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# THE EMERGENCE OF PHENOTYPIC NOVELTIES THROUGH PROGRESSIVE GENETIC CHANGE

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The processes by which important properties of animal and plant populations change drastically over a relatively short time have been a subject of concern for evolutionists, molecular biologists, and cancer researchers. In particular, it has been conjectured that living organisms possess genetic mechanisms for controlling the mutation rate and that these mechanisms, when triggered by environmental stress, generate bursts of genomic changes. Such mechanisms are assumed to be responsible for diverse phenomena including the induction of cancer in animal cells, DNA repair in bacteria, and most significantly, punctuated speciation events, that is, speciation events that are very rapid with respect to the total duration of species as unchanging entities (Thompson and Woodruff 1978; Echols 1981, 1982; Erwin and Valentine 1984; Wills 1984). The basic premises underlying the hypothesis of controllable mutation rate are that the persistence of a population under environmental stress depends on the appearance of phenotypic novelties and that these cannot be accounted for by a constant inflow of small genetic substitutions (Carson 1975; Erwin and Valentine 1984).

It has been further argued that mechanisms for controlling the mutation rate differ from those of natural selection and that the only effective way they could have evolved is by second-order selection or by group selection (Eshel 1973; Gould 1980; Dover 1982; Echols 1982; Wills 1984). If this were correct and if, as is currently asserted by a number of authors, evolution is concentrated in punctuated speciation events (Eldredge and Gould 1972; Gould and Eldredge 1977; Gould 1980), one must conclude that group selection rather than natural selection is the driving force in nature.

The basic viewpoint of population genetics is that evolution consists of movements on a genotypic adaptive landscape (Wright 1969). Recently, the notion of phenotypic adaptive landscape in changing environments has been introduced, and it has been shown that the frequency of local disturbances may determine the landscape's topography (Agur and Slobodkin 1986). An attempt to schematically represent the interplay between genetic and phenotypic evolutionary dynamics is

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Lewontin's (1974) useful metaphor of genotype-to-phenotype mapping; it comprises a paired set of surfaces, the genotype and the phenotype spaces, and paths of transformation of genotypes and phenotypes from one generation to another; the transformation is accomplished by unspecified genetic, epigenetic, and population-dynamic laws. In our model we consider particular transformation laws for the genotype-to-phenotype mapping by postulating the existence of a genetic-epigenetic network. The mapping picture thus becomes more detailed, with the ratio between the size of the subset in genotypic space and the resulting subset of phenotypes being determined by the specific transformation law. By restricting ourselves, in a very simple model, to only the most essential properties of the complex gene-expression network, we attempt to test the validity of the evolutionary concepts discussed above; our work shows how sudden evolutionary novelties can occur with no alteration in mutation rate, thus obviating the need to address the controversial question of group selection.

## GENOTYPE-TO-PHENOTYPE MAPPING

Molecular-biology techniques, notably those of recombinant DNA, have firmly established that genes are not colinear with their products (Knapp et al. 1978). Although varying in detail, prokaryotic and eukaryotic pathways of gene expression are characterized by an interlayer control of a *many-one and one-many* type and by an *error-damping* capacity. In a many-one type, many information units on one layer work to generate a single unit on the next layer; concurrently, in a one-many type, a single information unit on one layer determines the nature of many such units on the next layer. At the same time, various error-damping mechanisms tend to reduce the deleterious effects of mutations.

