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The Custom Fitting Problem and the Evolution of Developmental Systems

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Summary. When the complexity of a developmental system evolves to a certain point, appreciable variation must occur in the process. The problem the biologist faces is whether this point constitutes a limit to the evolution of complexity in developmental systems. If not, what mechanisms are employed to cope with the problem? The problem—essentially one in "custom fitting" of parts,—and the possible solution(s) to it that have evolved are discussed. The antibody producing system appears to be one that "solves" the custom-fitting problem.

Key words: "Custom Fitting" — Development — Evolution — Antibody response — Genetic Redundancy — Perturbation.

All real processes are subject to unpredictable fluctuations—thermal noise, and so on. In a sense these fluctuations are the essence of life. They are the motive forces in evolution; they drive the organism in its everyday function, as well as bring about its eventual destruction. Nevertheless, living systems tend to be so perfect in their working that the biologist can often ignore fluctuations and treat his system deterministically. In doing so, however, he invites a complacency that prevents him from appreciating how deeply fluctuation is woven into the fabric of biology. In the present communication I would discuss one facet of fluctuations that seems particularly relevant to the evolution and workings of developmental systems. It is called the "custom fitting" problem, and appears to hold the key to many of the ultimate answers in developmental biology and evolution of complex systems.

In that custom fitting is not generally treated explicitly in developmental biology, it is perhaps best to introduce it by a readily assimilated analogy. Consider an engineer or artisan who designs and builds various machines. His mechanisms fall into three classes according to their complexity and the consequent difficulties in design and construction. The simplest are those that can be designed and built using available (standard) parts. Somewhat more complicated mechanisms, the second class, require

some special (unique) parts or parts made to within finer tolerances than those available. What distinguishes mechanisms of the third class is that their complexity has reached the level where it is no longer possible to ignore the fluctuations that necessarily attend the mechanism's construction (and function). These fluctuations will lead in this case to situations where it is impossible to specify in advance the precise nature of certain parts to be used at certain stages of construction—although the *general* nature of these parts may be definable in advance. At such junctures the engineer is forced to "custom fit" parts *during* the mechanism's construction. [We will leave "custom fit" somewhat undefined for the moment.] In other words, a point has been reached where it is impossible to specify in sufficient detail *a priori* the nature of all the parts to be used in a mechanism's construction, because the situations into which the parts will have to fit are themselves unknowable in detail *a priori*.

The custom fitting problem, characteristic of this third class of machines, is, of course, a universal one, encountered whenever complexity transcends a certain level. Beyond that level the effect of (unavoidable) perturbations will be such that a system—its function, its construction—must be viewed probabilistically, not deterministically. This is not simply a problem in correcting errors. It is a problem in designing (non-deterministic, non-unique) mechanisms that function properly despite the fact that "errors" —unpredictable fluctuations, idiosyncracies—have occurred in their construction and will continue to occur in their function and maintenance.

Our concept of an organism is essentially that of a mechanisms of the second class. In meeting any given situation (e.g., a new carbon source) the *Procaryote* uses phenotypes (e.g., an induced enzyme) whose designs have been optimized specifically to perform the given task (e.g., hydrolysis of a disaccharide). Thus, it appears that perturbations in the processes that constitute a *Procaryote* do not prevent evolutionary selection for specific, molecularly detailed phenotypes and their *a priori* specification (in genotypes).

However, as an organism ascends the phylogenetic tree, will this always be true? There can be no doubt that in this ascent an organism could ultimately become complex enough to encounter the "custom fitting" problem. The only question is whether the problem will constitute a limit to complexity beyond which the organism cannot evolve, or whether the organism can evolve means for coping with the problem.

Evidence that higher metazoans *have* at least dealt with a special case of the custom fitting problem—and how they do so—comes from the immune system.

The immune system comprises a large number of genetic sequences (Talmage, 1959). [Whether this number is as large as the variety of possible antibody phenotypes—estimated to be in the millions—is immaterial here

(Talmage, 1959).] But the key point is this: It is *impossible* (in general) to evolve antibody phenotypes by *selection for their individual properties*. Some of the antigens that produce highly specific antibody responses never existed before the advent of the organic chemist, while others—e.g., elephant globulin in the rabbit—were encountered too infrequently to exert selective pressure. What has to be then, is that in some way the organism has "learned" enough about the *general* properties of various antigen-antibody interactions, that it possesses the potential to evolve the immune system *as a whole*, as a *set* of genes, not as the individual parts (specific antibodies). From this it follows that the number of individual antibody responses in the immune system must be sufficiently large that collectively they happen (by chance) to cover effectively the range of all possible antigens the organisms would encounter.

