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The spectrum of biological events: An insight beyond the modern synthesis

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Abstract

The last third of the 20th Century featured an accumulation of research findings that severely challenged the assumptions of the "Modern Synthesis" which provided the foundations for most biological research during that century. The foundations of that "Modernist" biology had thus largely crumbled by the start of the 21st Century. This in turn raises the question of foundations for biology in the 21st Century. Similar to the physical sciences in the first half of the 20th Century, biology at the start of the 21st Century is achieving a substantive maturity of theory, experimental tools, and fundamental findings thanks to relatively secure foundations in genomics. Genomics has also forced biologists to connect evolutionary and molecular biology, because these formerly Balkanized disciplines have been brought together as actors on the genomic stage. Biologists are now addressing the evolution of genetic systems using more than the concepts of population biology alone, and the problems of cell biology using more than the tools of biochemistry and molecular biology alone. It is becoming increasingly clear that solutions to such basic problems as aging, sex, development, and genome size potentially involve elements of biological science at every level of organization, from molecule to population. The new biology clubs together genomics, bioinformatics, evolutionary genetics, and other such general-purpose tools to supply novel explanations for the paradoxes that undermined Modernist biology.

Keywords: Cell biologist, molecular biologist, century biology, genomic tool, modern synthesis

Introduction

Biology has been re-integrated twice already, first by Darwin in 1859 and then during the "Modern Synthesis" of the 1920s and 1930s. In both cases, the success of these syntheses rested in part on ignorance. Charles Darwin could reasonably integrate biology in the 19th Century on a relatively elegant evolutionary foundation partly because a great deal was not yet known about cellular and biochemical machinery. This is not to say that Darwin could not have integrated the findings of 20th Century cell biologists and geneticists into his theory; he simply didn't have the opportunity to do so because the data were not yet available. He did the best that he could with the scientific material of biology that was widely available in his day, and he almost single-handedly effected the first integration of the biological sciences.

Nevertheless, Darwin's synthesis was seriously and legitimately questioned in the first years of the 20th Century [1] particularly due to the impact of new findings in genetics and cell biology. There was too much detail that was unknown during Darwin's time, most notably a workable theory for the inheritance of quantitative traits, for Darwin's synthesis to last without considerable reformulation. But the disintegration of the first attempt at scientific biology would naturally enough pave the way for the next, as Fisher, Haldane, Wright, Dobzhansky, Mayr, Simpson, and Stebbins, among many others, integrated genetics, paleontology, systematics, and cytology within a new, expanded, structure for biological thought that is often referred to as "The Modern Synthesis". After its genesis, this Modern Synthesis provided useful foundations for biological thought for the middle part of the 20th Century.

Like Darwin's synthesis, the form of the Modern Synthesis was shaped in part by ignorance of important features of life that were at the time unknown to science. Specifically, the molecular biology of the cell remained largely unknown. During the construction of The Modern Synthesis, molecular biology was in its infancy. The biochemistry and molecular biology of the gene had not yet been worked out, leaving evolutionary geneticists free to imagine that genomes were orderly libraries of stable hereditary information strongly shaped by natural

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selection. And so they did, in most cases. This made it possible for them to use simple models to supply excellent solutions to such important and previously unsolved problems as the inheritance of quantitative variation, the action of natural selection on Mendelian variation, the role of chromosome rearrangements in speciation, and so on. We are great fans of the achievements of the Modern Synthesis, particularly its clarity, its mathematically explicit foundations, and its capacity to make sense of a broad range of biological phenomena. In this respect, the Modern Synthesis shares many features with Newtonian physics.

Nonetheless, the view of life that most biologists had from 1935 to 1965 was highly simplified. Naturally, evolutionists, ecologists, and organismal biologists built directly on the foundations supplied by the Modern Synthesis during this period. But just as the comparative biologists of the late 19th Century could study anatomy and physiology based on a simple Darwinian foundation, so did many mid-20th Century developmental and cell biologists implicitly build their research on assumptions underwritten by the Modern Synthesis: hard inheritance, no orthogenetic "direction" to evolution, adaptation by natural selection, and so on. There were prominent Western scientists who dissented from this reliance on the Modern Synthesis, like C.H. Waddington. The scientific establishment of the Soviet Union, under the direction Lysenko, also offered substantial dissent from The Modern Synthesis. But for most Western biologists, the Modern Synthesis provided a useful foundation for their research.

