Thermodynamics

Conflicting arrows of time

Entropy is an important indicator in physics of the passage of time. Briefly, time increase is usually matched by entropy increase. Is it possible that the Universe contains regions in which time runs in a direction opposite to ours? This exciting, but unlikely, possibility has been investigated by L. S. Schulman (*Phys. Rev. Lett.* 83, 5419–5422; 1999), who has studied the entropy of two interacting gases of particles with opposing arrows of time.

If such regions exist, can each see the radiation emitted by the other? The laws of electrodynamics have also been proposed as indicators of the passage of time, because

radiation, once emitted, must be subsequently absorbed elsewhere. But electrodynamics, unlike entropy, can be shown to be time symmetric. Indeed, according to the simple cosmological equations for a model universe, such a universe may contract just as easily as it may expand. We know which solution applies to our Universe by comparison with observation.

This problem can be solved using Wheeler–Feynman absorber theory (J. A. Wheeler & R. P. Feynman *Rev. Mod. Phys.* 17, 157; 1945 & 21, 425; 1949). Suppose that electromagnetic radiation is emitted by a system, S, in both

directions of time and as equal parcels of energy. The normal radiation, R , is later absorbed by matter at S' and the remainder, r , goes backwards in time. The particles in the absorber S' are stimulated to emit radiation themselves, which also proceeds with equal energy: half (R') into the future and half (r') into the past. In due course r' reaches S, where it cancels the original wave r emitted by S into the past, leaving only the wave going forward in time, in agreement with observation.

Schulman extends this theory to his two gases with opposing arrows of time, assuming a purely theoretical interaction. He then finds that

the entropy histories of the two systems are affected by their interaction, but not as strongly as might be expected; and the results are “still consistent with electrodynamics”. On this basis, systems with opposing arrows of time may be able to coexist and see each other. Bizarre as it seems, he proposes that such objects could exist in our own Galaxy, and might have properties expected of dark matter.

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Hoxa3 died after birth with deficiencies in the pharyngeal tissues arising from the neural crest, such as absence of the thymus⁴. In contrast, *Hoxd3* mutants survived and displayed skeletal malformations⁵. This difference in the effects of single mutations, added to a rather poor conservation between protein sequences (Fig. 1a) and similar transcript domains, suggested that the two gene products carried different qualitative values. But quantitative traits were also observed when mutations were combined: for example, vertebral defects in *Hoxd3* mutants were worsened by removing *Hoxa3* function as well^{5,6}.

To analyse these interactions in more detail, Greer *et al.*³ replaced either one of these two gene loci by its paralogous partner *in vivo*. They used homologous recombination in an embryonic stem-cell line to substitute the protein-coding region of the *Hoxa3* gene with that of *Hoxd3*, leaving the rest of the transcription unit untouched. This meant that the engineered *Hoxa3* locus contained its own regulatory DNA sequences, but produced a HoxD3 protein (the *Hoxa3*^{D3} allele; Fig. 1b). The endogenous *Hoxd3* locus was modified in the same way to produce HoxA3. These mice (for example, *Hoxa3*^{D3}) were first crossed with mice carrying the corresponding null allele (*Hoxa3*^{null}). Mouse pups with one copy of each modification (*Hoxa3*^{null}/*Hoxa3*^{D3}) survived to adulthood, indicating that one dose of HoxD3 protein was enough to compensate for the normally lethal effects of *Hoxa3* inactivation. Therefore, when expressed from the *Hoxa3* locus, HoxD3

replaced the function of the missing HoxA3. In fact, adult mice lacking HoxA3 but carrying two *Hoxa3*^{D3} alleles were indistinguishable from their wild-type littermates.

In the reverse experiment, Greer *et al.* generated mice lacking *Hoxd3* function that had either one or two copies of the *Hoxd3*^{A3} allele, so that HoxA3 was produced from the *Hoxd3* locus. Again, two copies of *Hoxd3*^{A3} completely rescued the *Hoxd3* null phenotype. But mice with only one *Hoxd3*^{A3} allele were not completely normal, suggesting that the amount of protein produced was important.

Next, Greer *et al.* produced mice that had null mutations in both copies of either the *Hoxa3* or *Hoxd3* genes, but that expressed these proteins from either the *Hoxd3* or *Hoxa3* loci, respectively. As expected, these animals (for example, *Hoxa3*^{null/null}/*Hoxd3*^{A3/A3}) displayed all the alterations associated with HoxA3 inactivation, showing that these Hox proteins, when expressed from paralogous loci, could not compensate for their endogenous inactivation. Previous experiments (for example, refs 7–9) involving gain- and loss-of-function approaches suggested that paralogous Hox genes are functionally equivalent. This elegant bidirectional complementation³ now demonstrates that a Hox protein can prevent all of the defects caused by inactivating a paralogous gene, as long as it is produced from the latter locus.

As both genes are expressed in the same patterns, why do the characteristics of the knock-out mice differ if HoxA3 and HoxD3 are functionally equivalent? One possibility

is that post-transcriptional regulation leads to variations in the distributions of the proteins. This is unlikely, though, as antibody staining for Hox proteins tends to coincide with RNA data. This implies that the overall amount of group 3 proteins is the key determinant and that modulation of this parameter induces various phenotypes. Perhaps *Hoxa3* and *Hoxd3* are differentially regulated, in quantitative terms, in different developmental contexts. Accordingly, neural crest and mesoderm cells may require particular ‘group 3 thresholds’ to initiate developmental programmes, rather than a precise qualitative pattern of gene expression. So inactivation of single genes may lead to local quantitative changes that induce different sets of morphological alterations.

It is possible that individual inactivation of either *Hoxa3* or *Hoxd3* generated defects that have not yet been uncovered, such as a metabolic or psychological problem, and that these defects were not prevented by expression of the paralogous gene. However, these results may reflect a general principle of Hox gene function whereby large-scale amplification of Hox genes early in vertebrate evolution triggered a shift in the functional strategy of their protein products. Instead of a ‘vertical’ scheme, where genes have precise and unique attributes in regulatory pathways, a ‘horizontal’ scheme may be at work, in which developmental decisions are taken by integrating quantitative inputs rather than by relying on genes’ individuality.

In the experiments described by Greer *et al.*, Hox gene duplication was unexpectedly