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By Bob Grant

Should Evolutionary Theory Evolve?

Some biologists are calling for a rethink of the rules of evolution.

Evolution, by its very nature, is a dynamic process. But just as fluid are humankind's efforts to understand, describe, and conceptualize that process. Out went Lamarck, in came Darwin. Mendel's insights set the rules for genetic inheritance, then certain exceptions to Mendel's rules materialized. So forth and so on.

The most recent, broadly recognized codification of evolutionary theory is known as the Modern Synthesis. After nearly 3 decades of theorizing, experimentation, and writing by paragons of evolutionary thought—Ronald Fisher, J.B.S. Haldane, and Sewall Wright, to name but a few—British biologist Julian Huxley cemented the term in 1942 with the publication of his book *Evolution: The Modern Synthesis*. The theoretical framework brought Darwin's ideas into the 20th century and married them to the gene's-eye-view of biology that was emerging at the start of the century, with the rediscovery of Gregor Mendel's inheritance research.

According to the Modern Synthesis, populations containing some level of genetic variation evolve via changes in gene frequency induced mostly by natural selection. Phenotypic changes are gradual, and speciation and diversification into higher taxonomic levels come about over long periods of change. These ideas have remained largely unchallenged for more than a half-century.

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But since the 1940s, science's concept of evolutionary dynamics has, well, evolved. Indeed, these days, calling the Modern Synthesis "modern" might be a stretch.

More Slowly?

Some evolutionary biologists say that the body of knowledge concerning evolutionary processes has simply outgrown the confines of the Modern Synthesis, which was crafted before science had a strong grasp of genomics, molecular biology, developmental biology, and other, more recently derived disciplines, such as systems biology.

City University of New York evolutionary biologist and philosopher Massimo Pigliucci insists that expanding evolutionary theory so that it captures recent insights doesn't mean throwing out 150 years of sound thinking. "We're not talking a revolution," he says. "Nobody's going to deny Darwin and all that stuff. But it has been several decades since the last time evolutionary biologists actually sat around the table, so to speak, and came up with the basic principles of their field."

In the summer of 2008, Pigliucci and his colleague, University of Zurich researcher Gerd Müller, invited 14 other researchers to the Konrad Lorenz Institute in Altenberg, Austria, near Vienna, to discuss how to rethink the Modern Synthesis. This spring, Müller and Pigliucci plan to publish a tome that arose from the Altenberg meeting, with chapters written by its attendees. It will be titled, *Evolution: The Extended Synthesis*. "The word 'extended' is important because it implies quite clearly that there is no rejection of the previous synthesis," Pigliucci says. "There is no rejection of the Modern Synthesis. There is no rejection of Darwinism. It's an extension of it—we think a significant extension in a lot of different directions which neither Darwin nor the Modern Synthesis could have possibly thought of."

Of course, not all biologists agree. Critics argue, for instance, that the field has been adapting for years, and a handful of new data doesn't warrant formally expanding a theory that forms the field's fundamental framework.

To judge for yourself, here are just a few of the concepts that Pigliucci, Müller, and other Altenberg meeting attendees believe evolutionary theory should adapt to include.

Evolvability

What is it?

Evolvability, taken simply, means the ability to evolve or to produce heritable, phenotypic variation. Some lineages are suspected to be more evolvable than others, meaning that dramatically different phenotypes—what University of Vienna evolutionary biologist Andreas Wagner calls "game changers"—may arise quicker in these lineages, independent of how much baseline genetic variation is present. In this way, researchers who study evolvability consider it a metaproperty that, itself, can evolve.

Yeast colonies carrying the [PSI$^+$] prion assume a puckered phenotype

Courtesy of Susan Lindquist

Why is the Modern Synthesis lacking?

The Modern Synthesis addresses evolvability in a population genetics sense—some populations have more genetic variation than others and would therefore be expected to generate phenotypic variation at a faster rate. But it does not treat evolvability as a distinct trait of those populations, independent of the underlying genetic variation.

According to Wagner, the Modern Synthesis also fails to adequately conceptualize the major evolutionary milestones (i.e., photosynthesis, flight, multicellularity) that stand out against a backdrop of slow and steady evolution. "You can look at the history of life as the evolution of game-changing innovations," he says. "If you're interested in evolutionary innovation, you can't get away anymore with a very simple, one-dimensional notion of a phenotype. Now we can recognize that there is a deficiency in the Modern Synthesis."

[PSI$^+$] could act as a "capacitor and potentiator" of evolvability. — Susan Lindquist

Where is the evidence?

"There has been a surge in theoretical studies of evolvability, and now we're beginning to look at some of the first empirical results coming out," Pigliucci says.