Few restrictions of Modern Biology

It is important to note that, some of these ideas made it easy for biologists to be specialized in their research and teaching, if not actually isolated from the concerns of other biological disciplines. Thus, before 1980, the careers of cell biologists and evolutionary biologists could proceed in relatively blithe ignorance of the concerns or findings of their distal biological disciplines. They could each insist on the purity and autonomy of their intellectual interests, cell biologists invoking their field's secure foundations in biochemistry, evolutionary biologists relying on their field's deep theoretical and mathematical heritage of population genetics, quantitative genetics, and phylogenetics.

Here we offer a general description of the emerging "new biology", and illustrate it with examples drawn from research on molecular evolution, aging, sex, and development. Naturally enough, these examples are chosen because of our own research interests. They are not intended to reflect the full sweep of the new biology, only to illustrate it. Furthermore, we do not suppose that a single review article could conceivably do justice to all the relevant complexities of research on these topics. Instead, we discuss aspects of research on these questions that serve to illustrate our general view that a new biology has developed and, in conjunction, many important assumptions of 20th Century biology have been abandoned.

It might be thought that we suppose that the transition which biology is now undergoing requires the defeat or replacement of one set of biologists by another. But that is not our opinion. The senior author of this article found his way between these two kinds of biology, starting with one view of living things in 1971 and ending up with a very different one by 2001, and this was nothing unusual or creditable. We should be equally clear that, in arguing for the necessity of this intellectual transformation, we do *not* think that those who based their research on the Modern Synthesis were "bad scientists" and those who now abandon it are "good scientists." We are simply offering an overview of how a large number of us have changed our thinking, our biological Weltanschauung.

The crucible of the new biology: Molecular evolution
The previous view of gene evolution and molecular function

In the Modern Synthesis, genes were adaptive characteristics of species, not a level of evolution with a deep history or with branching processes potentially different from those of species. This view was linked to the assumption that species history was dominated by the fine evolutionary adjustment of sub-organismal traits to specific functional ends. Strong selection capable of quickly molding traits for current utility was also expected to erase the history of sub-organismal traits. This strong commitment to the power of selection may be why Mayr wrote the following in 1963:

"Much that has been learned about gene physiology makes it evident that the search for homologous genes is quite futile except in very close relatives". – Mayr [2] p. 609.

If the genes of each species are assumed to be perfectly tuned to current function, mechanistic convergence should often result, leading not only to erasure of evolutionary history, but also to extensive homoplasy in the molecular and cellular machinery of diverse species. Thus mid-20th Century biology usually assumed that species were the durable units of evolution while organs, genes, and cells evolved to match the functional demands placed on those species. When new species formed, it was expected that their genes would then diverge, and with them the cells and organs that they specified, in parallel with the opportunity for divergence that speciation supplied.

The assumption of parallelism across levels has now been widely dropped. By the start of the 21st Century, molecular evolution had taught us that genes duplicate within species, and protein-coding genes are often recognizably conserved for tens or hundreds of millions of years, longer than the duration of many species.

Some of the first glimpses into the complexity of molecular evolution came in the 1960s, when the sequences of proteins from different organisms began to accumulate. Knowledge of the sequences of proteins added a new hierarchical level to be studied. No longer did proteins have to be viewed simply as characters of species. Rather amino acids themselves could now be treated as constituent characters of evolving proteins. One goal of research on molecular evolution was to use these amino acid sequences to trace species history, yet it quickly became clear that the proteins themselves had their own evolutionary histories – sometimes duplicating separately within a species with both copies persisting indefinitely.

