

THE DARWIN COLLEGE LECTURES

# STRUCTURE

## In Science and Art

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# 1 The Structure of Life

SIMON CONWAY MORRIS

## Introduction

In a letter, written in 1683, Bernard de Fontenelle wrote, 'Do you say that beasts are machines just as watches are? Put a male dog-machine and a female dog-machine side by side, and eventually a third little machine will be the result, whereas two watches will lie side by side all their lives without ever producing a third watch'. More tersely, and much earlier, Aristotle had noted 'yet human is born from human, but not bed from bed' (*Physics*, III, 193b9). Such epigrammatic views of life may yet hold deeper truths, even though twentieth century thinking is more likely to dismiss them as conceits. Yet with the basis of life now firmly set in a molecular context, any concept of vitalism (or *élan vital*) has retreated beyond the fringes of scientific acceptability. By general agreement it is from a foundation of biochemistry that the properties of life must be in some sense emergent. To observe, however, does not guarantee an explanation. It is fashionable to scoff at creationists, yet the intricacies, interlocking and integration of life must still amaze. Similarly, to note that the structure of life is hierarchical gives us few *a priori* clues why it should be organised as it is.

What terms such as 'emergence' and perhaps 'hierarchy' might imply for a more complete understanding of the structure of life are potentially open to testing by at least two avenues. These are (a) the synthesis of life in a laboratory, or (b) discovery and investigation of an extraterrestrial biosphere. Both approaches are widely believed to be feasible scientific objectives, and until recently the former would have been deemed the first to succeed. The creation of life in the laboratory will be a triumph of chemistry. Recall, however, that any such synthesis would be by conscious manipulation and may have little bearing on the original course of events. The furore of interest in martian 'fossils' and the candidacy of moons such as Jupiter's Europa as abodes for extraterrestrial life are reminders against mundane complacency. And if not in our solar

system, then surely elsewhere in the galaxy and beyond? Possibly so, but the likelihood of extraterrestrial life may be much smaller than is often imagined.

That organisms are complex and integrated would have been evident to the first conscious humans, yet definitions of life remain elusive. Vitalism is discredited and so, at least at first sight, is the notion of organic design. The admiration of organic architecture, which has enjoyed a long-standing appreciation in terms of organismal construction, has been extended more recently to the microscopic and molecular intricacies of the cell. Yet, it is customary to deride the motives of the Reverend William Paley's hypothetical excursion across commons and heaths. It will be recalled that his perambulations were interrupted by the discarding of inanimate stones and the occasional stooping to pick up an abandoned watch. Paley's admiration of design, and by implication a Creator, are now dismissed. Now we are told the Watch-maker is blind, and as evolutionary biologists M. R. Rose and G. V. Lauder remind us there are rumours that the watch isn't even a Rolex. To mention organic design, evolutionary purpose or progress, or teleology is to invite ridicule and contempt.

Do these comments indicate a cryptic agenda, even to suggest that there is more to life than molecules? What emphatically is not in dispute is either the reality of organic evolution or the efficacy of natural selection. The former is uncontroversial, but can the latter process provide a unique and watertight mechanism? To the camp of hard- or ultra-Darwinists, notably Richard Dawkins and even more so Daniel Dennett, this mechanism provides a literally universal explanation. Notions encapsulated by such terms as particularity, pathway, constraint, direction and progress may be acknowledged, but play no effective part in the ultra-Darwinist vocabulary. Under such a regime it seems pointless to consider possibilities or outcomes. To be specific, in the case of humans, our world-view with moral responsibility and purpose has to be a neural wiring error. Predictably ultra-Darwinists protest, although why they should be allowed a special exemption to their materialist world-view is not clear. Indeed, it is difficult to avoid the conclusion that the world sketched out by Dawkins and Dennett is ultimately meaningless. Whether ultra-Darwinists like it or not, their speculations have political and social resonances. Even if they categorically deny whole swathes of human experience, one begins to wonder whether their world picture is quite as 'scientific' as they would claim. Consider, for example, the following passage:

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But hasn't there been a tremendous rebirth of fundamentalist faith in all these creeds? Yes, unfortunately, there has been, and I think that there are no forces on this planet more dangerous to us all than the fanaticisms of fundamentalism, of all the species: Protestantism, Catholicism, Judaism, Islam, Hinduism, and Buddhism, as well as countless smaller *infections*. Is there a conflict between science and religion here? There most certainly is. . . Safety demands that religions be put in cages, too – when absolutely necessary. . . . We tolerate the Hutterites because they harm only themselves. . . . Other religious memes are not so benign. The message is clear: those who will not accommodate, who will not temper, who insist on keeping only the purest and wildest strain of their heritage alive, we will be obliged, reluctantly, to cage or disarm, and we will do our best to disable the memes they fight for.

(D. C. Dennett, *Darwin's Dangerous Idea*, 1995, pp. 515–16; my emphasis)

Note the word 'infections', and then recall this piece of rant:

The discovery of the Jewish virus is one of the greatest revolutions that have taken place in the world. The battle in which we are engaged today is of the same sort as the battle waged during the last century, by Pasteur and Koch. How many diseases have their origin in the Jewish virus!

