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Reductionism in Evolutionary Biology: A Perceptional Artifact?

THE PROBLEM

What is a genotype-phenotype map? Gene loci produce gene products, gene products interact and these "epigenetic" interactions create and maintain living things, organisms with phenotypes: in some convoluted way, genetic information is mapped onto phenotypes. To characterize this map is to characterize living things and different subdisciplines in biology focus on its different aspects. In evolutionary biology, one unsolved problem is central: how deep can natural selection penetrate this web of epigenetic interactions? Do the effects of natural selection always reach the individual gene, the basis of the epigenetic system, or do they act on a higher level of epigenetic organization? Whatever the answer is, it will determine the level of organization that should be the focus of our research efforts. Maybe, however, no one-for-all solution exists. Different case studies might yield different answers, some favoring genes as the "unit of selection," some favoring higher level entities. This, in and by itself, is not a problem. A problem is that limitations in available

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methods seem to create a perceptional artifact, the assumption—more implicit than pronounced—is that the proper level of focus is the individual gene. A brief overview of a debate related to the problem will be given; reasons for the persistence of the problem will be discussed.

THE DEBATE, ITS CONCEPTS . . .

There are defenders of the idea that higher levels of genetic organization than the individual gene, in the limit, the whole genome, are the relevant players in evolution. For example, Lewontin[12] concludes the review of a formidable amount of experimental data and theory with the statement:

> The fitness at a single locus, ripped from its interactive context, is about as relevant to real problems of evolutionary genetics as the study of the psychology of individuals isolated from their social context is to an understanding of man's sociopolitical evolution. In both cases context and interaction are not simply second-order effects to be superimposed on a primary monadic analysis. Context and interaction are of the essence.

From the other side of the ideological fence, Williams[15] writes:

> No matter how functionally dependent a gene may be, and no matter how complicated its interactions with other genes and environmental factors, it must always be true that a given gene substitution will have an arithmetic mean effect on fitness in any population. One allele can always be regarded as having a certain selection coefficient relative to another at the same locus at any given point in time. Such coefficients are numbers that can be treated algebraically, and conclusions inferred from one locus can be iterated over all loci. Adaptation can thus be attributed to the effect of selection acting independently at each locus.

WHOM ARE WE TO BELIEVE?

The debate gained widespread public attention with Dawkins'[4,5,6] advocacy of gene selectionism. If nothing else, his contributions have led to conceptual advances: he introduced the concept of the "replicator" to the debate, a concept that was subsequently used and extended by others to a canonical terminological framework. In this terminology, natural selection takes place in a world of "replicators" and "interactors," implying the distinction between "units of selection" and "levels of selection."

According to Dawkins[4] a "replicator" is "any entity in the universe which interacts with its world, including other replicators, in such a way that copies of itself are made." DNA molecules, dividing cells, and asexually reproducing multicellular organisms, along with their genomes, may qualify as replicators, but sexually reproducing organisms and their genomes may not. Sexual reproduction is quite another matter, since genetic recombination is involved.

Hull introduces the concept of the "interactor" and defines it[8] as "an entity that directly interacts as a cohesive whole with its environment in such a way that replication is differential." The individual organism is the prototypic example of an interactor, but there may well be interactors on different levels of organization, such as cell lineages within multicellular organisms. Within such lineages, selective processes may occur, favoring cells that divide more rapidly than others. Here, the dividing cell is the interactor within the organism as its environment. The interplay between different levels of interaction may profoundly affect the evolutionary potential of each level, as emphasized by Buss.[3]

Given these terms, the process of natural selection is defined as "a process in which the differential extinction and proliferation of interactors cause the differential perpetuation of the replicators that produced them."[8] In these terms, a "unit of selection" is any level of organization that qualifies as a replicator, and a "level of selection"[2] is any level of organization on which interaction can occur. Note that interactors and replicators may, but need not necessarily, designate different things. In the above example of cell lineages, cells are interactors as well as replicators. Their genome is a replicator, but not an interactor. And the multicellular organism in which they proliferate, provided that it is sexually reproducing, is an interactor but not a replicator.

. . .AND SOME SHORTCOMINGS

The definition of the replicator, as given above, harbors a conceptual problem. If replicators were always replicated with perfect accuracy, we would not be here to think about them. Changes in genetic replicators are what allows evolution. Since the definition of replicators is purely structural, every change, be it through mutation or recombination, creates a new replicator. And those replicators that are most abundant in a population because they convey higher fitness onto their carriers are most likely to be hit by mutations and, thus, extinguished. Considering its transience, Dawkins'[6] standpoint—that the beneficiary of all adaptation is the replicator—seems somewhat contrived. The strictly structural replicator concept may be too Platonic an idea to be perfectly fit for evolution. Here is a further argument for its inadequacy: if we do not want to seem prejudiced, we have at least to admit the possibility that phenomena typical for other "many body" systems occur in organisms. For example, the information necessary to produce a character

may be "distributed" over a set of genes. If this is this case, the outcome may not be determined predominantly by the activity of individual gene products, but rather by patterns and strengths of epigenetic interactions. In other words, the organization of the epigenetic system might be the relevant carrier of information, analogous to what we know from different systems, e.g., neural networks. Changes in individual genes may very well have reproducible effects, but from them alone we may not learn much about the causal relationships that constitute this production system. It may have so many degrees of freedom that a multitude of allelic combinations may produce the same trait. All possible alleles on any contributing locus may be allowed, provided that the population contains appropriate alleles on other loci. No individual replicator might confer selective advantage to its carrier: "context and interaction are of the essence," as Lewontin says.

