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The Origins of Form

Ancient genes, recycled and repurposed, control embryonic development in organisms of striking diversity

When we no longer look at an organic being as a savage looks at a ship, as at something wholly beyond his comprehension; when we regard every production of nature as one which has had a history; when we contemplate every complex structure and instinct as the summing up of many contrivances, each useful to the possessor ... how far more interesting, I speak from experience, will the study of ***natural history*** become!

--Charles Darwin, the Origin of Species, 1859

Darwin closed the most important book in the history of biology by inspiring his readers to see the grandeur in his new vision of nature--in how "from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved." For the next century, many kinds of biologists--geneticists, paleontologists, taxonomists--sought to test and expand that vision. The result of their work was the so-called modern synthesis, which organized the basic principles that have guided evolutionary biology for the past fifty years.

In spite of the labels "modern" and "synthesis," however, an important element was still missing from evolutionary theory. Biologists could say, with confidence, that forms change, and that natural selection is an important force for change. Yet they could say nothing about how that change is accomplished. How bodies or body parts change, or how new structures arise, remained complete mysteries.

Contemporary biologists are no longer savages staring at passing ships. In the past twenty years biologists have gained a revolutionary new understanding of how animal and plant forms and their complex structures arise and evolve. The key to the new understanding is development, the way a single cell becomes a complex, multibillion- or trillion-celled organism. And development is intimately linked to evolution, because all changes in form come about through changes in development. As an animal embryo grows, it must make countless "decisions" about the number, position, size, and color patterns of body parts. The endless combinations of such decisions made during development have led to the great variety of animal forms of the past and present.

Advances in the new science of evolutionary developmental biology--dubbed "evo-devo" for short--have enabled biologists to see beyond the external beauty of organic forms into the mechanisms that shape their diversity. Much of what has been learned, about animal forms in particular, has been so stunning and unexpected that it has profoundly expanded and reshaped the picture of how evolution works. In the same stroke, evo-devo delivers some crushing blows against the outdated rhetoric of those who doubt that complex structures and organisms arise through natural selection.

Darwin always insisted that embryology was crucial to understanding evolution. In a letter to the American botanist Asa Gray, shortly after the publication of the Origin of Species, he lamented, "Embryology is to me by far the strongest single class of facts in favor of change of forms, and not one, I think, of my reviewers has alluded to this." Yet the puzzle of how a single egg gives rise to a complete individual long stood as one of the most elusive questions in all of biology.

Many biologists once despaired that development was hopelessly complex. Each kind of animal, they thought, would require its own unique developmental explanation. With the advent of genetics, biologists came to realize that genes must be at the center of the mysteries of both development and evolution.

After all, butterflies look like butterflies, elephants look like elephants, and we look the way we do because of the genes we each carry. Those physical resemblances, and many other attributes, would surely be traceable to the genes within each species.

The challenge, given such a focus on genes, was that until relatively recently no one knew which of the thousands of genes in every animal shape its formation and appearance. The impasse was finally broken by the humble fruit fly. Geneticists devised schemes to find the relatively small fraction of genes that control the patterning of the fly's body and the formation of its parts.

Just as the invention of the telescope revolutionized astronomy, new technologies were pivotal to conceptual breakthroughs in developmental biology. New techniques for cloning and manipulating genes, together with new kinds of microscopes, enabled the body-building genes to be observed in action. Chemical changes in an embryo could be visualized long before the appearance of physical structures. Workers could thereby directly observe the earliest events in the formation of segments, limbs, or a brain [see photomicrographs on next page].

I realize it may be hard to get excited about how a maggot develops. What can that teach us about the more majestic creatures people care about, such as mammals, the rest of the animal kingdom, our own species? Indeed, the common perception twenty years ago--reinforced by a wide cultural divide between biologists who worked with furry animals and those who worked with bugs or worms--was that the rules of development would differ enormously among such different forms.

The body parts of fruit flies, for instance, would not appear to have much in common with our own. We don't have antennae or wings. We walk around on two long, bony legs, not six little ones reinforced by an exoskeleton. We have a single pair of movable, camera-type eyes, not compound bug eyes staring out from a fixed position. Our blood is pumped by a four-chambered heart through a closed circulatory system with arteries and veins; it does not just slosh around in our body cavity. Given such great differences in structure and appearance, one might well conclude that there is nothing to learn from the study of a fly about how our own organs and body parts are formed. But that would be so wrong.