(H. R. Trevor-Roper, *Hitler's Table Talk 1941–1944*, 1988)

Not for a moment am I suggesting that Dennett himself has even the tiniest shred of sympathy for Hitler; indeed I would be astonished if he did not share our loathing of this malign individual. But biological theories are, in Dennett's view, paramount and, as this and accompanying passages imply, the fate of religions is evidently to become museum pieces before they presumably fade away in the new and unflinching light of materialism. Whether or not such views command assent, few would disagree that an understanding of evolution and the structure of life matter very much indeed. Self-evidently, we are both its product and remain embedded in it: the history of life permeates our entire frame. Yet uniquely, at least according to ancient tradition, we have been given responsibility.

These introductory remarks hint at a wider agenda, but I have neither space nor, more importantly, sufficient expertise to deliver a comprehensive analysis. To provide, however, some sort of focus to the remainder of this chapter let me now ask four specific questions, although here too it will become apparent that my answers remain drastically incomplete.

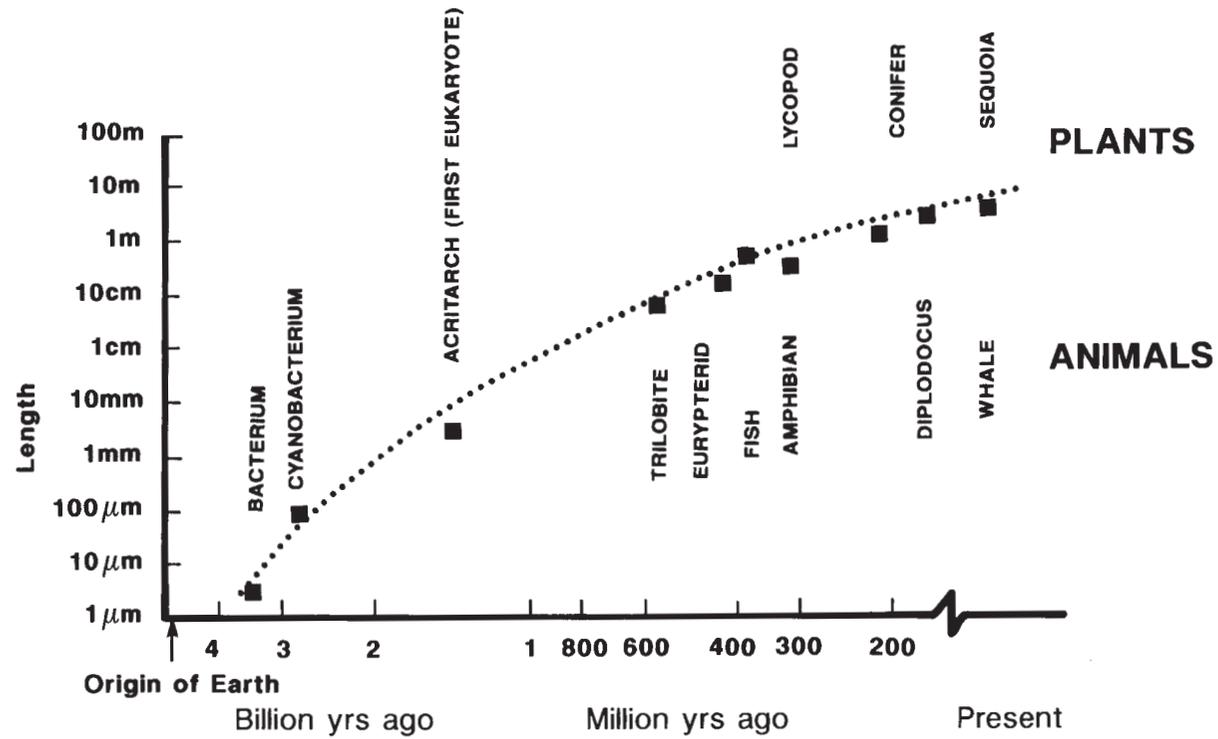


FIGURE 1. The complexity of life through geological time in terms of size. Note this metric is plotted as a log scale so that the largest creatures are about nine orders of magnitude ( $10^9$ ) bigger than the smaller. Note also the time-scale is not linear, but drastically telescoped towards the right.

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How did the complexity of life arise?

This is a remarkably intractable problem, and may be studied at several levels. Here I will consider at the subcellular level proteins and, as an integrated macroscopic organ, the eye. This latter structure has, of course, been seized upon by both proponents of Design and Blind Watch-makers. As I explain below, matters may not be quite as clear cut as is sometimes portrayed.

Was this process exceedingly gradual, run-away or even punctuated?

Evolutionary punctuation has had more than its fair share of attention, but in principle the processes of natural selection should approximate to a continuous ratchet. Untrammelled by the real world, runaway evolution might be expected to be the norm. It is not, and given that we live in a world hedged in with all manner of constraints this is probably an unrealistic claim. Yet a glance at Figure 1 might suggest a steady unfolding of life – bacteria to blue whales and giant redwood – until, that is, one checks the time-scale, telescoped towards the right. The longueurs of evolutionary lethargy, during the immense intervals of the Precambrian, are still surprising. Perhaps we underestimate the sheer complexity of cellular assembly, or alternatively maybe the milieu (sea too salty, or too little oxygen?) was persistently unfavourable for evolutionary innovation?

Is there a directionality to life?

No other proposal raises the ultra-Darwinist hackles so quickly. Given the billions of species, extinct and extant, to define *a priori* the trajectories of evolution might seem to be a redundant exercise. But even though the directions are many, the end-products are limited. Evolutionary convergence is the rule.

Is there an irreducible level of evolution?