Should we look for a modification of the available concepts, or must the debate be redefined radically? There may be more appropriate ways to think about evolution than in the replicator-interactor framework. If so, they have not yet been found.

In sum, the adequate level of description for evolutionary phenomena has been the source of an ideologically charged debate for some decades. Standard concepts have partly been introduced by gene selectionists, a fact that may account for their inadequacy with respect to phenomena involving many interacting genes. Polygenic phenomena may require more elaborate concepts. But given the available experimental methods and the body of quantitative theory that characterize the state of the art in the life sciences, can we reasonably expect anything but concepts supporting reductionism to arise? This question lies at the heart of the problem.

THE HIDDEN, CRUCIAL ISSUES

While many students of evolution would agree to statements similar to Lewontin's, such agreement is often mere lipservice, as suggested by the current prevalence of a, sometimes simple-minded, molecular viewpoint of evolution and development. What might be the reasons?

The canonical way to study epigenetic interactions is by constructing mutants and in order to find out about how gene products interact, mutants in more than one gene are needed. However, the combinatorial explosion of possible mutant genotypes sets a very low limit to the number of genes whose interactions can be analyzed: to determine qualitative order relationships in a biochemical pathway, one usually constructs mutants in two genes. Formal genetic analysis of mutants in three genes often requires great sophistication. Moreover, formal genetics is most often not useful for an understanding of epigenetic interactions that is more than qualitative. This is where the toolbox of molecular biology has led to significant advances. But still, organisms are sources of noise, distorting most molecular signals

heavily. Quantitative data on concentrations of gene products, on their activity, or on the strength of their interactions are sometimes hard and often impossible to obtain. These and other difficulties associated with molecular methods have not significantly increased the number of epigenetic interactions that can be analyzed simultaneously. And regardless of the method of analysis, one can only hope that all the factors uncontrollable by standard precautions such as, say, utilization of isogenic strains, do not contribute more than random noise.

Of the many phenomena we observe, we are likely to filter those that teach us causal relationships that are "simple," and available methods do not even allow us to *analyze* those that are complex: students of the epigenetic system are not blessed with multivariate data sets, let alone accurate ones. Thus, one must not be surprised by the prevalence of a reductionist viewpoint which is mostly supported by the lack of methods to investigate its antithesis.

Given that empirical methods have insufficient resolving power, is there any candidate body of theory, that (i) claims to be an accurate representation of epigenetic interactions and (ii) supports the possibility of higher order units of selection? The answer has two parts. The first regards models, the second regards concepts.

In biology, experiment and quantitative theory have a long history of interacting poorly. Next to no quantitative population genetical models on epigenetic interactions exist that are acceptable to the experimentalist, a deplorable situation that has its reasons in the methodological problems just outlined. But even browsing the literature for potentially relevant models, regardless of their empirical appeal, results in disappointment: the bulk of population genetical literature contains models in which a phenotypic trait is formed by *additive* interaction of some hypothetical, underlying genetic variables. Since vanishingly little data speaks in support of the assumption of additivity,[18] why use it? One reason is the formidable degree of complexity displayed by models involving even only a small number of loci. Lewontin[12] provides an example in which a simple dynamical system modeling five segregating loci in a population of diploid, sexually reproducing organism has approximately 4×10^9 equilibria, many of which might be stable. Such models have the potential to provide even the seasoned mathematician with a sense of despair. And if analytical approaches to many unrealistic additive models with few genes are not feasible, insight into realistic nonlinear systems with many genes seems even more hopeless. This is also reflected by the observation that the few available nonlinear models involve mostly small numbers of loci as well as types of nonlinearities tailored towards analytical tractability rather than biological realism. The distinction between additive and nonlinear models is emphasized here, because additive epigenetic interactions are bad candidates for higher order units of selection: changes at any locus are transmitted linearly onto the phenotypic level. Effects of allelic variation are therefore independent of the genetic context in which alleles occur.