Hemoglobin was a key molecule for the discovery of the deep history and complexity of protein evolution. Along with cytochrome C [3], hemoglobin was one of the first proteins with amino acid sequence information from multiple species [4]. Both these proteins showed deep homology across taxa separated by tens of millions of years of evolution, indicating that phylogenetic history at the gene level could now be studied on its own. In 1961, VM Ingram published a paper in *Nature* entitled "Gene evolution and the haemoglobins" [4]. Ingram presented a gene tree of hemoglobins, suggesting that the different hemoglobin chains evolved by duplication, and that myoglobin is a paralog of hemoglobins (Ingram fully articulated the concept of paralogy or "duplication-dependent homology" [5], though the word itself was not invented until

1970 [6]). Ingram recognized the importance of this idea, and considered it novel, with major implications for understanding gene evolution. Proteins have evolutionary histories of their own and deep histories at that.

Similarly, modernist preconceptions led some to discount the importance of endosymbioses in the origins of new life forms, like eukaryotes. Broad theories of endosymbiotic origins for species had been suggested in the late 19th and early 20th Centuries [7], but were ignored save for a few well-established cases like lichens. By the 1980s, the evidence for symbiogenesis in major cell biological events was voluminous [13, 14].

Even systematics has had to abandon many strictures that were part of the Modern Synthesis. If species are the durable unit of biology, and if natural selection quickly molds genes to current utility, then most genes should diverge at the time of speciation events, given views like Mayr's. Here again, analyses of newly abundant sequence data in the late 20th Century showed that rather than a highly congruent coalescence of genes at the times of speciation events, the coalescence times of alleles among species are highly variable. As such, species trees and gene trees often cannot be equated [15, 16].

These phenomena complicate the tree of life. Rather than a graph connecting species, the tree of life itself is hierarchical: A universal tree of species is largely a human-imposed ideal because the components of any particular species have evolutionary histories that are not congruent with each other. This incongruence has a clear and well documented mechanistic basis in horizontal transfer, symbiogenesis and differential lineage sorting (not to mention gene duplication explained above). These processes together undermine the existence of a tree of life defined only at the level of species, pointing instead to branching histories that often differ among levels of organization and scales of analysis.

Genomic elements of the new biology
The periodic and complete genome sequences
Of course it is a platitude to say that biology is an inherently hierarchical discipline. Natural science as a whole is inherently hierarchical. This is not to dismiss the existence of meaningful emergent phenomena, as the existence of life itself illustrates. But no statement in chemistry can be a false statement in physics, and no feature of life can contravene the findings of chemistry. When there is such incoherence, it has to be rectified, by correcting one or both of the conflicting disciplines.

Before the 20th Century, physics and chemistry existed in partial isolation from one another. The foundations of physics were of little interest to organic chemists, just as organic chemistry was of little interest to physicists. Each could happily pursue its interests in a parochial manner. With the coming of nuclear physics and then quantum mechanics, chemistry and physics became integrated to such an extent that there is now no clear boundary between them.

Perhaps the critical bridge that links physics and chemistry is the Periodic. Though aspects of the Periodic were intuited by chemists before the 20th Century, in the first half of the 20th Century the Periodic was the obvious bridge between physics and chemistry, between the theories of quantum mechanics and the properties of chemical bonds.

In the same way, the complete sequences of genomes that were first made available circa 2000 make the interdependence of the biological disciplines patently clear. It is also evident that genomes rarely if ever are tidy libraries of biochemical instructions for making cells, nor are they the abstract assemblages of numerous alleles of small effect. Genomes clearly show the imprint of accidents in evolutionary history, selection, and biochemical constraints. Genomes are laden with mechanistic and historical detail; if not always baroque, genomes are clearly not universally elegant in their construction. And their elaborate detail implicates biochemical, cellular, organismal, ecological, and evolutionary machinery simultaneously.

