionally equivalent)
11. Subcellular localization (degenerate mechanisms transport cell constituents and anchor them to appropriate compartments)
12. Subcellular organelles (there is a heterogeneous population of mitochondria, ribosomes, and other organelles in every cell)
13. Cells within tissues (no individual differentiated cell is uniquely indispensable)
14. Intra- and intercellular signaling (parallel and converging pathways of various hormones, growth factors, second messengers, etc., transmit degenerate signals)
15. Pathways of organismal development (development often can occur normally in the absence of usual cells, substrates, or signaling molecules)
16. Immune responses (populations of antibodies and other antigen-recognition molecules are degenerate)
17. Connectivity in neural networks (there is enormous degeneracy in local circuitry, long-range connections, and neural dynamics)
18. Mechanisms of synaptic plasticity (changes in anatomy, presynaptic, or postsynaptic properties, etc., are all degenerate)
19. Sensory modalities (information obtained by any one modality often overlaps that obtained by others)
20. Body movements (many different patterns of muscle contraction yield equivalent outcomes)
21. Behavioral repertoires (many steps in stereotypic feeding, mating, or other social behaviors are either dispensable or substitutable)
22. Interanimal communication (there are large and sometimes nearly infinite numbers of ways to transmit the same message, a situation most obvious in language)

perform degenerate roles. For example, fasciclin, a cell-adhesion protein found on the surface of *Drosophila* neurons, has no obvious structural or functional similarity to the cytoplasmic Abelson tyrosine kinase made in the same animals. A complete deletion of the gene for either of these two proteins results in no gross abnormalities in nervous system development, whereas the absence of both proteins leads to major defects (31).

Degeneracy in Multicellular Systems

The spatiotemporal pattern of gene regulation within a metazoan is orchestrated by a network of intra- and intercellular signals to fulfill the higher-order physiologic functions and needs of the organism as a whole. Various different components of signaling pathways in this network provide multiple examples of degeneracy. Growth factors that function at numerous sites during animal development have been shown, for example, to comprise a degenerate set in some experimental systems (32, 33). They exert their effects by binding to a population of cell-surface receptors that is also degenerate (34). Commonly, these receptors, in turn, initiate intracellular signals by catalyzing the phosphorylation of tyrosine residues in a number of different intracellular substrates. This phosphorylation has been shown to activate a number of parallel, intracellular signaling pathways that are either independent or connected in networks. By selectively inactivating individual pathways, it has been found that such networks often act in a degenerate fashion (35, 36). Moreover, components of networks of signaling pathways commonly bind to and affect the functional properties of more than one downstream target. Such branched signaling pathways and the ''cross-talk'' among them contribute to biological degeneracy (37).

Genes that have evolved to facilitate intercellular or systemic functions in multicellular organisms demonstrate the emergent properties inherent in degeneracy as well as, or better than, genes whose functions are limited to single cells. The immune systems of vertebrates, for example, provide protection only because animals have evolved the ability to generate the very large, degenerate population of antigen-recognition sites required for the clonal selection theory to operate. The degeneracy of the immunoglobulins made by an animal ensures that the animal possesses the ability to make antibodies that protect against essentially any foreign, infectious agent (10). Similarly, it seems as if an animal's ability to distinguish among almost any two olfactory cues depends on its possessing a degenerate repertoire of olfactory receptors (38).

The role of degeneracy in the development and function of nervous systems is as fundamental as it is in immune systems and, indeed, provides one of the richest examples for exploration. We shall therefore focus on it here. The functional properties of the nervous system of an animal depend largely on the patterns of structural and functional connectivity among the neurons in the system. But, with the possible exception of animals having exceptionally simple body plans, the exact pattern of connectivity is not genetically prespecified with great precision. Instead, the pattern arises during development in part by a process involving excess neuron production, exuberant extension of neuronal processes that compete for targets in an activity-dependent fashion, variant cell migration, and massive cell death. Despite the very large number of neurons within any vertebrate nervous system, it is almost certain that no two neural cells within an animal are identical in overall shape. Similarly, no two ''equivalent'' neurons taken from two different vertebrate individuals have exactly the same morphology, even if the animals are genetically identical. Typically, neurons in the brain receive synaptic input from many thousands of other neurons so that in humans, for example, there are approximately one billion synapses in each cubic millimeter of brain gray matter. The pattern of connectivity created by so many synapses within such a tiny volume of tissue in one animal could not be genetically prespecified and, thus, must be unique to each individual. Indeed, the degree of degeneracy in neural connectivity probably dwarfs that of any other system discussed in this review.

