ing x can vary over a wide range. In his report in this issue (*2*), Anderson collates the available data for E_{cond} and λ_c for these materials. In the case of LSCO, he obtains E_{cond} for three different values of x by integrating the directly measured specific heat, and obtains λ_c for roughly corresponding values of x by a plausible ansatz for the optical data (he notes that the values so obtained are consistent with those measured directly); acknowledging that the errors are considerable, he points out that the correlation between E_{cond} and λ_c as x is varied is precisely of the nature predicted by the ILT model, and argues that this cannot be a coincidence. In the case of Hg-1201, suitable thermodynamic data are not available, but by a plausible scaling argument, Anderson obtains a value of E_{cond} and hence a prediction, in the ILT model, of λ_c of 1.0 ± 0.5 μm. He then cites a recent paper (*4*) that, on the basis of magnetic susceptibility measurements on oriented powders of this material, infers a value of λ_c of 1.36 ± 0.16 μm; Anderson characterizes the agreement with the ILT prediction as "spectacular."

Enter, however, Tl-2201. For samples of this material near optimum doping, the condensation energy has been directly measured, and there is general agreement that the value of λ_c predicted by the ILT model is in the region of 1 μm, with error bars of at most a factor of 2; this prediction is spectacular, because on the basis of an empirical rule of thumb correlating λ_c with the (measured) normal-state c-axis resistivity, one would expect a much larger value (a discrepancy that is absent, or much less severe, in LSCO and Hg-1201). In earlier work, van der Marel and his collaborators (*5*) inferred from the absence of a c-axis plasma resonance peak in their optical data that λ_c must be at least 15 μm, but they did not establish the actual value of this quantity. In a report in this issue (*3*), Anderson's colleague Moler and her collaborators use an elegant magnetic imaging technique (see figure) to measure λ_c directly, with the result $\lambda_c = 19 \pm 2$ μm, about 20 times the ILT prediction. This discrepancy is acknowledged by Anderson to constitute a major difficulty for the ILT model; however, he argues that Tl-2201 is the only known case where its predictions are apparently inconsistent with the data and speculates that the material may manifest subtle metallurgical complications and not be a true single-plane material.

Thus, the current state of play with respect to the ILT model is that Tl-2201, assuming it really is a true single-plane material, contradicts its predictions by a large margin, whereas LSCO and [if the λ_c value from Panagopoulos *et al.* (*4*) is accepted] Hg-1201 can be argued not merely to confirm the model but to do so in a way that is too striking to be accidental. A final resolution may require reexamination of the structure of Tl-2201, more direct (by imaging, for instance) measurements of λ_c for Hg-1201, and combined thermodynamic and electromagnetic measurements on single samples of these and other one-plane materials.

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EVOLUTION

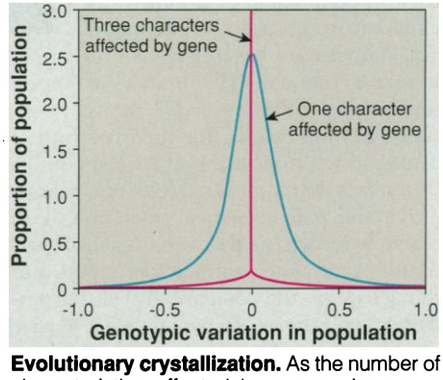
Complexity Matters

Günter Wagner

Are organisms like liquid droplets, infinitely malleable by the changing forces of evolution, or do they contain a "frozen core"—the Bauplan, or body design, which remains little changed under the varying adaptive pressures a lineage encounters during its history? Until quite recently, these questions have divided evolutionary biologists (as well as philosophers) into two almost nonoverlapping camps. On the one hand are the so-called reductionists, largely recruited from the ranks of population genetics and associated disciplines, who are strongly committed to the adaptationist program of evolutionary biology. This group tends toward a world view in which there are no limits to an organism's variability and its ability to evolve. On the other hand are those biologists who primarily study whole organisms or complex phenotypic traits of organisms. This second group emphasizes the need to understand the constraints on evolutionary change that arise as a consequence of the intrinsic functional and developmental complexity of organisms. On page 1210 of this issue, Waxman and Peck (*1*) present a new mathematical result that reconciles most of the differences between these two camps. Population genetic equations predict, so they show, that parts of the phenotype effectively "crystallize" as the complexity of systems increase. But what is the problem to which this result is the solution?

The intellectual history of the problem goes back to the synthesis of Darwinian evolutionary theory and Mendelian genetics forged by the fathers of modern evolutionary theory, R. A. Fisher, S. Wright, and T. Dobzhansky. Through the marriage of genetics and Darwinism, it became clear that the process of evolution can be understood, or at least described, as changes in gene frequencies over time (*2*). New genes arise by mutation and are either lost (most likely) or they replace their parental genes, by selection or genetic drift. This, it turns out, is the most elementary level on which evolution can be explained. Consequently, a lot of effort was and continues to be invested in research directed at understanding these elementary processes. This remarkably successful research program has been pursued with the implicit assertion that evolution of real and complex organisms is just more of the same, and that no qualitatively new phenomena emerge as a result of increasing complexity (*3*). In this view, complexity is fundamentally irrelevant to an understanding of evolution. A corollary of this line of thinking is that all aspects and characters of the organism are variable and constantly changing (although at different rates), and the concept of a "Bauplan" (the body organization characteristic of a larger group of organisms) is an illusion (*4*).