Epistasis and pleiotropism are special cases of the many-one and one-many types of control, referring to one gene pair hiding the effect of the other and to multiple phenotypic effects of single genes, respectively. The phrase one-many and many-one, however, should be interpreted in a broader sense: here, an information unit may represent a functional as well as a molecular element. Consider, for example, the mode of synthesis of tRNA in yeast, which exhibits the salient general features of eukaryotic gene expression. It has been shown in the yeast *Saccharomyces cerevisiae* that the gene for tRNA(Trp) is first colinearly transcribed into a tRNA(Trp) precursor; this is further spliced into a mature-sized tRNA(Trp). The splicing of the precursor involves novel enzymes of RNA metabolism, responsible for the removal of intervening sequences from within the precursor molecule (Knapp et al. 1978; O'Farrell et al. 1978). Moreover, secondary and tertiary structures of the precursor may play a major role in the splicing event (Ogden et al. 1979). The many-one type of hierarchy is manifested through the joint action of the various splicing enzymes, the tRNA precursor sequence, and its three-dimensional structure, in generating one mature tRNA(Trp) molecule. This important feature is concurrent with the one-many type of hierarchy; thus, mature tRNA(Trp) as well as many other RNA molecules are formed by the activity of a common set of enzymes, RNAase III for cleaving the RNA substrate and ligase for joining two separate chains (Knapp et al. 1978; for the generation of mature mRNA of β-hemaglobin in the mouse, see also Leder et al. 1980).

The synthesis of the polypeptide growth factor EGF can serve as an instance of the many-one and one-many control on the protein layer: the mouse EGF mRNA is transcribed into an EGF precursor of 1217 amino acids, which, after proteolytic processing, yields the mature EGF protein. It is believed that the same mRNA encodes eight different peptides and that in the absence of proteolytic processing the EGF precursor functions as a membrane protein (Kris et al. 1985).

Still farther down the path of genetic information transfer are multilayer developmental processes. Here, a single cellular product may act as an essential link in a chain of morphogenetic processes; a full battery of genes, associated with the differentiation of a single cell type, is activated by determinants that are manufactured during oogenesis (Wessells 1982). Thus, a successful model of segment formation in *Drosophila* has recently been presented (Meinhardt 1986; North 1986), which involves a complex network of functional interactions and is the first concrete realization of a concept long envisioned by embryologists (Hall 1983; Sander 1983).

Evidence about the pathways through which cell transformation is achieved is still circumstantial. However, in vitro experiments suggest that these pathways are also characterized by a many-one and one-many multilayer information processing. Oncogenes act pleiotropically, with their gene products affecting complex regulatory cascades within the cell (Land et al. 1983; Yoakum et al. 1985). Members of the heterogeneous group of oncogenes cooperate with one another in order to achieve full transformation. It is believed that this concerted action involves a combination of a few oncogenes from a larger repertoire of oncogenes. For example, it has been shown that complete transformation can occur by a combination of a *ras* gene either with *myc* or with the Ela gene of adenovirus (Land et al. 1983).

Another important universal feature of the biological processing of genetic information concerns the ability to dampen small genetic errors, such that not all slight modifications in the genome affect the phenotype. The most fundamental biological mechanism of error damping is the high redundancy of the genetic code, by which several codons can specify the same amino acid. In the phage $Q\beta$, for example, it has been shown that some nucleotide changes do not give rise to amino acid substitutions, either because they are located in noncoding areas or because the new codon is synonymous with the old one (Domingo et al. 1978). Among other error-damping mechanisms are the aforementioned splicing of precursor molecules and repeated DNA sequences; in *Plasmodium falciparum*, long sequences of DNA repeats encode the surface protein; it is believed that the redundant expression of the repeats enhances the parasite's survival chances by filtering out the effect of harmful mutational events (Nussenzweig and Nussenzweig 1985).

## MODELING THE GENOTYPE-TO-PHENOTYPE MAPPING

In our model, the genetic information is contained in a string of $n$ binary digits (bits), each assuming the value 0 or 1. We now seek a simple rule by which to process the information contained in this string so as to produce a new one, which

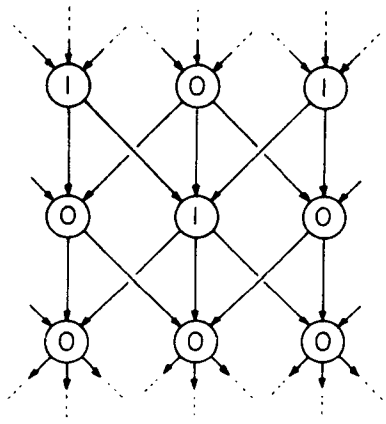


FIG. 1.—A small subset of our information-processing network. Each circle represents a nonlinear processor whose function is to receive from each of its three upper neighbors their information content in the form of a bit (either 0 or 1) and to generate from these an output bit according to the "majority rule." This rule specifies that the output is 0 or 1 according to whether a majority of 0 or 1 is present in the input triplet. The top processors contain the bits that constitute the "genetic message"; the bottom layer of processors generates a string of bits we call the "phenotype."