Validating the concept of evolvability hinges on deciphering the mechanism for evolvability's inheritance. What property might bestow on its holders the ability to evolve at a different speed than other species? One researcher claims to have found an answer. Susan Lindquist, a molecular biologist at the Massachusetts Institute of Technology who specializes in protein folding, says that [PSI$^+$]—a prion that results from the misfolding of the Sup35 protein in the yeast *Saccharomyces cerevisiae*—may serve as a conduit for the evolution of novel traits and a molecular vehicle for evolvability.

Sup35, the functional domain of which is highly conserved in a variety of organismal groups, normally serves as a translation termination factor. That is, it helps ribosomes recognize stop codons on mRNA and therefore mediates the normal translation of proteins. The misfolded [PSI$^+$] cannot perform this function correctly, and yeast cells containing aggregations of the prion read through about 5 to 10 percent of stop codons in a given cell. This means that cells with [PSI$^+$] could express normally silent sequences beyond the c termini of genes or express

different levels of normal proteins, because without a stop codon, mRNA may stick around longer in cells, enabling the cells to express more protein. These cells end up expressing a wide variety of phenotypes that essentially can't arise in normal cells.

When Lindquist coaxed several genetic strains of *S. cerevisiae* into carrying [PSI+], then subjected them and genetically identical cells with normal Sup35 to a variety of growth conditions, she saw phenotypic variation in the [PSI+] cells come out of the woodwork.[1] In nearly half of the conditions Linquist tested, having [PSI+] led to significant phenotypic effects in some of the strains. [PSI+] was essentially uncovering previously hidden phenotypic variation in the yeast cells, and in some of the conditions to which they were subjected this variation was advantageous.

This means that [PSI+] could act as what Lindquist calls a "capacitor and potentiator" of evolvability, because switching into the [PSI+] state makes a yeast population more likely to produce phenotypic diversity when environmental conditions change.

What's more, Lindquist showed that the [PSI+] prion can be passed from mother to daughter yeast cells when they divide either mitotically or meiotically. Even if a lineage were to revert back to the non-prion state (which occurs naturally once every 100,000–1,000,000 cell divisions or so, depending on the strain), selection may have fixed the advantageous adaptations that resulted from the [PSI+] read-throughs. Linquist says she's looking at differences in [PSI+] states among wild fungal populations now.

These results are interesting, but might create few waves in the flow of evolutionary history, says Indiana University evolutionary biologist and population geneticist Michael Lynch. "It's an observation that if you stress the hell out of an organism, it does weird things," he said. "There's no question you get more extreme phenotypes than you would in a benign environment. But there's no evidence whatsoever that the tendency for organisms to do this kind of thing when they're stressed is there because natural selection favored it."

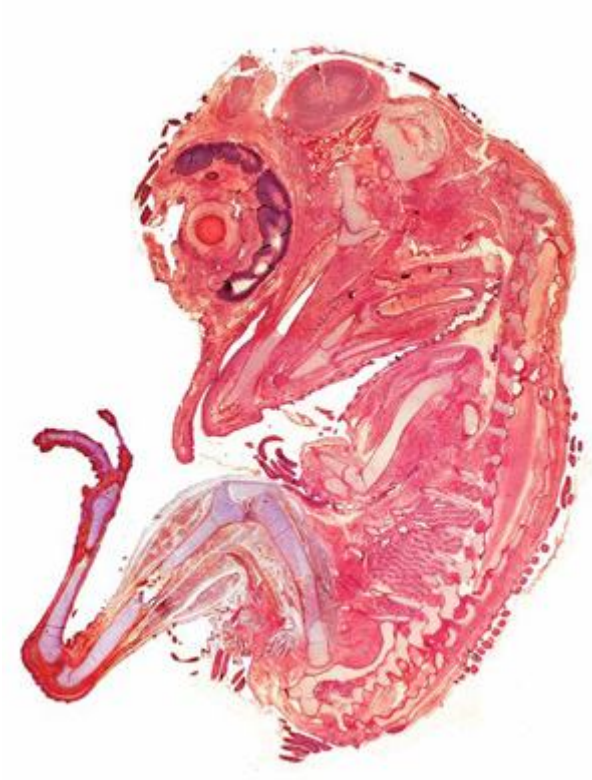
Facilitated Variation

What is it?

Facilitated variation is a simple way to refer to a complex set of physical and chemical forces, usually coming into play during development, that can affect structures and functions in a way that goes beyond simple, one-to-one (genome-to-phenotype) translation.

Researchers have proposed several mechanisms for facilitated variation, from the oscillation of certain regulatory elements that can affect segmentation in embryos to chemicals acting during development that can give organisms patterns of stripes or spots.