If there is, then evolution might be amenable to a general theory. The necessary level of inherency, upon which all else hangs, is usually equated with the molecule known as DNA, the primary replicator. This is the view, for example, of Dawkins. For example, in *River out of Eden* (1995, p. 153) he writes, 'Every detail

of the protein molecule is precisely specified, via the famous genetic code, by the ordering of the four kinds of letter in DNA'. This is true, but also drastically incomplete. For example, how proteins fold, how they are co-opted for multiple functions, how they dictate key steps in embryology, and indeed how complex organs emerge are unlikely to have much to do *directly* with DNA.

### **Simplicity and complexity: proteins**

The central paradox of life, surely, is that at many levels it is exceedingly complex and resilient to general explanations, yet the basic building blocks are simple. So too are the bricks or masonry that together form the cathedral. How then does the architecture of life arise? Consider the proteins, whose construction depends on approximately 20 amino acids (and in turn the triplet codons of DNA). This number, however, comprises a rather small fraction of the total presently known. Notably the organic-rich carbonaceous meteorites have yielded a rich harvest (70+) of extraterrestrial amino acids. Interestingly, despite this large number they all belong to one or other of two structural types. Evidently the processes of chemical synthesis have allowed a full exploration within this context, but the range is otherwise restricted. Thus only eight of the amino acids known in terrestrial proteins occur. Also the chiral mixture from the meteorites is even, whereas in life there is strong predominance for left-handed forms of those amino acids that can form mirror images.

Amino acids are relatively simple, and so too are some proteins such as bee and scorpion venoms. Most, however, are more complex, ranging from rope-like arrays to vast, intricately folded clusters. Rather remarkably, given the intricacy of their structure, some proteins can be induced to crystallise. This is often a tricky and laborious procedure, and the crystal forms are far from perfect, showing little of the regularity of an inorganic compound such as rock salt. Even so the crystals are amenable to study by diffraction methods (X-ray or radiation derived from a high energy synchrotron). The resulting pattern portrays, at a rather fundamental level, the structure of life. A wide range of proteins is already known, and structurally novel ones continue to be discovered. It is, however, possible to impose some sort of order based on structural similarities. Despite the diversity of forms, much of protein construction is quite repetitive, building on a hierarchy of secondary and tertiary structures. Beyond

this are the more inclusive categories of the protein families. Protein chemists are sometimes aware of the evolutionary implications of their work, but the structural distinctiveness of many proteins continues to place them in isolated positions, with no obvious links to the rest of the protein 'universe'. If certain protein families evolved before the oldest known ancestor of life then our ability to trace their evolution may be seriously compromised. Another major constraint on evolutionary interpretations is that proteins necessarily have a very wide range of functions. Even so, apparently very different protein families may on investigation have hitherto unexpected connections. For example, cytochromes (involved in electron transport) and globins (best known in the form of oxygen-transporting haemoglobin) may be related.

There is a divergence of opinion as to whether the total number of protein families is substantially larger than is presently known. There are, however, some indications that the number is limited, and may not be much greater than the approximately 1000 families identified. It is also an orthodoxy that this (relatively) limited variety is a historical accident, and that another world might have an approximately similar number of protein families, but otherwise of very different configuration. In the current absence of an extra-terrestrial protein bank, how might we explore this problem? One avenue could be by the generation of artificial proteins. The problems remain formidable and any successes will be set in an evolutionary limbo, at least initially.

Another argument for protein structures being on occasion more than historical accidents may lie with examples of functional convergence. Red/green vision depends on minor changes of amino acids at key sites in the light-receptive protein rhodopsin. In fish and humans the red pigment evolved from green pigment independently, but by identical amino acid substitutions (see also below). Such colour distinction depends on physically invariant wavelengths of electromagnetic radiation, so perhaps only certain amino acid substitutions are permissible. It would help to know why these substitutions are effective, but as yet we do not. And as noted below, maybe the argument for convergence can be extended to the entire light-sensitive protein itself. Another example concerns the production of glycoprotein (with a highly repetitive tripeptide 'backbone') antifreezes by fish inhabiting polar waters. Presumably because of the necessity to bind to incipiently forming ice crystals, the protein structure is strongly constrained. Not surprisingly this protein is very

similar in Arctic and Antarctic fish species, yet upon investigation their genetic origins are very different.

It might reasonably be objected that these two examples of molecular convergence represent extreme cases. In the example of red/green vision the constraint is effectively physical, if not in the realm of quantum mechanics. This too must be the case with the formation of ice crystals within cells or tissues, and other organisms appear to secrete a variety of different antifreeze proteins. Convergence, therefore, need not imply a unique solution, but the actual number found is a tiny fraction of the universe of potentially available structures. Some parallels might be found in aerobic respiration. In this case, the oxygen is 'handled' by various proteins, but its transport often depends on the protein haemoglobin. It has been described, perhaps surprisingly, by D. S. Goodsell as 'perfectly designed'. Haemoglobin is very widely distributed. It appears to have originated with the bacteria, and has been co-opted by some plants and many animals. The latter kingdom does possess a number of other respiratory proteins, but even so there appear to be constraints. Haemerythrin, for example, also employs iron, yet its principal occurrences are in phyla (notably priapulid worms and some brachiopods) that appear, on present evidence, to be only distantly related. Copper is also used in some proteins, and haemocyanin is characteristic of some arthropods (crustaceans) and molluscs, yet the molecular structure shows significant differences between the two groups. In this case, at least, the two types of haemocyanin may be convergent.