is the "expression" of the genome at the next layer; the information contained in this new layer is repeatedly transferred forward until a final (say, $m$th) string is obtained, which we designate the "phenotype." This type of multilayer, hierarchical processing has recently been introduced in an actual model for insect segmentation (Meinhardt 1986). Although it is evident that strings of bits can represent phenotypes such as amino acid sequences, one may perhaps question the validity of a similar description for multidimensional phenotypes. It should be noted, however, that the information for all biological properties, including the most complex ones, is contained in the linear sequences of the DNA. In general, any arrangement of information that is effectively representable and effectively retrievable can be linearized.

In order to build into the model the general features of genotype-to-phenotype mapping just described—namely, the many-one and one-many type of hierarchy—as well as the error-damping capacity, we use the so-called *majority rule*. In this scheme any three adjacent bits at a given level $k$ generate a new bit at the next one ($k + 1$) according to majority rule; that is, the new bit is 0 or 1 according to whether the corresponding triplet at level $k$ has a majority of 0's or 1's, respectively (fig. 1). For their evaluation, the bits on the side of the lattice require that additional "lateral" bits be supplied; we arbitrarily set these additional bits to 0. The many-one aspect of the rule is evident; the one-many property is reflected by the fact that each bit at layer $k$ is involved in computing the state of three bits at layer $k + 1$. The majority rule does not recognize errors as such, but rather excludes the effect of any minority in the controlling triplet. This activity mimics the error-damping activity of the type described above, in which mutations in

repeated DNA sequences, for example, are preserved without being expressed phenotypically. Below we describe another processing rule, the *fail-safe rule*, which has the capacity of recognizing and correcting errors, if they are not too large. The latter rule is probably more suitable for describing error-correction mechanisms (rather than error-damping mechanisms), such as the editing activity of DNA polymerase (Echols 1982).

Let us now consider a given phenotypic configuration (i.e., a given string at layer $m$). The local error damping performed by each majority-rule processor leads us to expect that this string may have been generated by any one of several strings at layer $m - 1$; each of these in turn must have several possible "ancestors" at layer $m - 2$, and so on. To each phenotypic configuration is thus attached a tree whose top branches represent the possible genotypes by which it can be generated. These top branches (each a bit string) are what we term the *domain of attraction* associated with the given phenotype. The set of all domains of attraction constitutes the *genotypic space*. In a relatively small lattice of size 7 by 5 (i.e., 5 layers of 7 bits each), the genotypic space is made up of $2^7$ (128) possible genotypes. Computer processing of all these genotypes reveals that this space is indeed divided into 27 domains of attraction, so that more than four genotypes, on the average, yield a single phenotypic configuration. This property, namely that different configurations of the topmost layer lead to the same state at the bottom layer is not a straightforward result of the local error-damping property built into the majority rule. In fact, below we show that the capacity for damping errors depends critically on the local neighborhood of genotypic space that is being explored. We expect similarly that the various biological error-damping mechanisms, each of which operates in its own local way, should lead to global statistical error damping at the level of the entire organism. Thus, we feel justified in advancing the following conjecture.

*Conjecture 1.*—If we consider the various successive levels of genetic information transfer, the variability in a given population should be largest at the genotypic level and decrease toward the terminal phenotypic levels.

