

astroarchaeologists were to find such an object, it would hardly be the first time that science fiction had become science fact. ■

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Evolutionary biology

Time, space and genomes

Nipam H. Patel

In most animals, the Hox genes — which control development — are clustered together. But why? New evidence supports the idea that the requirement for a temporal order of expression keeps the cluster intact.

Some of the most striking discoveries in developmental biology over the past century concern the set of genes called homeotic (Hox) genes. Genetic studies in fruitflies first showed that these genes have a major role in producing the head-to-tail (anterior–posterior) pattern of tissues along the body axis. Then came the startling finding that the order of these genes along a chromosome correlates with the anterior–posterior position of the body regions they control, and with the domains in which the genes are expressed. It soon became apparent that the same relationship exists in other animal groups, including vertebrates. Intriguingly, however, it seems that somewhere in the evolutionary lineage leading to the tunicate *Oikopleura dioica*, the Hox complex has disintegrated, as Seo and colleagues report on page 67 of this issue¹.

Evolutionary analyses have suggested that the common ancestor of bilaterally symmetrical creatures — which include most animals, the main exceptions being cnidarians and sponges — probably possessed at least seven Hox genes, organized into a single complex. Within the lineage leading to vertebrates, gene duplications led to an expansion of the cluster, and then the cluster itself underwent duplications, leading to the four copies of the Hox complex now found in humans and mice. All along, the collinearity of the genes — the correspondence between their physical order along chromosomes and their domains of expression and function — was maintained.

But why has collinearity been preserved? The ancestral bilaterian complex itself probably arose through several rounds of local duplications, explaining how the genes first became organized as a cluster. In general, however, gene order is constantly shuffled by chromosomal rearrangements such as inversions and movements of large DNA segments. Given the rate at which this process occurs, the maintenance of collinear organization over at least 600 million years of evolution must not just be due to chance². One possibility is that different Hox genes

once shared, and continue to share, regulatory elements. But although this idea might account for the preservation of some degree of organization, it seems inadequate to explain the extent to which the complex has been maintained. Another possibility is that the mechanism that allows the genes to be expressed in a strict anterior–posterior expression pattern requires some type of higher-level organization, involving the progressive chemical or structural modification of a large contiguous stretch of DNA.

The work of Duboule and colleagues over the past few years has added an extra dimension to the issue of collinearity. They have shown that the vertebrate Hox genes show not just spatial but also temporal collinearity³; that is, genes at one end of the complex are expressed not only in the anterior of the embryo, but also relatively early in development. Hox genes located further along the complex are expressed both more posteriorly and later. Duboule and colleagues⁴ have provided evidence that it may be the requirement to maintain temporal collinearity that is responsible for keeping the complex together. A Hox gene experimentally moved around within the complex can retain spatial information, but will have an altered temporal expression profile.

Continuing this theme, Seo *et al.*¹ provide

a fascinating example of an animal in which the Hox complex has not stayed together yet appears to maintain some degree of ordered spatial expression along the anterior–posterior axis. Their studies focus on *Oikopleura dioica* (Fig. 1). *Oikopleura* is a type of tunicate, but is quite distant from *Ciona*, the other well-studied representative of this group of animals. Tunicates are evolutionarily primitive relatives of vertebrates, and comparisons between living tunicates and vertebrates may help researchers to piece together the features of the common invertebrate ancestor that gave rise to vertebrates. *Oikopleura* also has a remarkable genome — it is very small (at 60–70 megabases) and compact (with one gene every 4 kilobases)⁵.

Seo *et al.* find that *Oikopleura* has a complement of nine Hox genes. As expected, *Oikopleura* counterparts of the vertebrate anterior Hox genes are expressed in anterior regions of the developing animal, and counterparts of progressively more posterior vertebrate Hox genes are expressed in correspondingly more posterior regions. What is fascinating, however, is that the *Oikopleura* Hox genes retain this pattern of expression even though they are no longer in any sort of complex. Seo *et al.* show that for at least eight of these genes, no other Hox gene is found within 250 kilobases on either side. It is not that these Hox genes are in a gene-poor region, however; each is surrounded by other genes at the usual high density found in this animal.

These results, then, would seem to indicate that spatial collinearity can be maintained without requiring the organization of the Hox genes into a complex. *Oikopleura*, however, appears not to maintain temporal collinearity. The expression of its Hox genes does not seem to begin in a progressive temporal order, but rather at roughly the same time. Extensive splits within the Hox complex are also seen in the roundworm *Caenorhabditis elegans* and in *Ciona*, two other cases in which temporal collinearity no longer applies. Even in fruitflies, the Hox complex is split into two, and many non-Hox

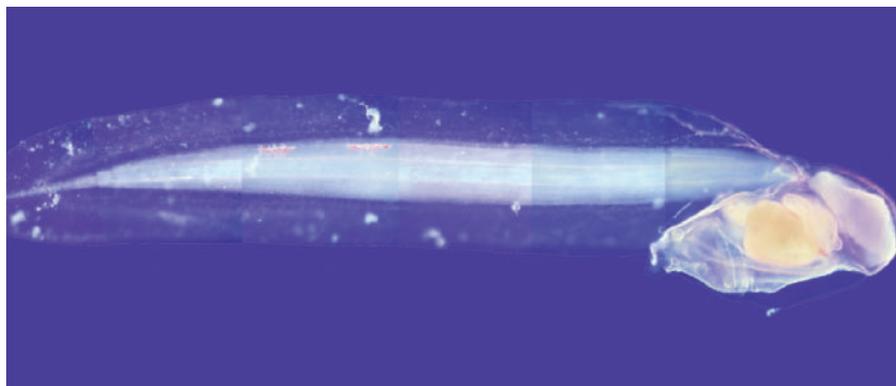


Figure 1 Distant relative. *Oikopleura dioica* has a simple body plan reminiscent of that of a tadpole, hinting at its close affinity to vertebrates. Remarkably, the generation time for this organism is only four days.