Clearly we do not know how such an evolution of a system (or group of subsystems), as opposed to evolution of individual macromolecules, occurs, just as we do not know how the vast immune system is maintained in the face of mutational pressure (lacking a capacity to "check" its individual phenotypes). For that matter, we do not even know the mechanism by which the specific antibody appears in response to the antigenic stimulus. Nevertheless, the organism does possess specific antibody responses as well as the evolutionary potential to develop this type of system.

The description of the immune system just given is an instance of solving the custom-fitting problem. What specific antigens an individual member of a species will encounter cannot be predicted; therefore, the species cannot (in most cases) evolve antibody responses specifically for these antigens. Yet, the organism, has managed to evolve (without selecting them, without "designing" them in detail) a *set* of highly specific immune responses large enough to cover the entire range of antigenic situations the species will encounter. In solving the "custom fitting" problem the organism has not used the method most commonly employed by craftsmen—i.e., altering existing parts (phenotypes) until they are proper for a given situation. [Several decades ago, the biologist did entertain this type of explanation for antibody specificity (Pauling, 1940).] Rather the solution is analogous to a craftsman who has a large collection of each kind of part (each part of a given kind being slightly different from any other—due to fluctuations in the process of their manufacture), and he hunts through his collection trying various parts of a given kind until he hits upon one that is good enough for the situation at hand.

Of course the major question here is whether a solution to the custom-fitting problem is restricted merely to immune systems—in which case it would be trival—or whether the antibody system typifies a general class of systems concerned with development, etc. in the higher Eucaryotes. In the absence of facts one is left for the present to conjecture.

The antibody system must involve a very large number of genes, and these, without a doubt, would be related to one another in primary structure. Thus, were the organism to possess a number of systems that have evolved to meet the custom-fitting problem, the organism would possess a number of sets of related genetic sequences. And this is, of course, what has been deduced from DNA reannealing experiments (Britten and Kohne, 1968).

As the complexity of the organism increases—as it ascends the phylogenetic tree—the custom-fitting problem becomes more acute. Consequently, those features of the genome characteristic of dealing with the problem (i.e., increasing genome size, degree of genetic redundancy) should become more pronounced. Insect genomes are relatively small in general, and they contain only a small amount of (moderately) redundant genetic sequences (Laird and McCarthy, 1968). Mammallian genomes are much larger and their degree of genetic redundancy is much higher (Britten and Kohne, 1968). It is particularly interesting to note that antibody responses follow a similar pattern. Whether or not such a response exists in insects is debatable (Gingrich, 1964). Although it exists in sharks, the response seems less "specific" than that found in mammals (Voss and Sigel, 1972). [By implication, the shark's antibody phenotypes are not only less specific, but fewer in number.] The bird, which is intermediate phylogenetically, shows an intermediate type of response (Gallagher and Voss, 1969; Voss, personal communication).

Since the immune system is the only concrete example of a solution to the custom fitting problem at present, it is perhaps useful to define what general types of molecules might be involved in custom fitting. Most proteins are allosteric; they interact with two molecular species, a "substrate" and an "allosteric effector". Whether such a protein functions properly in the cell—i.e., whether it yields "product" at proper rate, is determined not only by its own concentration, but by the levels of "substrate" and "effector" as well. If these latter levels are not definable with precision *a priori* (which could be the case in sufficiently complex systems), then it may be necessary on occasions to custom fit the protein—i.e., choose from a group of proteins of comparable function one whose binding constants for "substrate" and "effector" are commensurate with the demands of the situation. This would be accomplished in a manner analogous to the immune system case.

To recapitulate, my basic argument is this: uncertainty (fluctuation) is an inherent feature of development. Therefore, when the complexity of the resulting organism becomes great enough, this uncertainty must take the form of an unpredictability in the process itself so great that the properties of some individual components (e.g., enzymes) can be specified only in general, not in detail, in advance of their use in the process. The organism meets this problem by having a *set* of genes, not a *single* gene, for making

each such component, each gene in the set specifying a slightly different version of the component, and the set as a whole being large enough that it collectively covers the full range of specific characteristics of the given function that might be encountered in development.

Finally I would stress that custom-fitting is not confined to the molecular level (or to the development process). Something of this nature must occur, for example, in construction and function of the brain; it is most improbable that the nerve cell interconnections can be exactly specified in advance. [I don't think this comes as any surprise to the neurobiologist, however.]

Custom-fitting is also a characteristic of the evolutionary process itself. The exact nature of the species that emerges is not totally predictable. The interesting question here is how well defined the general classes are from which the existing specific examples are drawn.

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