That different genotypes can yield a single phenotype is exhibited in a clear manner by the influenza-A virus. Thus, the disease in the typical patient has been essentially unvarying at least during the past 400 yr, whereas the virus itself is unique among infectious agents for its antigenic variability (Choppin and Compans 1975; Fang et al. 1981; Winter et al. 1981). But the spectacular antigenic variability is even surpassed by the genetic variability of this virus. Analysis of a single human influenza-A subtype shows 0%–9% amino acid variation but a much larger proportion of nucleotide substitution (Air 1981). Duck viruses of the same subtype of influenza A, isolated at the same time in the same geographical area, are antigenically indistinguishable. Nevertheless, they vary extensively in the RNA's of their two surface antigens, presumably because of the accumulation of a large number of silent nucleotide substitutions (Sriram et al. 1980). Similarly, in *Plasmodium falciparum* the amino acid sequence of the tandem repeats within the circumsporozoite (CS) protein is more conserved than the nucleotide sequence (Nussenzweig and Nussenzweig 1985). Conjecture 1 is therefore evident when viruses and protozoans are considered. Interestingly, this is not the case for

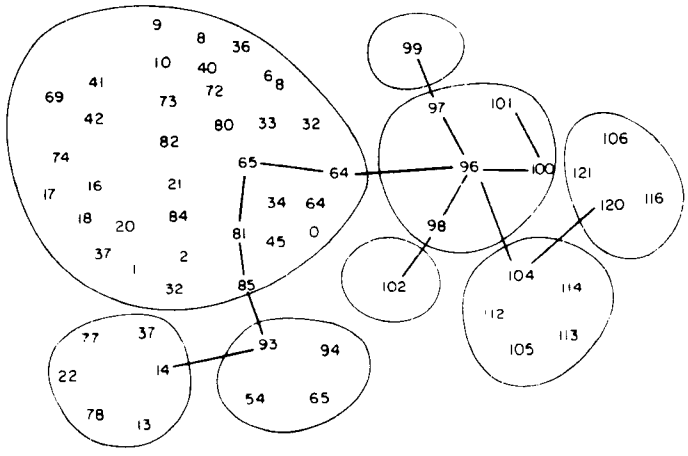


FIG. 2.—A subregion in the genotypic space of an "organism" consisting of five layers of seven bits each. Each number represents a given genotypic bit string in the decimal notation (thus, "16" means 0010000, i.e., $2^4$). *Circular lines*, The domains of attraction of the system (i.e., the set of genotypes leading to the same phenotype). *Straight lines*, Some of the paths in genotypic space that may be followed when genotype 96 (i.e., 1100000) is subjected to various sequences of one-bit mutations.

higher organisms, such as parthenogenetic clones of *Drosophila* that show an appreciable morphological variation. It should be emphasized that our model allows for both phenomena; it predicts (conjecture 5 below) that higher organisms should be able to adapt phenotypically to environmental hazards by modulating their processing rules.

Sorting out the 27 domains of attraction of the 7-by-5 lattice, we note that they vary greatly in size, ranging from one point (i.e., 1 genotype) to a sizable fraction of the total genotypic space. Figure 2 depicts a subset of the genotypic space of a 7-by-5 lattice, with the boundaries of various domains of attraction marked by solid lines; for the sake of compactness, each bit string (e.g., 0100001) has been converted to its corresponding decimal value (here, $33 = 2^0 + 2^5$).

Let us now analyze the effect of small mutations on the system. By "small mutation" we shall mean the inversion of a single genotypic bit (since individual bits in our model do not necessarily represent specific physical units and may also refer to functional units, we use the term "small mutation" rather than "point mutation"). Obviously, any mutation in a genotype corresponding to a domain of attraction of size 1, will move the system to another domain of attraction; in general, for most points in the genotypic space, there exists at least one mutation that leads to phenotypic transition. The size of the transition is generally small, but may exceptionally result in a global inversion of all phenotypic bits.