If unravelled, a protein would consist of a long chain or chains of amino acids. Its active function, however, depends on a precise sequence of folding, typically into helices, strands and loops. The sequence of amino acids is not random, in as much as specific substitutions at particular sites can lead to serious malfunction. Yet the rules are not hard and fast. For example, the same function can be achieved by proteins folded in very different configurations. In a somewhat different context, and although it is an extreme example, fully functional proteins can be constructed from a pool of as few as five types of amino acid. Moreover, proteins themselves can be artificially miniaturised yet engineered to remain functional. What then determines protein structure and function? At one level the answer lies in the amino acids, and their various properties that reflect electrical charge, solubility in water or hydrophobicity, sensitivity to acidity (as in histidine), size (especially the small alanine and glycine), and ability to form cross-links (as in cysteine). Considered in this fash-

ion the amino acids are strongly functional, but only on a local scale of ångströms. What happens when the amino acids are linked together to form a chain? Given that there are 20 amino acids, and a typical domain within a protein (which may contain at least several domains) consists of a sequence of about 150 amino acid residues (i.e. linked amino acids), the combinatorial total of different sequences is about  $10^{200}$ . This comfortably exceeds the estimated total of atoms in the visible universe. Many of these sequences would, of course, be very similar but even by imposing more stringent criteria of non-similarity the combinatorial total is still gigantic (at approximately  $10^{32}$ ). In principle, only a minute fraction of all possible sequences has been explored. Yet the total number of types of domain is much more limited, and so apparently is the number of protein families. As noted above it is generally believed that alien worlds will draw on some other section of this combinatorial space, and so have alien proteins (if they have proteins at all). This conclusion may be premature; maybe where oxygen is carried by at least iron or copper then the proteins will be little different from haemoglobin, haemerythrin or haemocyanin.

Just as there is an astronomical number of potential amino acid sequences in the category of domains, so the angular conformations that each amino acid can adopt ensures that even in a small protein the number of possible configurational states is again colossal. Proteins have carefully controlled shapes because they usually have a precise function. How does the protein manage to adopt the required shape; after all, although the reactions do not involve covalent bonds, the process is remarkably rapid and occurs at temperatures below those that favour many chemical reactions.

The end-product is stable and ordered; that is, it has a low entropy. The starting point is much less ordered, so one way to envisage this construction is as an 'energy funnel', that channels the components to the final protein (Figure 2). This process may be more familiar than is perhaps realised. Consider a hot liquid that cools to a solid: disorder gives way to order, high entropy to low entropy. In many cases, especially if the cooling is very rapid, the end result is not a crystalline state but a glass. Such a material is referred to as metastable. One consequence of this is that the glass is locked into a form that forbids it to adopt a more ordered crystalline state, even though this latter state would be energetically more stable. In terms of protein synthesis, the necessarily rapid progress of folding threatens to produce the analogue of a 'glass'. This would be a disaster, but how is it avoided? It seems likely that the various components

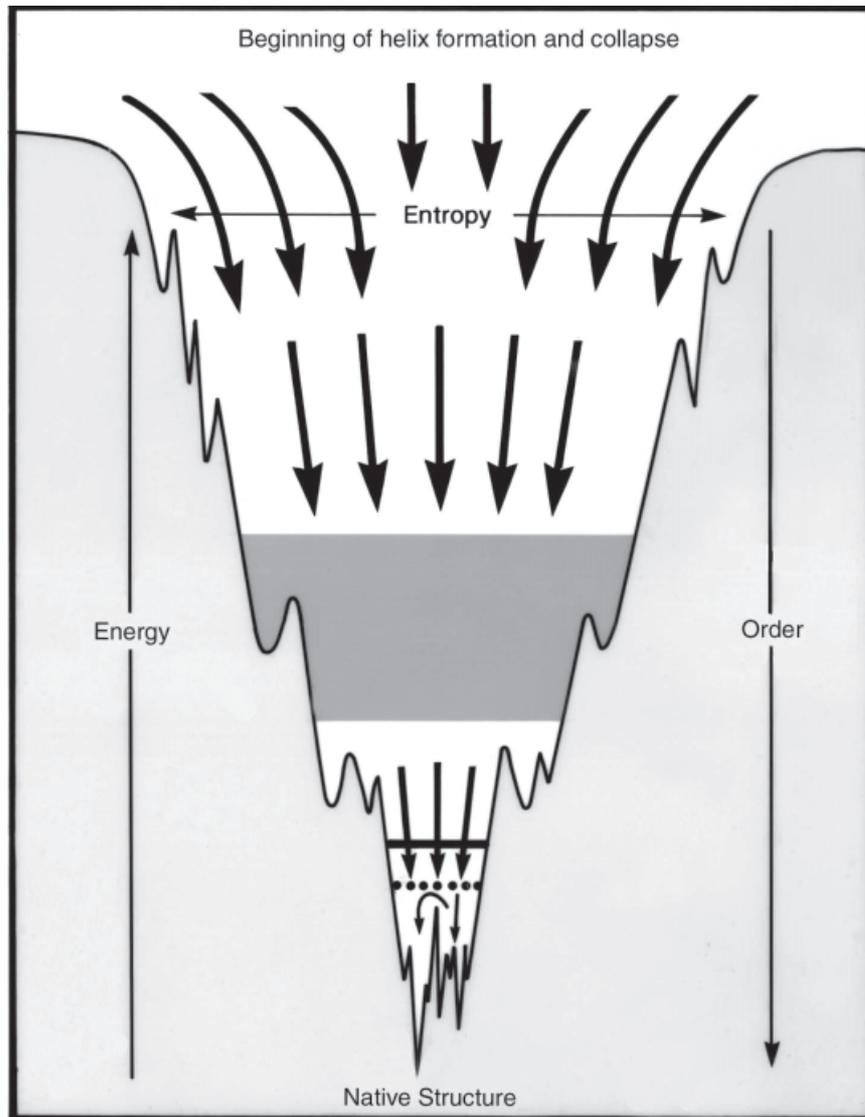


FIGURE 2. A diagrammatic scheme to illustrate the concept of an 'energy funnel' whereby a helical protein collapses into its folded and functional configuration. The entropy progressively decreases as the protein becomes more ordered and an increasing number of correct contacts are made by the molecule. An important part of this model is the transition through a 'molten globule state' followed by 'glass transition'.