Facilitated variation may also spark quicker evolutionary change than would



A developing finch embryo is shaped by chemical and physical forces before it is subjected to selection

result from random mutations, because developmental changes can create additional phenotypes upon which selection can act.

Why is the Modern Synthesis lacking?

The intricacies of developmental biology did not feature prominently in the formulation of the Modern Synthesis. Genotypes were assumed to translate more or less directly into phenotypes, and evolutionary change stemmed from the slow, gradual accumulation of random genetic mutations. But with the rise of the EvoDevo field—which incorporates the vagaries of embryonic development into a broader view of evolution—this simplified picture is becoming more complex. Stuart Newman, developmental biologist at New York Medical College, says that complex gene interactions and sudden morphological reorganizations during development, to which the EvoDevo perspective has opened a window, are not dealt with sufficiently by the Modern Synthesis. “It turns out that in many experimental and natural setups, you find discordance between genotype and phenotype,” he says.

Where is the evidence?

Like many of the concepts considered part of an Extended Synthesis, facilitated variation is largely a theoretical concept. Pigliucci himself admits that facilitated variation is a concept in waiting for illustration in natural systems. However, a recent example of the phenomenon at work in natural populations comes from a bird species that is invading new North American territories and habitats, while displaying remarkably rapid adaptive change.

Alexander Badyaev, an evolutionary biologist at the University of Arizona, has been studying little songbirds called house finches, which were native to deserts in the American Southwest and Mexico before they began spreading throughout the United States in the 1940s through the pet trade and natural dispersal.

Badyaev tracked the birds through 19 generations over a span of 15 years at a study site in Montana, and found that the population was developing unique beak morphologies as adaptations to the new environment at a surprisingly rapid rate. According to the Modern Synthesis, beak shape should change as random

mutations create a pool of phenotypes, which eventually get whittled down to those that are most advantageous. But the new habitats were so different from their original habitats, the only way for finches to survive would be if their beak shape had changed rapidly—too rapidly to have resulted from just random mutations. If that were the only way for them to evolve, the original desert-dwelling house finch populations would have been wiped out by the pressures present in their new habitats, Badyaev reasons. Instead, they're thriving.

"You're not only what you eat, but what your parents ate, and potentially what your grandparents ate." — Randy Jirtle

How was this possible? To answer the question, Badyaev looked into the developmental patterns that give rise to the beak's structure in house finches. He found a complex interplay of processes, such as the migration of five islands of neural crest cells that constitute skeletal beak components in the embryo. Interacting embryonic processes result in an initial level of phenotypic variation greater than what would be predicted from underlying genotypic variation alone.[2]

Because the drivers of this baseline phenotypic variation acted during development in the egg, Badyaev says, selection was essentially blind to the creation of this initial pool of phenotypic variation. It was only later, when young birds began feeding on the foods available in their new habitat, that selection could determine which beaks were more or less suited to the environment. "Selection does not see the developmental process by which this beak was produced," he notes. "But it's exactly there that resides the opportunity for diversification."

Multilevel Inheritance

Epigenetic changes make mice that are larger and yellower than their genetically identical counterparts

Courtesy of Jirtle Lab

What is it?

Multilevel inheritance describes passing on phenotypic changes to subsequent generations in ways that lie outside the genetic code of DNA. Chief among these modes is epigenetic inheritance, where elements such as chromatin structure, remodeled histone proteins, or methylated DNA—often mediated by environmental conditions—can be passed from parent to offspring without changing the actual sequence of the inherited genome.

Why is the Modern Synthesis

lacking?

Though science did not have a clear concept of the molecular mechanics involved in genetic inheritance at the time its architects were constructing the Modern Synthesis, they believed genes were the primary units of inheritance. Evolution was defined as a change in the genetic composition of populations.

Where is the evidence?

For epigenetic inheritance to play a profound role in evolutionary change, scientists must demonstrate that the changes last, are stable, and cause heritable effects through several generations.

Last year, Eva Jablonka, an epigeneticist at Tel Aviv University in Israel, published a review article in the Quarterly Review of Biology that details more than 100 published cases of transgenerational epigenetic inheritance, documented in groups from bacteria and protists to plants and animals.[3]

In one recent experiment, two groups of genetically identical Arabidopsis plants were exposed to either hot or cold conditions for two (P and F1) generations. The next generation (F2) from both experimental groups was grown at normal temperatures, but the offspring (F3) from both groups were grown in either hot or cold conditions. The F3 plants that were grown in hot conditions and descended from P and F1 plants also grown in hot conditions produced five times more seeds than did the F3 plants grown in hot conditions but descended from cold-treated ancestors.[4] Because the chance of accumulating mutations within just two generations that led the heat-conditioned plants to thrive in hotter conditions was essentially nil, the authors conclude that inherited epigenetic factors affecting flower production and early-stage seed survival in those plants had to be at play.