The largest domain of attraction of the 7-by-5 lattice is the one yielding a phenotype represented by a string of seven bits in state 0. Evidently, when a system is located in such a large domain of attraction, it can move within its boundaries for some time without causing a phenotypic transition. This property

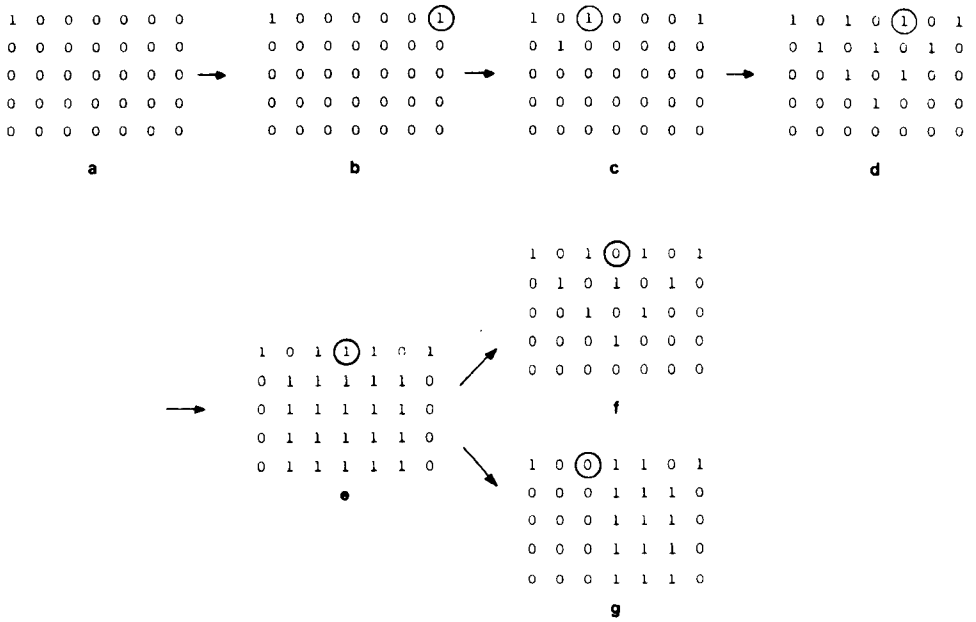


FIG. 3.—Punctuated and gradual patterns of phenotypic change. A 7-by-5 "organism" with phenotype 0000000 and initial genotype 0000000 is subjected to a sequence of one-bit mutations. *a–d*, The mutations (circles) are absorbed by the error-damping mechanisms at work in the system; the variability decreases from the top layer downward. This is a period of phenotypic stasis during which the system wanders inside a large domain of attraction (see fig. 2). *e*, An additional mutation results in a large phenotypic jump, with several of the previously silent mutations instantaneously expressed. Through additional mutations, the phenomenon is *f*, fully reversible, or *g*, partly reversible.

is reflected in figure 3, which exhibits in detail the bit-string structure for a sequence of mutations leading from genotype 64 to genotype 14 in figure 2. From figure 3*a* through 3*d* we see that when the mutation density is low, small mutations in the genome are filtered out by the information-processing machine.

Once a certain density of mutations is reached, though, the system can no longer absorb the errors and any additional random small mutation will cause an immediate large change at the phenotypic layer (fig. 3*e*). Sudden phenotypic modifications may thus be achieved through the agency of small mutations occurring at a constant frequency. From this information, we arrive at our next conjecture about biological systems.

*Conjecture 2.*—A threshold of mutation density should exist, which, when reached, will cause the last occurring mutation and a group of related mutations, whose effect has been damped earlier, to be simultaneously translated into phenotypic properties.

The model predicts that a given population may harbor individuals who, although phenotypically fit, have an evolutionary potential much larger than that of their congeners. This occurs because they are located rather close to the boundary

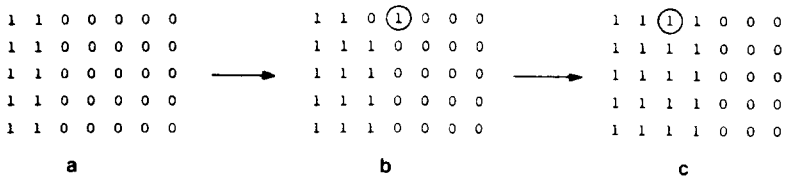


FIG. 4.—Gradual phenotypic change. A system with initial phenotype 96 (*a*) is subjected to two small mutations, both of them expressed instantaneously in the phenotype (*b*, *c*).

between two or more domains of attraction and may pass to another domain of attraction once an additional small genetic change occurs.