## The Structure of Life

of the protein are assembled separately, then jostle together in a so-called 'molten globule state' that then leads rapidly via a glass transition state to spontaneous assembly.

It is conceded that this thermodynamic scenario is simplified. Some success has also been achieved with modelling the folding of simple protein, yet a complete understanding of the assembly of large complex structures remains a formidable hurdle. Nor is it necessary to think only in terms of energy funnels (Figure 2). In some cases protein construction is aided by other proteins, known as chaperones. This might open the prospect of an infinite regress of constructional agents; in other words do chaperones need chaperones? Not necessarily, if the chaperones have precise tasks and/or have been co-opted from proteins with other functions.

The range of proteins can only excite our admiration. Consider silk, familiar in the webs of spiders and also the main component of insect cocoons. The silk glands of a spider are complex, with different branches acting as local 'factories'. Up to eight gland types are recognised, each producing a specific type of silk to be employed in a variety of functions that reach their acme with the sophisticated orb spinners. Inside the body the silk is liquid, but as it is extruded through the nozzle-like spinnerets the molecules, which are notably rich in such amino acids as alanine and glycine (the latter is the simplest of the amino acids), are aligned. The solidified silk consists of ordered blocks set in a disordered matrix, and thus forms a composite material combining resilience, strength and low elasticity; after all there is little point in the spider building a trampoline. Just how remarkable spider silk is will be apparent when it is learnt that its strength is half that of best steel, and before breaking under its own weight the dragline of silk would need to be some 80 kilometres in length.

To conclude, the construction of proteins and their incorporation into complex biochemical cycles can only excite our admiration. It is emphatically not my intention here to question whether they are a product of evolutionary processes: quite clearly they are. Rather, I would stress that it is precisely how they evolved that still presents us with an as yet unsolved challenge.

## The eye

The insights into protein structures stem from the genius of John Kendrew and Max Perutz, but are largely a product of the last 20 years' research. The

complexity of proteins and the intricacies of the biochemical pathways and cycles with which they are involved have led some biochemists, such as M. J. Behe, to see the hand of Design. This view has not been greeted with enthusiasm. For our predecessors it was the corresponding intricacies of macroscopic arrangements that excited very similar interests. Of these none appeared to give greater strength to the argument for Design as the eye. The apparent perfection of this organ and its obvious purpose were agonised over by Darwin. Yet, since then, this organ has been triumphantly accommodated in the Darwinian framework, both in terms of its various building blocks and its progressive construction. It is not my intention to dispute these observations, but matters may not be as straightforward as is sometimes proposed.

The demands on eye construction are various, but three items stand out. These are the necessity of having (a) light-sensitive cells that can produce an electrical signal, (b) transparent tissue as a cornea and perhaps a lens, and (c) a genetic programme to ensure eye construction in the correct order and right place during embryology. The first item, light sensitivity, refers to the retina and more specifically proteins known as the opsins, for example rhodopsin. These trap light photons and promote an electrical discharge that is transmitted via the optic nerve to the brain. Opsins have a characteristic molecular structure, consisting of an amino acid chain folded into seven helical units that are wedged between two membranes. Where do the opsins come from? It is known that bacteria possess similar proteins, that act as light-driven proton pumps (a proton being a positively charged hydrogen ion) whereas the light-activated receptors in eyes eventually trigger an electrical charge in the adjacent nerve cell. This certainly does not rule out a common ancestry, but the sequence of amino acids in either protein is completely different. One explanation is that the two molecules diverged so long ago that all sites have been replaced. An alternative view is that the similarity is an example of molecular convergence. The opsin proteins are not only sensitive to light, but in some vertebrates are also involved with colour discrimination. It is perhaps surprising to learn that the distinction between red and green depends on the substitution in the opsin of only seven amino acid residue sites, of which a mere three are really important. This is the case not only in vertebrates, where the principal amino acid substitutions arose independently in mammals, reptiles and fish, but also squid. So too the discrimination of blue wavelengths, as is found in deep-water fish, is dependent on specific amino acid sites. How these trivial

changes actually lead to different colour perception is only now beginning to be understood.

For the light to arrive at the retina the overlying area of tissue needs to be rendered transparent. Moreover, in advanced eyes the ability to focus light presupposes a lens. A moment's consideration will show what an extraordinary demand this entails. The absolute need for transparency means that the normal mechanisms of maintenance and repair, typically provided by the agency of a blood system, must be excluded. Accordingly, the lens once formed must be exceptionally stable, resistant to degradation and insult. To be able to see clearly for 70 years is a tall order. It might be supposed that the demand could be best met by a custom-built protein, an evolutionary novelty. Not so. Eye lenses are built largely of proteins known as crystallins. This is a rather inappropriate name because in life they are not actually crystalline. They have, however, a small size and this together with an arrangement as a very regular structure confers transparency. The real surprise is that crystallins are derived from a variety of proteins that evolved for very different purposes. There is, nevertheless, a common strand because such proteins are characteristically resistant to stress and damage. Many belong to a group known as the heat-shock proteins. As their name suggests these proteins are resistant to environmental stress and abuse, and thereby suitable to co-option in the eye.