The first and perhaps most important lesson from evo-devo is that looks can be quite deceiving. Virtually no biologist expected to find what turned out to be the case: most of the genes first identified as body-building and organ-forming genes in the fruit fly have exact counterparts, performing similar jobs, in most mammals, including humans. The very first shots fired in the evo-devo revolution revealed that despite their great differences in appearance, almost all animals share a common "tool kit" of body-building genes. That discovery--actually a series of discoveries--vaporized many previous ideas about how animals differ from one another.

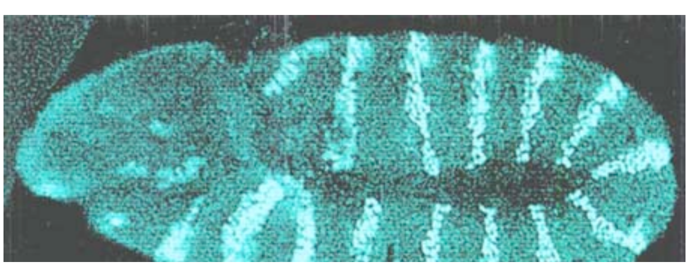
For example, the origin of eyes has received a lot of attention throughout the history of evolutionary biology. Darwin devoted considerable effort in Origin to explaining how such "organs of extreme perfection" could evolve by natural selection. What has puzzled and intrigued biologists ever since Darwin is the variety of eye types in the animal kingdom. We and other vertebrates have camera-type eyes with a single lens. Flies, crabs, and other arthropods have compound eyes in which many, sometimes hundreds, of individual ommatidia, or unit eyes, gather visual information. Even though they are not close relatives of ours, squids and octopuses also have camera-type eyes, whereas their own close relatives, the clams and the scallops, have three kinds of eyes--camera, compound, and a mirror-type.

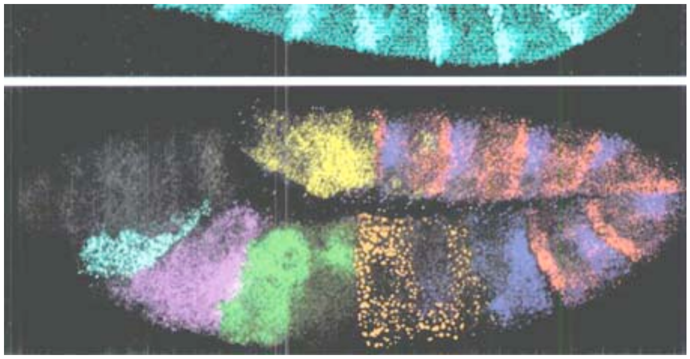
The great diversity and crazy-quilt distribution of eyes throughout the animal kingdom was, for more than a century, thought to be the result of the independent invention of eyes in various animal groups. The late evolutionary biologist Ernst Mayr and his colleague L. von Salvini-Plawen suggested, on the basis of cellular anatomy, that eyes had been invented independently between some forty and sixty-five times. Discoveries in evo-devo have forced a thorough reexamination of this accepted idea.

In 1994 Walter Gehring and his colleagues at the University of Basel, Switzerland, discovered that a gene required for eye formation in fruit flies is the exact counterpart of a gene required for eye formation in humans and mice. The gene, dubbed Pax-6, was subsequently found to play a role in eye formation in a host of other animals, including a species of squid [see illustration on opposite page]. Those discoveries suggested that despite their vast differences in structure and optical properties, the evolution of different eyes has involved a common genetic ingredient.

Ernst Mayr once wrote:

If there is only one efficient solution for a certain functional demand, very different gene complexes will come up with the same solution, no matter how different the pathway by Which it is achieved. The saying "Many roads lead to Rome," is as true in evolution as in daily affairs.





Chemical changes in various regions of an animal embryo (here, a developing fruit fly) reflect the activities of tool-kit genes; the changes can be imaged by laser-dye probes long before the physical form of an animal emerges. The upper image shows the pattern of activity of a single gene, Engrailed, that marks the back end of each developing segment of the insect's body. In the lower image a different set of laser-dye probes reveal where each of seven Hox genes are active, corresponding to various parts of the body; for example, bright yellow indicates the segments that will form the fly's rear end, whereas fuchsia and light blue mark segments that will form mouthparts.

But Mayr's view is incorrect. The architects of the modern synthesis expected the genomes of vastly different species to differ vastly. They had no idea that such different forms could be built with similar sets of genes. Stephen Jay Gould, in his monumental work, The Structure of Evolutionary Theory, saw the unexpected discovery of common body-building genes as overturning a major tenet of the modern synthesis.