In sum, available quantitative models are often biologically unrealistic or mathematically intractable, and frequently both. Moreover, their simplicity makes them inadequate tools to investigate the central conceptual question, which is: what level

of complexity of epigenetic interactions is required to make selection affect a group of genes as a cohesive whole? What is a cohesive whole, anyway? In other words, if we look for higher order units of selection, what are we looking for? Note that the debate outlined above is only concerned with those biological entities that can *in principle*, i.e., because of their ontological status, be units of selection. It does not provide us with any operational criterion that would identify units of selection irreducible to lower levels of organization. Our current depth of understanding of such irreducible phenomena is best summarized by Mike Simmons, vice president of the Santa Fe Institute, who characterizes "complexity," a closely related and similarily ill-understood term: "It's a lot like the Supreme Court's definition of pornography: it's very hard to define, but you know it when you see it."

Despite the absence of any criteria other than heuristic ones, some distinctions can help to localize the problem. On a very elementary level of understanding one might say that also in the unrealistic case of linear genotype-phenotype maps, genetic variables produce the phenotype "jointly" and respond therefore as a unit to selective forces on the phenotype. However, as discussed above, this is unlikely to be satisfactory. Caution is also appropriate when the existence of correlations between alleles at different loci is taken as a hint towards the presence of higher order units of selection. Such correlations may exist for reasons unrelated to selective forces, e.g., genetic drift.[13] Their existence does not necessarily mean that the respective genes are functionally related in any way.

Wimsatt[17] proposed an operational criterion for higher order units of selection that makes use of Lewontin's notion of context dependence. It is based on the fact that on a nonlinear fitness landscape (i.e., a genotype-phenotype map where the phenotype is fitness itself), one's position on the landscape determines what amount of variation in the units of genetic variation is translated into variation in fitness. Details of a somewhat technical discussion can be found in Wimsatt[17] as well as in Lloyd.[10] According to this criterion, most nonlinear epigenetic interactions imply the existence of higher order units of selection. One might, however, feel ill at ease with such an abundance of higher order units of selection and it might be argued that more than simple nonlinearity is required. Consider, for the purpose of the argument, three fundamentally different types of hypothetical genotype-phenotype maps from N units of genetic variation, $\{G_1, \ldots, G_N\}$, to some phenotype (fitness), P. First, the linear map $P = G_1 + \ldots + G_N$; second, a "simple" nonlinear map, such as the quadratic form $P = \sum_{i,j} G_i G_j$; third, some map that can not be written down in closed form and that transforms genotype space by folding, contracting and stretching it in some complicated way, as in many well known examples from the theory of nonlinear dynamics. The persistence of biology as a field of active research indicates that the latter type is the one closest to reality. According to Wimsatt's criterion, no map of type one, but many maps of type two will imply the existence of higher order units of selection. However, common sense suggests that maps one and two are very similar with regard to one basic property. Statistical regression analysis, linear or nonlinear, can be used to predict P from $\vec{G}$. We feel that in both types we can quantitatively "understand" the production of the phenotype in

terms of each underlying variable, since we can describe the map analytically; we can precisely map the "causal" relationship between each of the variables and the phenotype. Therefore, we might be tempted to call the phenotype not emergent, but reducible. The gene and no higher level of organization would be the unit of selection. According to this viewpoint, only those maps that drive even Laplace's demon close to capitulation, might pose a problem. The theory of dynamical systems teaches us that our failure to analytically understand some type three maps may be an intrinsic property of the map, and not of our incompetence. In these cases, only a phenomenological description of the system as a whole may be possible. Currently, however, merely heuristic criteria are available for identification of the kind of nonlinearities that make maps "complex."

At issue is our notion of causality, as the above examples demonstrate. When can we speak of "distributed causality?" Is causality distributed in every system with more than one independent variable? Is any form of nonlinear dependence sufficient? Do we need genuinely complex maps? It seems that we have not developed notions of causality adequate to the analysis of complex systems, a shortcoming that biology shares with the physical sciences.

THE FUTURE

Three imperfections—experimental, theoretical, and conceptual—mutually consolidating each other's persistence, form a stable ecology that prevents any major shift in our perception of evolutionary processes, a shift towards entities more inclusive than the individual gene. The virtual absence of quantitative experimental data on complex epigenetic interactions, together with the sparse representation of such interactions in our mathematical models are especially fatal: experimentalists deride theorists, but, equally deplorable, the bulk of available experimental data is unfit for theory development. Our simplistic notion of causality further stabilizes the deadlock. These imperfections, taken together, prevent us from identifying order on higher levels of organization. Our perceptional filter is not fit to detect it.

The sociological peculiarities of the life sciences indicate that only experiment, if anything, will be able to destabilize this ecology. Do we have reasons to hope for advances? "Cross-talking" in signal transduction processes, "genetic redundancy" in development and, "networks" of genetic regulators are catchwords that have appeared in the jargon of molecular biology in recent years.[7,9,14] Their usage is still anecdotal but already widespread. The underlying empirical observations are reminiscent of phenomena observed in completely different systems, systems with distributed representations of information, systems that are among the best understood examples of complex behavior, systems that will not be described efficiently on the level of their parts.[1] The paradigm shift may be on its way.

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