A well-informed minority of organismal biologists, however, never were convinced of this radical view. Theirs is a more pluralistic view: yes, they agree, many characters are highly variable and their differences



Evolutionary crystallization. As the number of characteristics affected by a gene increases from one (blue) to three (red), one genotype becomes dominant.

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among species and populations can be understood as adaptations. But at some stages of evolution certain characters effectively "click in" and remain fixed in the descendent group of species (*5–7*). For instance, the chorda dorsalis (the embryonic precursor of our vertebral column) is absent in invertebrates, variably present in the relatives of vertebrates (ascidians and related groups) and absolutely fixed in vertebrates. The first who most clearly saw a connection between this pattern and increasing complexity was Rupert Riedl in the 1970s (*6*). He postulated that with increasing complexity some characters become more important because more and more new characters are functionally or developmentally predicated on them. Once such characters have accumulated many "responsibilities," mutational change will be detrimental and thus these characters become evolutionarily fixed. This increasing burden leads to fixation of characters. The problem with this view, however, was that it did not connect well with the then current population genetic theory.

Standard population genetic theory supports a liquid genome metaphor. In the balance between mutation and selection, each population settles into a state in which the most fit genotype is always surrounded by a sizable swarm of mutant genotypes buzzing around the best genotype (*8*), so much so that the concept of wild-type becomes meaningless. Variation is the name of the game. Only the amount of variation depends, in a continuous manner, on the relative strength of stabilizing selection, genetic drift, and mutation. Well, not exactly, according to the report by Waxman and Peck (*1*), which shows that there is a complexity limit beyond which genes can freeze into a fixed state and where the swarm of genetic variation suddenly disappears like fog in the sun. In the Waxman-Peck model, the complexity limit is reached once the genes affect more than two characters that are under simultaneous stabilizing selection.

To be precise, this freezing phenomenon has been described before (*9*), but it was seen as an arcane result of mathematical population genetics of uncertain significance and familiar to only a very few specialists. The significance of the present report is that Waxman and Peck have shown that this obscure property of mutation-selection equations has a connection to a generic property of organisms: complexity. Each gene has many effects and functions, each character is functionally connected to multiple others. Since this is the case, the freezing of genetic and phenotypic states is a necessary outcome, just as many organismal biologists have suspected for more than a century.

This sounds great and simple, but nothing in science is ever really simple. There is always the question whether the models are producing artifacts rather than pointing to fundamental insights. There is also no definite empirical proof as to whether the Bauplan concept is a perceptual artifact or a real pattern. Both are empirical questions that need to be settled. What makes the result by Waxman and Peck nonetheless exciting is that new emergent phenomena can be discovered that are not obvious from the study of simple models. More complexity is not just more of the same, but can lead to qualitatively new phenomena. This has long been know to physicists, but there are only a handful of examples where "complexity effects" were described in population genetic models (*10*). These and the report by Waxman and Peck show the need to study the population genetic theory of complex adaptations as a separate problem.

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IMMUNOLOGY

Fixing Mismatches

Michele Shannon and Martin Weigert

Complex biological processes evolve by co-opting bits and pieces of preexisting cellular machinery and using them for new purposes. On page 1207 of this issue, Cascalho *et al.* (*1*) provide a new example of this strategy in the case of somatic mutation of antibody variable (V) genes. The mutation of V genes is the key mechanism by which the body develops and modifies the antibody repertoire, the huge diversity of antibodies that allows us to keep pace with emerging and antigenically altered pathogens. V gene mutation differs from spontaneous mutation in two ways: The rate is extremely high (six to seven orders of magnitude higher), and luckily, this hypermutation is confined to a region in and around expressed V genes. Cascalho *et al.* have discovered that a protein ordinarily involved in correcting mutations is involved in causing V gene hypermutation.

Somatic hypermutation is not the first immunological process to co-opt ubiquitous proteins. The other key immunological process for generating diversity, V(D)J recombination, also evolved by using this strategy (*2*). Rearrangement of variable (V), diversity (D), and joining (J) gene segments to produce functional antibody and T cell receptors requires the lymphocyte-specific RAG-1 and RAG-2 (the products of recombination activation genes). In and of themselves, though, the RAG proteins cannot complete the process of gene recombination; instead, the RAGs primarily recognize specific sequences and nick the DNA. Ubiquitous factors then take over to complete the recombination process. Many of these co-opted factors have been identified by educated guesswork and experiments with mouse strains impaired in V(D)J recombination. For example, the *scid* mutation renders mice both radiation-sensitive and recombination-deficient (*3*). The connection between these two phenotypes became obvious when the *scid* mutation was shown to affect DNA-dependent protein kinase, part of the machinery for repairing breaks in double-stranded DNA (*4*). Thus, to accomplish V(D)J recombination, the immune system co-opted DNA repair machinery.

The new studies by Cascalho *et al.* demonstrate that DNA repair machinery has been enlisted by the immune system once again—this time for V gene mutation. The authors investigated whether a mouse genetically engineered to lack a DNA repair function is also defective in somatic hypermutation. This candidate gene strategy

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