This degeneracy of connectivity at the microscopic scale complements the high degree of intraspecific variation observed in the gross anatomy of animal brains. A striking example is provided by people who do not form the major fiber tract interconnecting the two cerebral hemispheres (the corpus callosum). Several such persons have been discovered to possess this abnormality only after MRI scans. These individuals may be quite asymptomatic during daily pursuits, although subtle abnormalities can be detected upon detailed psychological testing (39). Although, in the past, variations in the gross shape of the brain were studied carefully in efforts to find correlations between anatomical features and mental abilities or propensities, it now is accepted that these efforts are largely fruitless. Instead, it is recognized that many different patterns of neural architecture are functionally equivalent, i.e., functional neuroanatomy is highly degenerate.

Even within the brain of a single individual, the detailed pattern of connectivity is not fixed, because neural activity within the nervous system at one time can affect the efficacy of intercellular communication at a later time. Most of the salient changes are thought to occur at synapses, sites at which neurotransmitters are released to subsequently bind to receptors on the postsynaptic cells. Many distinct forms of synaptic plasticity have been studied. It has been shown that intercellular communication can be either potentiated or depressed. Moreover, synaptic changes may last only a short time (measured in seconds or less), or they may persist for as long as a given measurement can be made. Because it is plausible that these changes underlie an animal's ability to learn, remember, or forget, their mechanism has been the subject of intense and extensive experimental scrutiny (40).

It has become increasingly apparent from such studies that a number of degenerate mechanisms contribute to the overall changes in synaptic efficacy whether they are tested biochemically, neurophysiologically, or behaviorally. For example, after stimulation, changes have been reported in the anatomic shape of both presynaptic and postsynaptic cellular structures. Presynaptically, plasticity has been correlated with the number of synaptic vesicles docked at release sites, with the concentration of neurotransmitter per vesicle, and with the probability of release when the cell fires. The postsynaptic response can be modulated by changes in the numbers, kinds, and phosphorylation states of the neurotransmitter receptors and by the transmembrane potential across the postsynaptic cell membrane. This response, in turn, is modulated by the nature, number, and distribution of various ion channels and pumps within this membrane as well as by the previous pattern of synaptic inputs on the cell, the pattern of gene expression in the cell nucleus, and the transport and turnover of proteins within the dendritic arbors. The complexity of the system includes many sites at which a variety of changes can modulate synaptic efficacy in a similar manner. Whenever evidence for each of these changes has been sought experimentally, it has been found. Thus, synaptic plasticity exemplifies degeneracy in full measure.

To provide coordinated outputs in mammalian brains, linkages of degenerate networks are achieved through a process called reentry. Reentry is a dynamic process of ongoing spatiotemporal correlation occurring between functionally segregated neural areas that is mediated by signaling through massively parallel, reciprocal fibers (41). This process ensures linkage and integration of complex functions and behaviors, even in the absence of logic and programming. Reentry has been modeled successfully (42) and even has been demonstrated to occur in human brains during conscious attention (43). The functioning

of several neural models explored so far (see, for example, ref. 42) depends on the presence of a large number of different, alternative reentrant circuits that dynamically yield a similar output, i.e., such circuits are degenerate.

The major outcomes of neural activity that ultimately contribute to animal survival are those manifested when motor neuron activity initiates or inhibits muscular contractions. The selective advantage of a flexible, multiply jointed body plan in various species is obvious, but, here again, the evolution of such a system both requires and generates degeneracy. Consider the arm movement of a monkey that wishes to brush away a fly that has landed on its nose. How many different patterns of muscle contractions might it use to accomplish that task? There are so many different degenerate patterns of neuromuscular activity that could accomplish that same task that specifying how any particular pattern is selected is a significant challenge to theories of motor control (44).

All of the observations we have reviewed here, and those summarized in Table 1, point to a central question: what accounts for the omnipresence of degeneracy at so many levels of biological organization in a variety of species? Clearly, any attempt to answer this question must begin by considering the evolutionary paths that give rise to degeneracy.