Genomics is fundamental for the new biology
The new genomic foundations of biology are not nearly as convenient as those of the Modern Synthesis:
- Genomes can have abundant DNA sequences that are of no apparent functional benefit to the organism.
- Much genomic DNA arises from the proliferation of DNA sequences that have evolved to proliferate within genomes, not benefit organisms.
- Protein-coding DNA sequences are often phylogenetically ancient, of far greater age than the species that bear them.
- Genomes can change rapidly due to selection mechanisms operating on multiple levels simultaneously, as well as processes of transposition, mutation, and recombination.
- Because the genome is a complex and shifting patchwork subject to many evolutionary and biochemical constraints and pressures, simple models of cellular or organismal function will often fail.

Common mid-20th Century assumptions about how cells, organisms, and species work have thus been undermined. This might seem like warrant for despair about the future of biology, but there are two mitigations to consider. First, this complexity was always there. Darwin and many later biologists realized that their simple models were erected like piers over swampy ground. They just didn't know how deep the muck was. Second, we now have powerful genomic tools for addressing complex phenomena throughout biology. It is the use of these genomic tools in the unfolding of the new biology that we are particularly concerned with in this section of our article.

Genomic tools of the new biology
Biologists discovered the lacunae of the Modern Synthesis through the use of some of the same tools that are already being employed to build 21st Century biology. However, not all of the genomic tools that biology now uses were important in the transition to the new biology, and they might have escaped the notice of some. We start with the obvious genomic tools and proceed to those that have received less attention.
- Rapid DNA sequencing is the key technology that undermined the Modern Synthesis by revealing the complexity and variety of genomes.
- Massive parallel assays of gene expression, from mRNA production to protein level, have revealed the interconnected gene networks on which cellular and organismal functions are based. These data have undermined the 20th Century notion of simple pathways of gene-enzyme determination for most biological processes, favoring instead the "network" concept of biological machinery.
- Phylogenetic bioinformatics allows us to infer the sequence changes of nucleic acids and proteins with

proper statistical validity, disclosing both the unity of the biochemical machinery of life and the speed at which that machinery can evolve.

- Quantitative-genetic and genomic mapping are combining to build a genetics that can move from organism to organism with greater speed and power than the old "model organism" and "single mutant" genetics of the 20th Century.
- Molecular ecology is putting DNA sequence variation and ecological processes together to increase the power of ecological research, and in so doing has revealed the high levels of complexity and species diversity, especially microbial, underlying ecological phenomena.
- Large-scale mutagenesis, RNAi and other gene expression modifications, and experimental evolution complement genomic mapping in the unraveling of gene networks, particularly by probing biological systems for their causal controls.

But there is much more going on in the transformation of biology than the mere addition of genomic technology to standard experimental strategies. The new technologies are bringing together the old disciplines of biology, from biochemistry and molecular genetics to ecology and evolutionary biology.

We will illustrate the flavor of the new biology with research on three fundamental topics: aging, sex, and development. In each of these instances, well-established 20th Century views of the causal mechanisms that define each of these phenomena have been undermined, as we will now show.

Evolutionary biology supplied a better explanation in multiple areas

Though most evolutionary biologists showed little interest in aging before 1980, there was nonetheless a quiet tradition of evolutionary theory devoted to the explanation of aging in terms of a progressive weakening of the force of natural selection. This line of thinking started with tangential, if not elliptical, remarks published by R.A. Fisher in 1930 [32] and J.B.S. Haldane in 1941 [33], but it was Peter Medawar who took up this theme at length, particularly in his famous 1952 essay, "An Unsolved Problem of Biology" [34]. W.D. Hamilton [35] then supplied the first mathematically cogent analysis of the age-dependent weakening of the Forces of Natural Selection. This work was placed on solid formal foundations by Brian Charlesworth, whose 1980 book [36] marked a definitive summation of this minor, primarily British, theoretical tradition.

It turned out that many of the major features of aging that were puzzling and counter-intuitive for cell biologists could be explained in terms of evolutionary theory. For example, the absence of aging in fissile organisms could be explained readily in terms of the absence of decreases in the forces of natural selection that arise when reproduction proceeds by symmetrical fission. Likewise, much of the comparative biology of aging fits readily within the framework supplied by the evolutionary theory of Hamilton and Charlesworth [31].