In a "hot" area, that is, in an area in which several mutations have recently occurred, an additional mutation can shift the phenotype to its previous state, either fully (fig. 3*f*), or partly (fig. 3*g*), depending on the position of the reverse mutation. Thus, we arrive at the third conjecture.

*Conjecture 3.*—The threshold effect is expected to be reversible in the sense that a single or a few additional mutations in the hot area can shift the phenotype to an earlier state.

The sequence of single mutations leading (see fig. 2) from genotype 96 to genotype 120 and resulting in a gradual phenotypic change is depicted in figure 4. Even when the general mutation density is low, some locally dense mutations are not absorbed by the error-damping mechanism, but rather are expressed as small phenotypic variations.

It should be noted that the majority rule is one of the simplest nontrivial rules for processing arrays of identical simple three-bit "machines" (Wolfram 1983). More-complex rules (multibit rules, long-range interactions among distant bits, feedback mechanisms, etc.) can only further enrich the repertoire of phenotypic outcomes. Thus, we assumethat biological information-processing systems, being much more intricate than our simple model, will be able to generate phenotypic changes of varying sizes from a constant inflow of small mutations.

*Conjecture 4.*—Both punctuated and gradual patterns of phenotypic evolution can be generated by a slow accumulation of small mutations.

In any system devoted to the treatment of information, there is a trade-off between the ability to resist errors and the total capacity for handling information (see, e.g., Huberman and Hogg 1984). A good system is one with some favorable balance between resilience and memory. In our model there is a trade-off between the average size of the domains of attraction, reflecting the homeostatic ability, and their number, that is, the repertoire of phenotypic variability. The balance between these two factors is determined directly by the processing rules, such that systems with different rules behave differently in this respect. A simple illustration is given in figure 5. A system employing such strong error-damping rules as the fail-safe rule (according to which a given bit is 1 if and only if all 3 upper neighbors are 1) filters out several small mutations (fig. 5*a*). When a few fail-safe processors shift to majority rule, say, those of the first layer (fig. 5*b*), some genetic variability becomes phenotypically apparent. When more processors shift

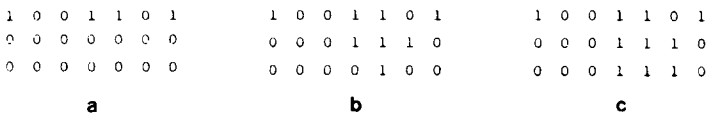


FIG. 5.—Effect of the type of the processing operation on phenotypic variability in a 7-by-3 lattice. *a*, All processors use the fail-safe law: under this rule, each processor generates a bit of 1 if and only if its three input bits are 1. This is a strong error-damping rule, and the genotypic space comprises a small number of large domains of attraction. In this example all four small mutations are filtered out. *b*, Shifting the first layer of processors to majority rule, we see that the phenotype already bears a small trace of the genotypic mutations. *c*, A shift of all processors to the majority-rule mode increases the number of genotypic mutations that are expressed phenotypically.

to majority rule, a larger fraction of mutations is expressed phenotypically (fig. 5*c*). Obviously, when all processors are fully linear, no error correction is possible. These observations lead us to the next conjecture.

*Conjecture 5.*—Biological systems may be able to modulate most efficiently the balance between homeostasis and phenotypic variability by adjusting the level and type of nonlinearity involved in the processing of genetic information.

## THE GENERAL RELEVANCE OF OUR MODEL

Lewontin (1974) emphasized the need for and the difficulty of describing both the genetic states of populations and the laws for transformation of the states in a way that would be dynamically and empirically sufficient. We have attempted here to replace the classical picture in which evolution consists of movements on a genotype adaptive landscape by a hierarchical, multilevel, adaptive landscape, relating movements in genotype space to movement in phenotype space. The model presented consists of a network of nonlinear processors and resembles a class of array systems known as *cellular automata* (von Neumann 1966); despite the model's simplicity, we believe that its assumptions are in accord with the fundamental facts of genotype-to-phenotype mapping.