Degeneracy and Evolution

Degeneracy is a prerequisite of natural selection because natural selection can only operate among a population of genetically dissimilar organisms. This implies that multiple genes contribute in an overlapping fashion to the construction of each phenotypic feature undergoing selection. Moreover, because, in general, several different gene networks contribute to the expression of each feature, and because selection has no way of assigning responsibility for any phenotypic parameter to particular gene loci, degenerate systems will be maintained and favored. Moreover, some of the most generally used mechanisms for generating genetic diversity over time often facilitate an increase in degeneracy. Examples include gene or chromosomal duplications and the utilization of gene products in novel contexts to create novel structures. A detailed investigation as to why loss-of-function mutations in yeast so commonly have little or no detectable phenotypic effect concluded that interactions among a network of unrelated genes could better account for this observed robustness than the existence of duplicated genes with similar, merely redundant functions (45). Computer simulations of changes in gene frequencies in populations of organisms have provided models by which two genes performing apparently interchangeable functions can be evolutionarily stable (46).

Although two distinct, degenerate structures or mechanisms may function equally well in an organism to achieve a goal set by natural selection, this effect does not imply that these mechanisms are fully equivalent, as might be suggested if the term redundancy were applied. Despite a convergence of function, each variant confers its own novel properties on the organism and offers a unique target for evolutionary molding. For example, the degeneracy of the genetic code permits different genes to respond very differently to selective pressures, even though they give rise to identical polypeptide chains. This occurs because of their different susceptibility to processes, such as gene conversion or viral insertion, that are dependent on specific polynucleotide sequences. Furthermore, families of homologous proteins having distinct physiologic functions can arise by a process of gene duplication and divergence, and this entails some degree of functional versatility in each novel gene product as it is selected.

The process of sexual reproduction provides striking examples of key principles related to degeneracy and redundancy. The survival of a species critically depends on individual organisms producing a great number of gametes, far more than possibly could be used to generate viable offspring. Although this large oversupply could be said to illustrate the use of redundancy to ensure against random loss or failure, it must also be recognized that no number of gametes could ensure the survival of the species if they all contained identical genetic material. Continued existence of the species in the face of a variable environment requires that gamete populations not only must be large but also genetically diverse. Only this provides the necessary degree of degeneracy needed to adapt over evolutionary time.

Genetic variants not only create new opportunities for evolutionary change, but the existence of an unfilled or novel niche in the environment also favors the selection of a degenerate set of genes. Consider, for example, an environmental change that increases the reproductive advantage of larger organisms of a species. This might select for animals with more cells, or larger cells, or animals having more extracellular material. Multitudinous complementary mechanisms could contribute to each of these changes, including increasing rates of synthesis or accumulation of chemical compounds, decreased rates of breakdown, increased cell proliferation, and decreased cell death, etc. A large number of factors can contribute to determining the rates of each of these processes. Upon which will natural selection operate? The obvious and inescapable answer is that no biological factor is completely exempt from selection, and, therefore, we can expect adjustments in many or even all of these factors as an organism adapts to a new environment. Although increasing the size of cells or the number of cells may yield effective degenerate responses to a particular selective force and, thus, result in equivalent fitness, such changes clearly are neither strictly equivalent nor redundant. Each genetic variant has a unique potential for good or ill, and each combination of variants contributes to a novel phenotype to be subjected over time to evolutionary winnowing.

What is true regarding the response of species to selection for size would, of course, apply equally for selection on the basis of shape, appearance, behavior, fecundity, longevity, disease resistance, and all other global properties of the organism. When considered in this light, one appreciates more clearly the fallacy of speaking of a gene or genes for size, shape, intelligence, etc. All observable properties of an organism are determined by the workings of a degenerate network of many genes.

We have emphasized that the processes of evolution and natural selection necessarily are accompanied by degeneracy. Indeed, in the absence of degeneracy, it is likely that most mutations eventually would result in lethality, for then there would be no tradeoff between individual gene action and gene network interaction. Tradeoff is found in other contexts. In somatic selectional systems such as the immune system, for example, there is a tradeoff between the specificity and the range of binding of antibodies to foreign antigens (10). This tradeoff is a reflection of degeneracy, and, again, without it, the mere increase in the repertoire of different antibodies could not lead to a robust and broad-ranging immune response. Given the existence of degeneracy, different antibodies even in identical twins can give similar overall output responses.