It was left to evolutionary experimentalists to show that aging would readily evolve as predicted by evolutionary theory [37, 38, 39]. Furthermore, it was a straightforward project to use evolutionary and quantitative genetic approaches to uncover specific physiological mechanisms that underlie aging in particular species, such as *Drosophila* [40]. Notably, the causally demonstrable mechanisms of aging in *Drosophila* have proven to be different from the molecular mechanisms

assumed by cell biologists from the 1950s to the 1990s, revolving instead around resistance to stress, investment in reproduction, and metabolic reserves. Most importantly, the initial application of genomic tools has revealed that aging is a "many-headed monster" at the level of molecular machinery, a genomically baroque phenomenon quite unlike the well-defined, universal, aging mechanism sought by 20th Century cell biologists.

Recombination is a by-product of normal DNA repair mechanisms

The suspicion that evolutionary biologists were "barking up the wrong tree" started to grow among biologists in the 1980s. One of the important points brought to the debate was the intimate relationship between the molecular machinery of recombination and that of DNA repair. DNA repair is one of the most fundamental needs of all organisms. It became apparent that a side-effect of double-strand break repair in cells with homologous chromosomes might be recombination. Given this fact, why did there have to be some type of ecological selection for recombination? Selection for the maintenance of the chromosome would suffice. As of the first years of the 21st Century, evidence that chromosomal recombination is a by-product of DNA repair has continued to grow. This is not to say that we are arguing the evolution of sex is *only* determined by selection for DNA repair. Rather, we are making the point that biologists are now considering a much greater diversity of evolutionary mechanisms for sex, including mechanisms at multiple levels of the biological hierarchy.

Growing information about transposable elements made it clear by 1980 that some DNA molecules could copy and spread among genomes as a result of selection on such DNAs to spread within and among genomes, not as a result of selection between organisms. Furthermore, the spread of such parasitic elements depends critically on the occurrence of sexual recombination and horizontal gene transfer. So long as cells and organisms did not recombine DNA with each other, transposable elements would be selected to control their proliferation within genomes.

This paved the way for the proposal that sex originated as a device for parasitic DNAs to spread from cell to cell. Experiments with autonomous conjugative elements with deleterious effects showed that such parasitic elements could spread *de novo* in bacteria, making it plausible that ancestral unicellular eukaryotes may have evolved sex by analogous means.

The problem of the maintenance of sex also was attacked from the vantage point that sex didn't have to be beneficial to be maintained. It was shown mathematically that, when potentially asexual females suffer from continued fertilization by males, anisogamous sex could be maintained even if it was not evolutionarily beneficial in itself. Recently, the natural history of sex has been interpreted in terms of the ability of new parthenogens to avoid sex with males. It is a notably inelegant feature of this research that it brings in genomic detail as well as historical effects in the analysis of the evolution of sex.

Homology modelling-Tool kits of recent area of Human genetics

In the 1980s and 1990s, biologists began discovering deep homologies in body patterning genes like *Hox* genes. The view that many derived from the Modern Synthesis had been that organismal structures like segmented bodies, eyes, limbs,

and hearts, evolved essentially *de novo*, multiple times, independently in various lineages, in close conformity with the requirements of function. Like the concept of genes in the days preceding the advent of modern genomics, the common assumption was that organismal structures were simply traits of species. Species might have a particular morphological trait for a particular function, or they might not have that trait if that function was not selectively favored. Few paid attention to the intermediate possibility – that morphological traits themselves are a complex patchwork of shared and derived elements, and thus are more analogous to baroque ornamentation. For example, 20th Century biologists often assumed that distinct developmental processes often arose separately in different lineages – especially when comparing different phyla, which were regarded as having different "body plans". But the discovery of conserved developmental genetic processes for patterning the bodies of taxonomically and morphologically disparate organisms forced biologists to consider common descent at deeper levels of biological organization.