Crystallin proteins are an astonishing example of evolutionary opportunism. The fact that a variety of proteins has been so utilised indicates the range of derivative versatility, but the constraints of function are omnipresent. This is made most apparent, perhaps, by considering what might be called a 'reverse eye'. Many animals can produce light, typically by the action of an enzyme known appropriately as luciferase. Light emission is under precise nervous control, and often linked to sexual display or warning. To be effective the tissue above the light-emitting organ must be made transparent. Light-producing organs are often arrayed across the body. In squid, for example, the location of light production means that the associated lens has to be derived from muscle tissue. This is hardly a promising starting point, but once again transparency is achieved by massive production of crystallins.

The ubiquity of opsins and crystallins show that for light reception and transparency, respectively, the constraints on eye formation are very strong. Yet, viewed across the animal kingdom, eyes show a very wide range of structures and anatomies. This variety is typified by the compound eye of insects

and the camera-like eye of vertebrates and squid. This variety of architectures and the fact that animals of very different ancestry may have similar types of eye has led to the reasonable suggestion that the eye has evolved separately many times and because of constraints of function there are examples of striking convergence. But despite the clear evidence for separate histories – whatever eye the common ancestor of squids and humans possessed it was assuredly not built on a camera-like construction – it now transpires that all eyes have much in common.

Eyes may also be lost, both in the evolutionary history of a group and in unfortunate individuals who are born or hatch with eye defects or blindness. The eye is a complex structure and presumably relies on dozens, if not hundreds, of genes that encode its various parts. In principle, failure of any one of the genes might prejudice a functioning eye. It is now known, however, that a key gene, *Pax-6*, has a crucial role in eye formation. Its absence, not surprisingly, leads to blindness. Less expected, perhaps, is that excess production of this gene also causes major defects.

How does *Pax-6* actually work? We do not know. Natural mutations where eyes develop on inappropriate parts of the fruit fly body are known. Genetic technology now allows the manipulation of the *Pax-6* gene such that inoculation of a larva leads to its subsequent ectopic expression. That is, eyes may be induced to grow, for example, on the legs. Not only that but these ectopic eyes are electrically active. Conceivably they may transmit images to the brain. Are we being squeamish or simply sentimental to register concern for such manipulations? The sense of order and just proportion is deeply engrained in human sensibility. As Roger Shattuck reminds us, the myths of the neglected pathway, unheeded warning, of improper fruit plucked surely hold deeper truths that should admonish against meddling and unrestrained curiosity.

*Pax-6* is often referred to as a master-control gene. Flies without *Pax-6* will be blind; flies with *Pax-6* applied indiscriminately hatch as optical monsters. Other animals, such as the vertebrates, and squid, have a very different type of eye from the fly, but one that is built to a very similar plan. Much is made of the similarity of the eye design in vertebrates and advanced cephalopods such as the squid. Similarities there certainly are, but also some interesting differences. Best known is the layering of nerves (leading to the optic nerve) and the sensory cells (the retina). In vertebrates the nerves overlie the retina, whereas in the squid the more 'logical' arrangement of the light receiving retina above

nerves occurs. Another significant difference is the mode of formation of the lens, which in the squid is formed from a series of cytoplasmic processes so that the end-product is effectively acellular and, unlike the vertebrate lens, inflexible. Somewhere in the mists of the late Precambrian the common ancestor of the squid (as a mollusc) and vertebrate swam or more probably slithered. In each case an architecture evolved that led to a camera-like construction, but completely independently. In each case one might infer a master-control gene, broadly similar to *Pax-6*. What was quite unexpected was that blindness and other eye defects in vertebrates (and squid) were connected to an exact equivalent of *Pax-6*. It will come as no surprise, therefore, to learn that application of the squid *Pax-6* to the fly also leads to ectopic eyes. Not, fortunately, actual squid eyes: the ectopic expression remains as compound eyes.

The underpinning of eye formation by *Pax-6* shows how in principle a visual organ may develop anywhere on the body. In the great majority of cases the eyes are located on the head, presumably because an anterior position and proximity to the brain are desirable. But apart from ectopic meddling, in nature eyes can be found in unusual but still functionally plausible locations. Marine worms inhabiting tubes that feed with a crown of tentacles on suspended material in the sea water have eyes on the tentacle tips. Advance warning of attack leads to sudden retraction into the safety of the tube. And eyes occur on other tips, such as the genitalia of butterflies, where no doubt they have their uses.

The role of *Pax-6* would seem to encapsulate the new view of biology: the power of the gene and their primacy over the bodies, which, in Richard Dawkins' phrase, are mere 'lumbering robots'. Yet simply invoking *Pax-6* whenever the evolution of the eye is discussed is not in itself sufficient. To be born without *Pax-6*, or at least not have it in a functional state, may be a tragedy. But the converse, that is the possession of *Pax-6*, does not guarantee sight. Thus, in the eyeless nematode worms, *Pax-6* is still present and active. What is it used for? Most probably it is still in a sensory role, because it is also known that *Pax-6* is involved in olfaction. What is likely is that originally *Pax-6* had more primitive functions, and interestingly there is evidence for it being involved in the regulation of both rhodopsin and crystallins, and hence photo-reception in general.