The model exhibits various aspects of the dichotomy between genotypic and phenotypic evolution, stemming from the nonlinear nature of the relation between genome and phenotype. The essence of the disparity is that many mutations are not directly translated into phenotypic changes. This property reflects the resilience, or the homeostasis, of biological entities, by which a considerable number of genotypic errors can be filtered out with no phenotypic effects. The homeostatic ability of our model depends on the network's topology, and on the types of processors involved. For instance, adding layers of information processing increases the average size of the domains of attraction in our system, resulting in a more powerful homeostasis. The model thus provides a simple explanation for the relationship between homeostasis and complexity.

Model systems displaying resilience have been studied previously. What characterizes ours is that it shows error resistance even though it lacks "forcing structure." "Forced," or "canalized," systems are clustered systems whose

states can be determined by single variables (Kauffman 1978; Alberch 1982), and it has been argued that homeostasis of biological systems is caused by canalization alone (Waddington 1975; Kauffman 1978). Our theoretical work suggests instead that resilience can prevail in the absence of forcing. A natural validation of our results seems to be provided by viral systems. The fuzzy distinction between different viruses, as exemplified by the HTLV-I, HTLV-II, and HIV viruses, and the ongoing generation of new viruses, implies that their morphologies are hardly canalized. The error-damping character of information treatment in viruses is nevertheless exhibited in the decreasing variation from the genotypic level through the phenotypic-symptomatic level.

Our work shows that beyond a critical threshold, mutations that have silently accumulated are instantaneously translated into phenotypic changes, whose size depends on local configurations of the genome. Thus, even under a regime of constant input of small mutations, a lineage of our model organisms can have periods of stasis alternating with bursts of phenotypic novelties and gradual changes. These results imply that gradual and punctuated evolutionary modes are not mutually exclusive, and that punctuated evolution is not necessarily generated through genetic revolutions, that is, by catastrophic genetic events. Our work has focused on events at the individual level, those affecting the generation of phenotypic novelties. Recently, Newman et al. (1985) and Lande (1985) have analyzed the dynamics of change in the population mean of an intrinsically continuous character and have shown that random drift can cause rapid transition between adaptive peaks in a fixed landscape.

The existence in nature of both gradual and punctuated modes of evolution is well exemplified by the influenza-A virus. Whatever its sources, the evolution of this virus shows alternating gradual and punctuated patterns, giving rise to epidemics and pandemics, respectively. In epidemics, gradual mutational changes result in minor alterations of the surface proteins of the virus such that viruses slightly different from their predecessors are formed. In pandemics, new influenza strains emerge, bearing novel surface antigens. Current opinions hold that pandemic influenza-A subtypes do not evolve intrinsically in the human-influenza gene pool, but result rather from recombination between human and animal strains (Laver and Webster 1979; Tyrrell 1976; Young et al. 1979; Fang et al. 1981) and from a reactivation of the virus, by some unknown mechanism, after it has remained latent in man for long periods, perhaps as a cDNA copy integrated in the host DNA (Nakajima et al. 1978; Laver and Webster 1979). However, since a certain degree of nonlinearity has been demonstrated in the synthesis of the influenza-A hemagglutinin (Choppin 1976), it is plausible that novel phenotypes can emerge intrinsically in a continuously mutating population of viruses. This assertion, which can be verified experimentally, may have implications for future control of the disease.

In quantitative genetics, it is assumed that the transmission of such non-Mendelian diseases as schizophrenia and diabetes is effectively under the control of a quantitative character, namely, liability: in any individual whose liability lies above threshold, the disease will be manifested (Christiansen and Feldman 1986). Our model provides a simple example in which liability can be exhibited and

shows how the threshold phenomenon may actually function, that is, how more than one phenotypic trait may be affected by genes whose effect had been masked before a critical, but not necessarily major, mutational event.