There are not as many roads to Rome--or in other words, evolutionary paths to eyes and other complex structures--as biologists once thought. Natural selection has not repeatedly forged eyes from scratch. Rather, eye formation has common genetic ingredients, and a wide range of eye types incorporate parts, such as photoreceptor cells and light-sensing proteins, that have long been under the command of the Pax-6 gene.

Other tool-kit genes have been identified that take part in building various kinds of limbs, hearts, and other structures. Because parts of the genetic tool kit are shared among most branches of the animal kingdom, they must date back, at least, to some common ancestor of those branches. That would place their origin far back in time, before the Cambrian explosion that marked the emergence of large, complex animal bodies, more than 500 million years ago.

Here, then, is another somewhat counterintuitive insight from evo-devo: One might think that increases in animal complexity and diversity would be driven by the evolution of new genes. But it is now clear that most body-building genes were in place long before most kinds of animal body plans and complex organs emerged.

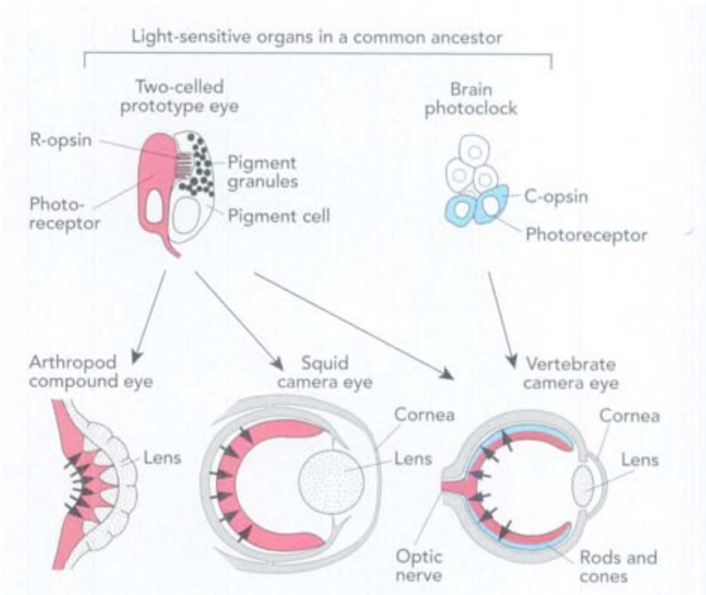
The discovery of such an ancient genetic tool kit, as exciting and rewarding as it is, raises a conundrum. If the sets of body-building genes among animals are so similar, how do such vast differences in forms arise?

Studies of many animal groups have shown that the diversity arises not so much from the content of the tool kit, but from how it is used. Various animal architectures are the products of applying the same genetic tools in different ways. For example, one of the most obvious features of large, complex animals such as vertebrates (fishes, amphibians, reptiles, birds, mammals) and arthropods (centipedes, spiders, crustaceans, insects) is their construction from repeating parts. Segments are the building blocks of arthropod bodies, vertebrae the building blocks of backbones. In both cases, important structures emerge from subsets of these building blocks--the many appendages of arthropods from their segments, the ribs of vertebrates from the vertebrae.

One of the dominant themes in the large-scale evolution of these animal bodies is change in the number and kind of repeating parts. The major features that distinguish classes of arthropods are the number of segments and the number and kind of appendages. Similarly, vertebrates differ fundamentally in the number and kind of vertebrae (cervical, thoracic, lumbar, sacral).

Extensive study of arthropod and vertebrate development has shown that those major features depend on a set of tool-kit genes called Hox genes. In general, Hox genes shape the number and appearance of repeated structures along the main body axes of both groups of animals. Individual Hox genes govern the identity of particular zones along that main body axis, and determine where various structures will form. A large body of work--on birds, frogs, mammals, and snakes, as well as insects, shrimp, and spiders--has proved that shifts in where Hox genes are expressed in embryos are responsible for the major differences among both vertebrates and arthropods.

Those shifts account, for instance, for the way a snake forms its unique long body, with hundreds of rib-bearing vertebrae and essentially no neck, in contrast to other vertebrates [see photograph on next page]. The shifts explain why insects have just six legs and other arthropods have eight or more. The new imagery of evo-devo can pinpoint when and how the development of these animals diverges. The study of Hox genes has shown how, at an entirely new and fundamental level, these animals are the products Of variations on ancient body plans--not wholly independent inventions.