Some other features call for comment. Above, it was noted in terms of molecular substitution of amino acids that red/green colour discrimination is

based on trivial differences. So too with *Pax-6*. Thus the protein expressed by *Pax-5* differs from that of *Pax-6* by only three amino acid residues, yet the genetic expressions are very different. Nor is *Pax-6* the only master-control gene for eyes, at least in the fruit fly (*Drosophila*). Several others have been identified and they too can, when absent, result in blindness or if misapplied produce ectopic growths, although in at least one case (known as *eyes absent*) the gene has other functions as well.

Eyes have evolved many times. In the five billion years of future evolutionary history one may be almost certain that any new eyes that emerge to survey the scene will rely on rhodopsin and crystallins. But bricks alone a cathedral do not make, and so too with the functioning eye. It was the string of transitional states leading to the coherent and integrated whole, swivelling in its socket and iris contracted, that provided such a stumbling block to pre-Darwinians, then and now. In fact, the concept of the 'eye' is very broad and reveals many levels of complexity between the eye-spot of a worm and the implacable gaze of the hawk. Making the reasonable assumption that an eye will be more effective if its visual acuity is enhanced, then as D.-E. Nilsson and S. Pelger have shown it is relatively straightforward to portray an 'evolving' sequence (Figure 3). The starting point is trilayered, consisting of protective, light-sensitive and pigmented units. Increasing visual acuity is achieved by a changing spatial resolution that depends on first an increase in surface area by folding into a bowl-like shape, followed by a constriction to define an aperture. This latter arrangement acts as a pinhole eye, but further optical resolution is achieved by a crystallin-rich lens. The surprising fact is how quickly such an organisation can arise. The entire sequence can be achieved in 1829 steps, each representing a 1% difference in eye form. Translated into generation times this suggests that from a simple eye-spot a fully-fledged eye could easily evolve in considerably less than a million years.

Such a figure is quite consistent with the multiple appearance of eyes. But does it point to a more profound problem? If the paradigm of evolutionary sophistication, the eye, can emerge via the agency of a rather small number of incremental steps – each representing an adaptive advantage – in a geological instant, then it is perhaps surprising that evolution was not a runaway process? Such instances are known, yet overall the time required on rather conservative estimates to evolve complex organs is up to three orders of magnitude more than the time available. Darwin's famous plea for sufficient time, which was

The Structure of Life

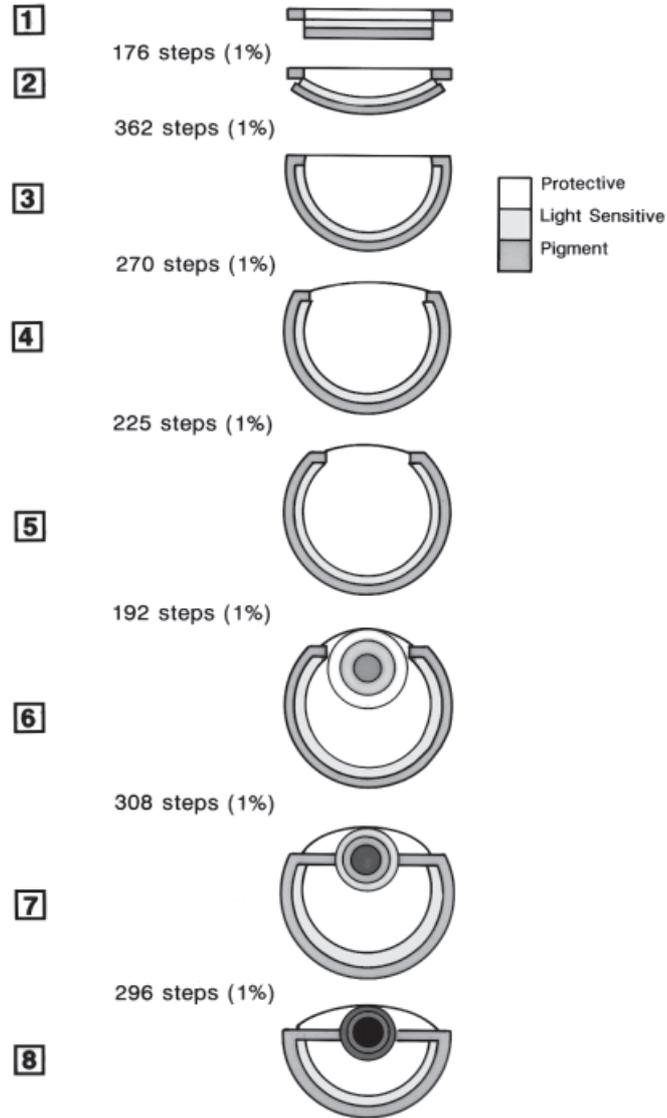


FIGURE 3. The hypothetical transformation of a light-sensitive patch into a complex camera-style eye in eight major stages connected by 1829 sequential steps of 1% modification, equivalent to approximately 360 000 generations.

shortly afterwards granted by the geologists, appears to have been unwarranted.

In the specific case of the eye there are provisos concerning yet further complexities ('bells and whistles') such as colour discrimination, an iris or fovea, and sclerotic housings. Yet all these are, in the first analysis, ancillary. More importantly, a complex eye is of little use if the brain is insufficiently large or densely 'wired' to process the input, or the body too simple to take effective action, although in this context we should note that relatively primitive animals such as some jellyfish are equipped with sophisticated eyes. Even so, the logic of very modest increments of change leading to the emergence of complex organs is unlikely to be limited to the eye. Nor is it clear that the further integration of such organisations need be any more than additive. Again, this section should not be taken as an argument against evolution. Indeed the incremental steps portrayed in Figure 3 are just what we would expect. But the potential for evolutionary change may far outstrip the aeons of available geological time. Maybe the sheer difficulty of organic assembly is being underestimated, or, alternatively, conceivably the limits on diversity are more stringent than is generally realised.