New Rules for Biology

While the nature of the transition from 20th Century biology to 21st Century biology seems clear to us in both overview and for some particular applications, the most important changes defining this transition might be usefully listed:

- We should no longer assume that a biological research problem can be satisfactorily solved using the intellectual tools from only one biological discipline. This might be the case, but it is likely that most valid one-discipline solutions are the 'low-hanging fruit' already picked by 20th Century biology.
- We cannot assume in advance the existence, level, or focus of natural selection on a particular biological attribute. The attribute could arise from (i) accidental evolutionary events, (ii) selection on a DNA sequence that evolves independently of the replication of its host, or (iii) unanticipated pleiotropic effects of selection on other characters.
- We cannot assume fixed relationships between structures and functions. Most evolutionary histories are complex, with structures adopting different roles in the course of their evolution, and functions being underlain by different structures during the course of their evolution. That is, the causal hierarchies of biology are not necessarily fixed, even in overall structure.
- We cannot assume the stability or distinctness of rate among biological processes. Genetic evolution may occur on a comparable time-scale to that of ecological change, for example.
- Unlike stereotyped scientific practice, 21st Century genomic technologies and techniques of data analysis give us the opportunity to be "led" by the data in an hypothesis-free manner. When appropriate, we may "listen" to the data, rather than forcing a particular hypothesis on it.
- In the same spirit, experimental evolution and experimental ecology let organisms show us how they respond to particular biological regimes, which is complementary to performing critical experimental tests of a priori hypotheses.
- Numerical exploration of theoretical models for complex biological mechanisms will be more informative than assuming away most of the biology in order to achieve a mathematically-refined global analysis. Again, like genomics and experimental evolution, such numerical work can be exploratory and open-ended, rather than seeking a pre-determined outcome. The low cost of computation makes such open-minded numerical work vastly more feasible.
- Modern statistical and bioinformatic techniques are likewise considerably more powerful, which allows us to collect and analyze information on a vast scale. These data allow a more thorough exploration of the complexities of biology.

Some may feel that the view of life supplied by nascent 21st Century biology is painfully complicated, if not perverse. For our part, we think that the historical complexity and versatility that we now know to characterize life are inspiring and challenging. In many ways, we are reminded of the transition from the complacent physics of the 19th Century to the turbulent modern physics after Einstein's 1905 scientific revolution. The old Newtonian certainties were destroyed, but in their place physicists found both a better foundation for their field and a spectrum of exciting research problems. We feel that biology has found its way to the same level of maturity.

Discussions and conclusion

Present-day biologists are instead dealing with the C-value paradox in terms of the evolution of non-coding DNA, the proliferation of transposable elements, and kindred phenomena. This does *not* imply that evolutionary theory simply no longer applies. Instead, new evolutionary theories have been developed, such as Lynch and Conery's theory of reduced effective population size leading to less efficient selection against the proliferation of non-essential, even deleterious, DNA sequences, and thus greatly expanded genome sizes in endemic species with small population sizes. It is not our concern to argue for or against this particular theory, only to point out that this scientific debate was not a live issue for biologists in 1970. And it certainly wasn't an obvious corollary of the systems biology perspective then extant, either.

The fundamental landscape of biology is undergoing a major upheaval, much as it did in the first decades of the 20th Century [1]. This upheaval will take time to fully reveal its implications. The sequencing of several important eukaryotic genomes around the year 2000 was no more an instant transformation of biology than the re-discovery of Mendel was in 1900. Decades are required to change the foundations of a scientific field as complex as biology. Furthermore, the new biology is not without its anticipatory prophets, and we do indeed consider Barbara McClintock, Sewall Wright, Ludwig von Bertalanffy, C.H. Waddington, Emile Zuckerkandl and others to be such. But biological research is undergoing a period of rapid, and profoundly beneficial, transformation reminiscent of the events surrounding the Modern Synthesis. We further hope that biology curricula and textbooks will eventually come to reflect this disciplinary transformation, much as the teaching of biology was reformed to reflect the Modern Synthesis during the middle part of the 20th Century.

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