ESSAY

This title is false

Comparing gene networks to Greek philosophy could help biologists to see the truth, argue **Mark Isalan** and **Matthew Morrison**.

The title of this Essay raises interesting possibilities for the canny reader trying to determine its veracity. If true, then we must accept what it claims: it is false. If false (and there are often reasons to mistrust what you read), its opposite must be the case: the statement is true. And yet it states it is false.

The result, like a dog chasing its tail, should be familiar to anyone who has thought about a gene network or biological process. Common descriptions of biological interactions, such as 'This gene represses itself' or 'gene A activates gene B. Gene B inhibits gene A', are similarly self-referential, potentially causing endless cycles.

Self-referential arguments called 'liar paradoxes' have troubled philosophers for more than 2,000 years. The paradoxes are attributed to both Epimenides (sixth century BC) and Eubulides (fourth century BC). The former, a Cretan, may well have started the ball rolling with his declaration that "all Cretans are liars". Although this formulation is not strictly a paradox (a resolution is that some Cretans are liars), there are stronger formulations, including: 'The following statement is true. The preceding statement is false'.

One way to resolve liar paradoxes is to allow the answer to change over time: 'If the following statement is true, then the preceding statement is false, then the following statement is not true,' and so on. We propose that such paradoxical arguments have analogous counterparts in gene networks, and that the trick to resolving both lies in looking at them explicitly over the dimensions of time and space.

Circular thinking

Scientists have long sought the best language with which to describe biological interactions. Since the 1960s, researchers such as physicist Stuart Kauffman pioneered Boolean models of gene networks. These systems use sequential time-steps to sort out the order of events in the system. Certain networks are straightforward (A makes B makes C), but others contain loops, resulting in a repeating list of events within which can lie recurrent patterns. Generally, as the theoretical biologist René Thomas conjectured in the 1980s, positive

feedback (for example, A makes itself) results in stable states (such as 'on' and 'off'). On the other hand, negative feedback (for example, A inhibits itself) can create stable, oscillatory or even chaotic patterns, depending on the strength of the inhibition and other factors.

Biologists are used to thinking about many systems, including networks of genetic transcription and translation, in such dynamic terms. But they often describe opposing interactions statically, for example with arrow diagrams. Using arrows to point to the factor being activated, and lines blocked with a short bar to point at the factor being repressed is usefully simple, but also potentially misleading.

For instance, consider one of the best-studied genes, the tumour-suppressor protein p53, which is mutated in more than 50% of human cancers. By the early 1990s, after more than a decade of intensive research, it was known that p53 induces production of a protein called Mdm2, which inhibits p53. This simple relationship was interpreted as

'autoregulation', meaning that negative feedback gave stable control of protein levels. It was not until 2000 that it was revealed that concentrations of p53 protein oscillate over time — just as the 'true' and 'false' states oscillate in a liar paradox. Only then were the details of the proteins' dynamic behaviour truly appreciated.
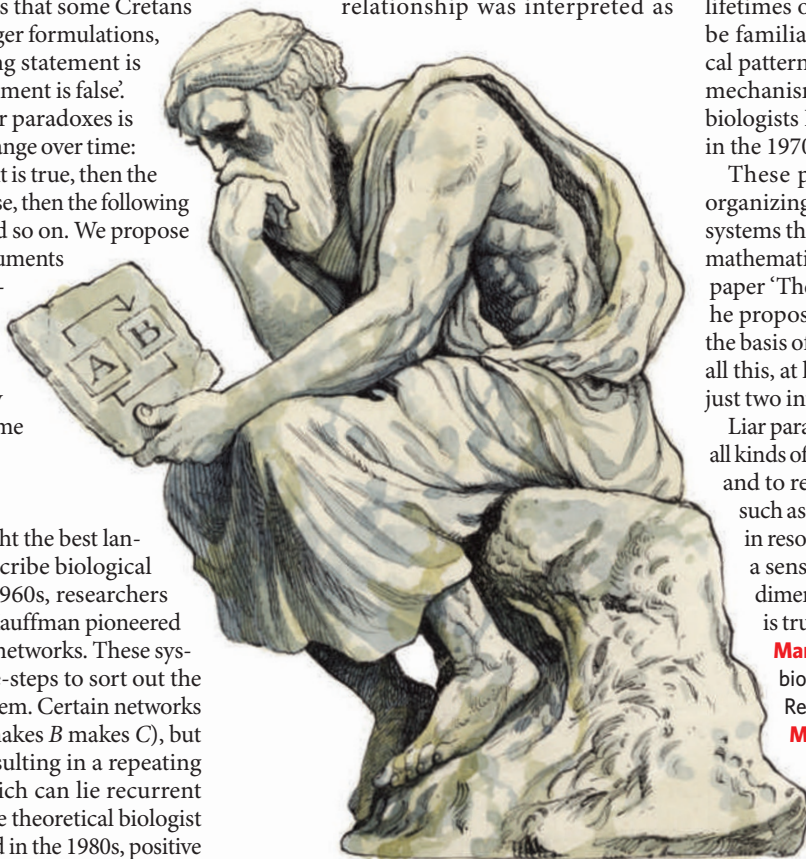
Clear patterns

The same network relationships can produce strikingly different behaviours, depending on the dimensions considered. This can be seen more clearly if we generalize the p53 example to: 'A makes B; B inhibits A'. Take into account both time and space, and something almost magical can happen. Consider: 'A diffuses slowly and activates B. B diffuses fast and represses A'. If one were to chart the result of this interaction, using colour to map when A or B is active over time, complex patterns emerge: spots, stripes or waves, depending on the strength and rates of reaction and the lifetimes of the resulting products. This will be familiar to anyone interested in biological pattern formation: it is the repeat-pattern mechanism proposed by the developmental biologists Hans Meinhardt and Alfred Gierer in the 1970s.

These patterns belong to a class of self-organizing, self-repairing reaction–diffusion systems that were originally discovered by the mathematician Alan Turing. In his classic 1952 paper 'The chemical basis of morphogenesis', he proposed that such reactions could form the basis of all sorts of biological patterns. And all this, at least in theory, can be controlled by just two interacting factors.

Liar paradoxes have inspired us to reconsider all kinds of processes with interdependent steps, and to remember the importance of factors such as time, space and extent of interaction in resolving the true output of a network. In a sense, much of biology may be a multidimensional variant of 'The next statement is true. The previous statement is false'. ■

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See http://tinyurl.com/liaressay for further reading.

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