### The body

Our examination of the eye shows how its construction can be understood at a number of levels. What of bodies themselves, the integrated whole? Consider the hand in Figure 4; it is clearly deformed, but oddly as a mirror image. Thus, although it is a left hand with four of its fingers, the other four fingers would belong to the opposite hand. Apparently in life the woman with this deformity, who was otherwise normal, could fold the two parts of her hand together but could only exercise limited movement of the fingers.

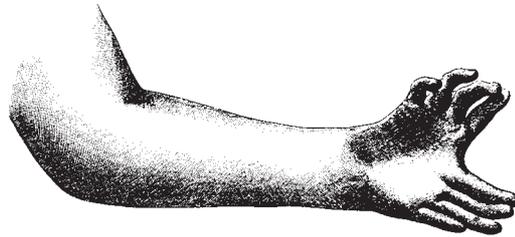


FIGURE 4. The double-hand of a woman.

This example is more than a curiosity. Amongst the early, and now classic, experiments in embryology were those of selective excision of part of a developing embryo followed by its repositioning. In vertebrates, such as the chick, the limbs first emerge as buds. At this stage, by removing a piece of the posterior margin and transplanting it to the anterior edge of the bud, in subsequent development of the embryo a mirror-image limb results. Just why this should be so has only become apparent recently. Although clearly some ‘active principle’ was involved in this limb duplication, and the history of the investigation involved various false leads, the genetic underpinning is now known to involve a protein product referred to as sonic hedgehog. Its application to the anterior margin of a limb bud, via the agency of a viral infection carrying the *sonic hedgehog* gene, leads to a monster with digits displayed in mirror image. In flies, the application of the same gene (known as *hedgehog*) produces similar duplications. Earlier I noted that the sprinkling of a fly body with ectopic eyes might not be free from moral implications. So too might we view the distortion of symmetries. To observe that they occur naturally, as indeed they do, albeit rarely (Figure 4), may not justify conscious manipulation. Such interferences are deliberate, and thereby imply a principle of responsibility.

For the most part the genetic gloss put on to embryology and the construction of body form has revealed the molecular underpinning of development, even though the actual mechanisms remain almost entirely obscure. In prospect is the mapping of development on a genetic basis. And this is leading to surprises that by invoking the commonality of developmental pathways have led in one celebrated case to a literal inversion of established thinking. A now famous paper by Étienne Geoffroy Saint-Hilaire, published in 1822, was ostensibly on vertebrates, yet it also included figures of the lobster. Not as a gastronomic diversion, but to argue that once inverted the basic body architecture – notably of the nerve cord – approximated to that of the vertebrate. This hypothesis was ridiculed by Geoffroy Saint-Hilaire’s one-time friend, Georges Cuvier, as part of a larger assault on Geoffroy Saint-Hilaire’s evolutionary philosophy.

This debate remained largely dormant for many years, although the consensus remained almost entirely with Cuvier’s rejection of vertebrates being little more than inverted lobsters. Yet in one sense he was wrong. Vindication of Geoffroy Saint-Hilaire’s basic thesis comes from the genetic expression of bodyplan construction. Some years ago it became clear that specific regions of

the developing embryo of both fruit flies (which as arthropods are closely related to lobsters) and mice (which for this purpose approximate to humans) are coded for by specific genes, in particular their expression defines various regions. Much greater was the surprise when it was realised that these genes were equivalent in flies and mice, except that they were expressed on opposite sides. The concept of inversion had been vindicated.

To shower plaudits on Geoffroy Saint-Hilaire and opprobrium on Cuvier would be, however, to miss the point. In the context of the original debate, as T. A. Appel, a historian of science, has shown, the argument had little to do with evolution as neither party believed in organic transformation, at least in any Darwinian sense. Rather the argument was between a view of life espoused by Cuvier that looked to organic function set in an ecological context as against an alternative discernment of morphological principles, if not laws, akin to the eternal verities of physics. And even with the acceptance of evolution this tension remains with us; that is, the figure of organic change constantly adapting to the local environment versus the constancy of morphological form, encapsulated in the comment 'that if you have seen one beetle you have seen them all'. In contrast to the evolutionary flux, this latter view envisages a universe of potential morphology, which could be anatomical or molecular, of which only a very small fraction is actually occupied. Are these discrete 'clouds' of morphology historically and accidentally determined, or do they represent in some sense stable nodes with the intervening gulfs regions of mal-adaptedness?

### **The phylotypic stage**

The concepts of constraint and constancy of form may have Platonic echoes, but they are no strangers to evolutionary theory. A central question in evolution, and especially embryology, is the emergence of form. To the first approximation an egg is fertilised, it develops into an embryo from which the adult emerges. In the case of vertebrates the adult forms are very different: salmon, sheep and snake. So too are the eggs, which show a wide variety of cellular arrangements and accommodation of the yolk. Yet, it is customary to consider the developmental programme via a seductive analogy of an hour-glass (Figure 5) whereby the different types of fertilised eggs are channelled through a bottleneck of imposed similarity – the phylotypic stage – before diverging into the