The phenomenon of evolutionary convergence may reflect, in part, the ability of degenerate systems across different levels of organization to yield similar functional results. It is clear in this case, as it is in the case of knockout animals, that degeneracy is not ''planned.'' Any ''compensation'' that occurs is a statistical result of the tradeoff between specificity and range that follows in complex systems having degeneracy. It is striking how universal this property is, ranging as it does over all levels of biological organization (see Table 1). We surmise that this far-ranging, across-levels property results from evolutionary selection of those individuals having sufficient fitness, regardless of the variations and accumulated mutations that occur within and across their many levels of organization. By these means,

evolution brings about degeneracy at various combinations of levels, without necessarily selecting for changes at each level.

Relating Degeneracy and Complexity

A series of formal analyses has been carried out to provide and relate measures of degeneracy and complexity (1, 47, 48). These analyses use measures used in statistical information theory, such as entropy and mutual information, but they do not rely on assumptions related to messages, codes, or noisy channels. We present here a brief verbal description of results obtained upon applying these measures, mainly to give the reader the flavor of the analyses. For mathematical details, we suggest consultation of the original publications.

In biological systems, degeneracy is almost invariably accompanied by complexity. A complex system may be considered as one in which smaller parts are functionally segregated or differentiated across a diversity of functions but also as one that shows increasing degrees of integration when more and more of its parts interact. Put otherwise, a complex system may be viewed as one that reveals an interplay between functional specialization and functional integration. Intuitively, it is easy to see that, below a certain level of complexity, there will be very few ways in which structurally different parts can interact to yield the same output or functional result. Accordingly, at low levels of complexity, degeneracy will be low or nonexistent. For a defined function, however, redundancy can still exist even in relatively simple systems.

Applying suitable quantitative measures (1), we have found that degeneracy is high in systems in which very many structurally different sets of elements can affect a given output in a similar way. In such systems, however, degeneracy also can lead to different outputs. Unlike redundant elements, degenerate elements can produce new and different outputs under different constraints. A degenerate system, which has many ways to generate the same output in a given context, is thus extremely adaptable in response to unpredictable changes in context and output requirements. The relevance to natural selection is obvious.

In our limited experience so far, we have found that systems selected for high degeneracy with respect to any given set of outputs also show high complexity (1, 47, 48). Although a general functional dependence of degeneracy on complexity has not yet been formally derived, it is an interesting conjecture that the two properties go hand in hand.

Issues and Applications

We began this review by comparing the failure to recognize the generality of the concept of degeneracy with Poe's purloined letter—in plain view, but crumpled and subject to false clues. Perhaps a better literary analogy might be to Moliere's Monsieur Jourdain, who was pleased to learn he had been speaking prose all his life. Certainly, the case for the ubiquitousness of degeneracy in biology needs no further reinforcement. However, we may usefully consider a few more speculative issues related to human activities. The first concerns human communication, specifically language and speech. It is well known that speech is redundant, but it is less explicitly appreciated that it too carries out degenerate functions. The very existence of metaphor, anaphor, and polysemy attest to the powerful role of equivalent but nonidentical structures in conveying meaning. Ambiguity, which often reflects degeneracy, can also function in a positive fashion, at least in poetry as well as in any creative endeavor with heuristic or associative needs.

We have mentioned that, in modern technology, engineers build separate modules for designed functions and usually keep interactions between them to a necessary minimum. This powerful policy generally meets both economic and design constraints. But with the development of nanotechnology and the reduced cost of electronic chips and memories, it is conceivable that engineers will turn to the deliberate construction of complex degenerate systems. Like biological systems, such systems necessarily will be selective rather than instructive. Clearly, there will be uses for such systems, particularly in areas in which computation and logic fail. One such example is in unpredictable environmental situations in which the recognition of novelty is important and programmed planning is not possible.

The further understanding of how degenerate systems become linked and synchronized across levels is a major challenge in modern evolutionary biology. It is not yet evident whether coordinative linkages similar to reentrant connections in the nervous system are necessary to correlate different levels of organization in other, more wide-ranging, biological systems during evolution and development. We suspect that they will be found. Whether or not such linkages are frequent, degeneracy remains a necessary consequence of natural selection. Its further analysis will be particularly important in any attempt to deepen our understanding of biological complexity.

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