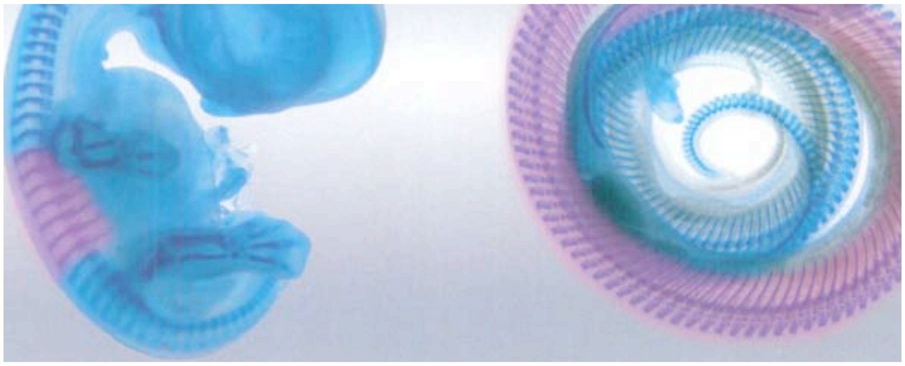


Formation of a vast range of eye types--the camera eyes of vertebrates and squids as well as the compound eyes of flies--is controlled by a single gene, called Pax-6. Recognizing the role of the Pax-6 gene has been a key piece of evidence in tracing the evolution of the eye. Each animal eye evolved from simpler photoreceptive structures in a distant common ancestor of the arthropods, cephalopods, and vertebrates. The ancestor possessed two kinds of light-sensitive organs (upper half of diagram), each one endowed with a distinct type of photoreceptor, as well as with light-sensitive proteins called R-opsin and C-opsin, respectively. One organ was a simple two-celled prototype eye; the other, called the brain photoclock, was a part of the animal's brain and played a role in running the animal's daily clock. The arthropod and squid retinas (red) incorporated the photoreceptor from the simple prototype eye, whereas the vertebrate eye incorporated both kinds of photoreceptor into its retina (red and blue). Rods and cones, the photoreceptors of human vision, are shown in blue. Their orientation with respect to the light source (black arrows) is opposite that of the photoreceptors in the arthropod and squid eyes.

Shifts in the expression of tool-kit genes during development not only account for large-scale differences in animal forms; they can also explain differences among closely related species, or even populations of the same species. For example, the three-spined stickleback fish occurs in two forms in many lakes in northern North America [see photograph on opposite page]. One is a short-spined, shallow-water, bottom-dwelling form. The other is long-spined and lives in open water. The two forms have evolved rapidly in these lakes since the end of the last ice age, about 10,000 years ago. The length of the fishes' pelvic spine is under pressure from predation. In the open water, long spines help protect the stickleback from being swallowed by large predators. But on the lake bottom, long pelvic spines are a liability: dragonfly larvae seize and feed on young sticklebacks by grabbing them by their spines.

Pelvic spines are part of the fishes' pelvic fin skeleton. Short spines in bottom-dwelling populations can be traced to a reduction in the development of the pelvic-fin bud in the embryo. David Kingsley, a geneticist at Stanford University, Dolph Schluter, a biologist at the University of British Columbia in Vancouver, and their collaborators have demonstrated that the change in spine length in short-spined sticklebacks can be traced to one specific tool-kit gene. The expression of the gene is altered so as to reduce the pelvic fin bud and, ultimately, the pelvic skeleton. The research has connected a change in DNA to a specific event in embryonic development, which in turn gives rise to a major adaptive change in body form that directly affects the ecology of a species.

The insights from the little three-spined stickleback may reach far beyond the fish's particular ***natural history***. The pelvic fin is the evolutionary precursor of the vertebrate hind limb. Hind-limb reduction is not at all rare in vertebrates. In two groups of mammals--the cetaceans (dolphins and whales) and the manatees--the hind limbs became greatly reduced in size as the animals evolved from their land-dwelling ancestors into fully aquatic forms. Similarly, legless lizards have evolved many times. The study of sticklebacks has shown how natural selection can lead to changes in major features of animal skeletons in a relatively short time.



Hox genes determine the form, number, and evolution of repeating parts, such as the number and type of vertebrae in animals with backbones. In the developing chick (left), the Hoxc-6 gene controls the pattern of the seven thoracic vertebrae (highlighted in purple), all of which develop ribs. In the garter snake (right), the region controlled by the Hoxc-6 gene (purple) is expanded dramatically forward to the head and rearward to the cloaca.