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genes sit within the clusters. Although studies of fruitflies established the rules of spatial collinearity, this insect shows little, if any, evidence of temporal collinearity. On the other hand, evolutionarily more primitive insects appear to maintain temporal collinearity in Hox-gene expression. These findings tend to support the idea that temporal collinearity does require an intact Hox complex — although this may not be the only selective force holding the cluster together.

Another interesting lesson is emerging from comparisons of fruitflies, *C. elegans*, *Ciona* and *Oikopleura* with animals such as humans and mice. The former group of species make excellent experimental models, because of their rapid development and small genomes. But it is curious that the presumed ancestral bilaterian Hox complex has

been split to varying degrees in each of these model systems — and temporal collinearity no longer applies. It might be that other aspects of their development and genome organization also differ substantially from their slower-growing and relatively large-genomed relatives, including humans. To be fair, however, the conclusion will probably be that every animal has its own unique and fascinating properties. ■

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Statistical physics

Hear the noise

Simon Kos and Peter Littlewood

At the nanoscale, thermal fluctuations and noise dominate. But instead of being a hindrance, the details of the noise itself can reveal the physical properties of the system.

Almost two centuries ago, the atomic nature of matter was elegantly revealed by brownian motion — as exemplified by the random motion of pollen particles in water as they are bombarded by water molecules. Now Crooker *et al.*¹ provide, on page 49 of this issue, a textbook demonstration of fluctuations at work in the spectroscopy of a small number of alkali atoms — a quantum version of brownian motion.

In 1905, Einstein² pointed out a subtle consequence of the fluctuations in classical brownian motion: the same random forces that make a pollen particle jitter would also cause friction if the particle were dragged through the water. In other words, the fluctuation of the particle at rest has the same origin as the dissipation of the motion of a moving particle that is subject to an external force. Einstein's result is a general one, codified in the 'fluctuation–dissipation theorem', which is one of the deepest results of thermodynamics and statistical physics. Einstein's observation also had a crucial consequence for the state of thermal equilibrium, in which the fluctuation of the stationary particle is characterized by a single number (the diffusion constant), and the friction of a moving particle is characterized by another number (the mobility). The fluctuation–dissipation theorem states that these two numbers, previously considered independent of each other, are, in fact, connected by a simple relation: they are proportional to each other

through the absolute temperature, a characteristic of the state of thermal equilibrium.

Brownian motion follows Newton's classical equations. However, the invention of quantum mechanics, and the discovery of Heisenberg's uncertainty principle, brought discrete energy levels and new kinds of fluctuation into play. It took several decades to develop the proper techniques of quantum statistical physics, and the fluctuation–dissipation theorem did not reach its final form until the work of Kubo in the 1950s. Its formal derivation for quantum systems is even more mathematical and less transparent than in the classical case; many of us struggled to understand the physical context of this elegant but esoteric mathematical statement when we first met it in an undergraduate course. But the final result again has a clear physical interpretation: the dissipation in a quantum system is caused by transitions between its energy levels; the noise spectrum should, therefore, have peaks at frequencies corresponding to the differences in energy between these levels. All of the physical properties of a quantum system depend on the values of these energy levels: the 'colour' of an atom and its nuclear magnetic resonance frequency are two examples that involve measuring the energy spectrum.

Quantum physics began with the study of the emission lines of the hydrogen atom — the particular wavelengths of radiation emitted as the atom's electron makes transitions between energy states. In their experiment,

Crooker *et al.*¹ study the magnetic fluctuations in vapours of hydrogen-like alkali atoms of rubidium and potassium. These atoms have a single valence electron, whose direction of spin, or magnetization, can change. Crooker *et al.* measure birefringence, a phenomenon well known in solutions of helical organic molecules such as sugars: because of the helicity of the molecules, right- and left-polarized light propagates through the solution with different speeds, and hence incident linearly polarized light leaves the sample with its direction of polarization rotated.

The same effect happens for alkali atoms in their ground state where the helical orientation is provided by the spin of the valence electrons. Crooker and colleagues' experiments show that the polarization of light fluctuates in time, as the spin magnetization itself fluctuates. But rather than following the maxwellian distribution of classical thermal noise, the temporal fluctuations have a complex spectral structure — hyperfine structure — owing to a delicate interaction between the spin of the valence electron and that of the atomic nucleus. These lines can be resolved, as predicted, despite being narrower than the linewidth of the probe laser. Noise produced by a summation of random events grows more slowly than the system size. Crooker *et al.*¹ show that the noise per atom scales inversely as the square root of the number of atoms, as expected.

Often we study systems by perturbing them — by measuring their response to an external probe. But this approach becomes increasingly difficult for the small systems that are now the focus of many studies in nanoscale or biological sciences. These experiments¹ remind us that 'listening' to the intrinsic noise of a system in equilibrium can provide the same information as does probing it with an external field (which in the present case would be equivalent to performing a conventional magnetic resonance experiment on the electron spins). Crooker *et al.* have provided an elegant example of a general principle, one that might be exploited, for example, in chemical sensors by measuring the thermal vibration of small cantilevers³, or could be used to measure the fluctuations of a single electron spin on a surface using a scanning tunnelling microscope^{4,5}. For the moment, however, it is a practical demonstration of an arcane yet fundamental piece of science, first intuited by Einstein during his *annus mirabilis* a century ago. ■

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