Small perturbations of the parameters in nonlinear systems can lead to dramatic changes in behavior; thus, Goldbeter and Segel (1980) examined the developmental transitions in the cyclic-AMP signaling system of *Dictyostelium discoideum*. They suggested that it is the parameter variation along a "developmental path" that moves the system from one behavioral domain to another. Oster and Alberch (1982) presented another developmental model, that of early skin morphogenesis. As a result of nonlinear interactions in the epithelial layer, the skin developmental program appears in this model to be governed by bifurcations, dividing the cellular parameter space into discrete domains. Oster and Alberch pointed out that once the developmental system is near a bifurcation boundary, minor genetic alterations will result in large phenotypic changes. In spite of the general implications of these models (see also Alberch 1982), phenotypic novelties are still associated almost automatically with catastrophic genetic events.

Unlike our own model, however, those just described refer exclusively to epigenetic environments, that is, interactions among proteins, among cells, and among tissues. This approach has little application to the evolution of simple organisms, such as viruses, whose developmental pathways are extremely limited. Moreover, the mounting evidence concerning the direct impact that environmental stress may have on gene expression (notably the evidence suggesting that signals related to changes in cytoarchitecture elicit responses at the level of the genes; Ben-Ze'ev 1985, 1986) makes the distinction between genetic and epigenetic environments rather fuzzy. For these reasons, the underlying premise of our model is that the genomic-phenotypic information flow shows no sharp distinction between genetic and epigenetic phenomena.

Evolutionary theory, unlike molecular biology, biochemistry, and other areas in biology, investigates such properties as fitness or diversity, which are *supervenient*; that is, they can be exhibited by physically different organisms, and two physically identical systems must both have or lack the property in question. Determined by multiple physical mechanisms that vary among populations, supervenient properties cannot be identified with any single physical basis (Sober 1984). The study described here may be of some aid in clarifying this ambiguity. Our model allows for supervenience because phenotypic equivalence does not imply genotypic equivalence, whereas in constant environments, genotypic equivalence does yield phenotypic equivalence. The model offers the possibility of encompassing a whole ladder of biological traits, from genomic configurations through physiological or symptomatic states, within a common, abstract formalism. In particular, we have used a cellular-automaton-type model for illuminating the biological problems at hand: observing, for example, that the balance between resilience and variability can be most efficiently controlled in our "machines" by modulating the processing rules, we expect a similar mechanism to operate in natural organisms. A related approach is developed by Holland (1975) in his adaptation theory.

One of the motivations for the present study was the need to identify mechanisms that might ensure the persistence of populations during periods of environmental stress. An accelerated production of novel phenotypes should be advantageous in times of stress, since a larger repertoire of such novelties increases the probability that at least one emerging phenotype will be adapted to the new conditions. It is currently believed that an inherent biological mechanism increases the mutation rate under stress. We suggest here a more efficient possibility, namely, that the production of novel phenotypes can be controlled in a powerful way by temporarily shifting the balance between resilience and variation. This can be achieved by tuning the level and type of nonlinearity applied in processing genetic information. One plausible way of exerting such control over the biological processors may involve adjusting the production of enzymes that operate on precursor mRNA's, tRNA's, and proteins; an unspliced molecule may transfer to subsequent layers mutations that would normally be eliminated from the mature molecule. Such adjustments are expected to be reversible even during the lifetime of a single organism; hence, their clear contribution to individual fitness. If they exist, they must endow biological systems with a dimension of resilience not previously envisaged.

SUMMARY

Genotype-to-phenotype mapping is modeled by a discrete, multilevel, nonlinear network whose properties are error-damping capacity, pleiotropism, and determination of single events by multiple factors. The model relates movements in genotype space to movements in phenotype space and points out the dichotomy between the genomic and the phenotypic levels of organization. A constant inflow of small mutations leads in this model to phenotypic novelties, alternating with episodes of stasis and gradual phenotypic changes. The model predicts decreasing variability with increasing levels of organization in lower organisms; higher organisms should be able to shift the balance between homeostasis and variation by adjusting the level of nonlinearity in the processing. Such a mechanism may act under environmental stress, when homeostasis should be temporarily suppressed in order to increase the phenotypic repertoire. Applications to viral evolution are discussed.

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