In addition to showing how evolution can change the number and kind of repeated body structures, evo-devo is shedding light on how novel structures and new patterns evolve. Bird feathers, for instance, are prominent examples of novelties that have emerged from changes in the ways tool-kit genes are expressed. So are the hands and feet of four-legged vertebrates, the insect wing, and the geometric color patterns on the wings of butterflies. It is easy to imagine that insects invented "wing" genes, or birds "feather" genes, or vertebrates "hand" and "finger" genes. But there is no evidence that such genes ever arose. On the contrary, innovation seems to be more a matter of teaching old genes new tricks.

The implications of that insight are particularly significant for understanding human evolution. We humans have long supposed that we hold some unique position in the animal kingdom. Surely we must be the most genetically well-endowed species. Yet the reality, as molecular biologists now know from sequencing the genomes of our own and other species, is that the genes of human beings are very similar in number and kind to the genes of the chimpanzee and of the mouse--in fact, of all other vertebrates. No one should expect to account for the evolution of bipedalism, language, speech, or other human traits by finding novel genes. A more likely explanation will come from understanding how our "old" genes, shared with other primates, mammals, vertebrates, and more distant animal relatives, have found new applications.

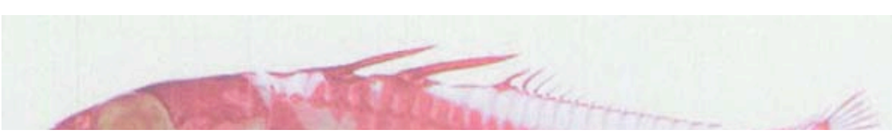
Darwin knew very well the difficulty people would have in picturing how complex structures or "contrivances" arose. In fact, as scholars such as the late Stephen Jay Gould and Randy Moore, a biologist at the University of Minnesota in Minneapolis, have pointed out, Darwin's choice of the term "contrivances," which appears fifteen times in Origin, was a deliberate one, used for rhetorical effect. It evoked a term the Reverend William Paley used in his 1802 book, Natural Theology. Paley saw the fashioning of "contrivances" in nature for specific purposes as revelations of God's design:

Contrivance must have had a contriver; design, a designer.... It is only by the display of contrivance, that the existence, the agency, the wisdom of the Deity, could be testified to his rational creatures.

Paley's argument is the essence of the idea of "intelligent design," now being touted as a new "alternative" to evolutionary science. Darwin admired Paley's book, and declared that he had virtually committed parts of it to memory. He then structured much of his argument in Origin as a direct refutation of Paley. Where Paley compared the design of the eye with the design of the telescope, Darwin explained how such contrivances arose by natural selection, without the intervention of a divine contriver.

But Darwin's explanation, no matter how brilliant, was founded on the extrapolation of natural selection over vast periods of time. He had no access to fundamental knowledge about the development of eyes or their detailed evolutionary history. The new knowledge of tool-kit genes makes it clear how such complex structures are built. Evo-devo makes it possible to connect this everyday, observable, and experimentally accessible process to the long-term process of evolutionary change. Evo-devo shows how complex forms and structures evolve, not only in ways that lead from one species to the next, but also in ways, such as the making of body plans, that have shaped the major differences in the higher taxonomic ranks.

The major tenet of the modern evolutionary synthesis is that the evolution of forms above the species level ("macroevolution") can be extrapolated from processes operating at the level of populations, within species ("microevolution"). For those who have doubted that the modern evolutionary synthesis could explain macroevolution, the new insights from evo-devo should resolve the question. Through the lens of evolutionary developmental biology, biologists can finally see beyond external forms into the very processes that forge them, completing the picture of how the endless forms of nature have been, and are being, evolved.



Major difference in the skeletal patterns of closely related populations reflects a difference in how a single tool-kit gene is used. Two forms of the three-spined stickleback fish (Gasterosteus aculeatus), which differ in the size of their pelvic fins, have repeatedly evolved in freshwater lakes. Long pelvic spines protect the open-water form from attack by other fish. Yet in the bottom-dwelling form (lower image), whose principal predator is dragonfly larvae rather than other fish, the tool-kit gene controlling the formation of the pelvic fin has been selectively turned off.

New patterns evolve when old genes "learn" new tricks. The eyespot patterns in the Morpho butterfly (below left) and the Caligo butterfly (above) evolved when genes that play a role in building other body parts and body patterns were co-opted. No new "spot" genes were involved.

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By Sean B. Carroll

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