"The Modern Synthesis was never monolithic. I don't think that we need to talk about it as a major movement that's happening now. It's happening all the time." — Richard Dawkins

The poster child for tractable epigenetic changes in mammals is the yellow agouti mouse that Randy Jirtle studies at Duke University. These fat, yellow mice owe their appearance to epigenetics, specifically, an epigenetic modification that removes methyl groups from the normally methylated agouti gene. When this modification occurs shortly after fertilization in a developing mouse fetus, the mouse will exhibit the yellow fur and high-weight phenotype, as well as an increased risk of developing cancer and diabetes. Its genetic code, however, remains unchanged from normal mice.

Jirtle and his colleagues have successfully jiggered the methylation or demethylation of the agouti gene simply by altering the nutritional intake of nutrients that serve as methyl group donors in mouse mothers.[5] They've shown that upping the amount of choline, betaine, folic acid, and vitamin B12 in the diet of pregnant yellow agouti mice can reduce the incidence of the deleterious

phenotype in offspring by allowing for the remethylation of the agouti gene. But should those mice be born with the agouti phenotype, they can pass that deleterious epigenetic trait onto their offspring, regardless of their diet during pregnancy. This means that environmental conditions (in this case, diet) can cause phenotypic changes that can be passed on through cell division and mating. "You're not only what you eat, but what your parents ate, and potentially what your grandparents ate," Jirtle says.

But this mode of inheritance needs to penetrate more than a few generations before it earns a spot in evolutionary theory, says Vincent Colot, a molecular geneticist who studies chromatin-based epigenetic inheritance in Arabidopsis at Ecole Normale Supérieure in France. Epigenetic inheritance is widespread, he says, but that doesn't mean it lasts and causes evolutionarily meaningful effects. "If [epigenetic changes are] not stable for 20 to 30 generations, is it relevant to evolution and adaptation?" asks Colot. "That's not clear yet."

What the critics say:

Massimo Pigliucci and his colleagues emphasize the fact that they suggest expanding—not revising or reimagining—the Modern Synthesis, but several evolutionary biologists bristle at the suggestion that (even subtle) official modifications are needed.

There's no need to formally revisit the Modern Synthesis, argues Douglas Futuyma, an evolutionary biologist at the State University of New York at Stony Brook, because evolutionary theory is flexible enough to incorporate well-substantiated new ideas as they arise. "I think the evolutionary synthesis has already been extending itself almost continually for the last few decades," he says. "I'm not saying that there's nothing interesting [in the Extended Synthesis]. I just think the self-conscious labeling of it as a new point of view or a challenge to the old, most people don't buy."

For example, Futuyma points to the groundbreaking, mid-century discovery and description of transposable elements by famed geneticist Barbara McClintock. When she found that parts of the genome could jump around and cause mutations or change gene expression, skewing Mendelian ratios and inheritance patterns, this disrupted the predictable Mendelian system that went into building the Modern Synthesis. Here, evolutionary biology absorbed and incorporated this principle without the need for a formal reconsideration of evolutionary theory. "Basically, population geneticists took the standard models of mutation and selection, and adapted them to this new phenomenon," Futuyma says. "This kind of addition has gone on constantly throughout my entire career."

Richard Dawkins, renowned evolution popularizer, agrees that science's fundamental understanding of evolutionary theory is not in need of official expansion. "I think that we have already expanded the Modern Synthesis," he says. "The Modern Synthesis was never monolithic. I don't think that we need to talk about it as a major movement that's happening now. It's happening all the time."

Other skeptics cite the dearth of concrete evidence for some of the concepts that Pigliucci and his colleagues suggest using to expand the Modern Synthesis, such as the lack of sufficient examples of transgenerational epigenetic effects. "Usually epigenetic characters aren't inherited past one or two generations," says Jerry Coyne, a University of Chicago evolutionary geneticist who studies speciation using Drosophila as a model organism. "Given the billions of characters that have evolved over evolutionary time, that's not going to change our concept of evolution."

"One has to have a certain degree of reservation about claims that are made on the basis of one or two examples that are going to be a major challenge or a new expansion," Futuyma adds. "Otherwise you're talking about jumping on one bandwagon after another."

The push for a radical re-think of evolutionary theory is far from reaching a critical mass, agrees Michael Lynch from Indiana University. "There's no general clamoring in the community for a new synthesis," he says. "There are more things to explain, but I think a lot of us are happy with the fundamental framework to do that explaining in."

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