The bet is on...

From Newton to Hawking, scientists love wagers. Now Lewis Wolpert has bet Rupert Sheldrake a case of fine port that: “By 1 May 2029, given the genome of a fertilised egg of an animal or plant, we will be able to predict in at least one case all the details of the organism that develops from it, including any abnormalities.” If the outcome isn’t obvious, then the Royal Society will be asked to adjudicate. Watch this space...

Lewis Wolpert

I HAVE entered into this wager with Rupert Sheldrake because of my interest in the details of how embryos develop, and how our understanding of this process will progress. In my latest book, *How We Live and Why We Die*, I suggest that it will one day be possible to predict from an embryo’s genome how it will develop, and believe it is possible for this to happen in the next 20 years.

I am, in fact, being a little over-keen because 40 years is a more likely time frame for such a breakthrough. Cells and embryos are extremely complicated: for their size, embryonic cells are the most complex structures in the universe.

Animals develop from a single cell, a fertilised egg, which divides to produce cells that will form the embryo. How that egg develops into an embryo and newborn animal is controlled by genes in the chromosomes. These genes are passive: they do nothing, just provide the code for proteins. It is proteins that determine how cells behave. While the DNA in every cell contains the code for all the proteins in all the cells, it is the particular proteins produced in particular cells that determine how those cells behave.

Every cell of the embryo contains many copies of several thousand different proteins. These proteins have a plethora of functions: acting as enzymes to break down and build other molecules, providing structures for the cell, interacting with each other, and many more. The complexity of the interactions between millions of molecules is amazing.

As the proteins determine how the cells behave, it is their activity that causes the embryo to develop. Underlying this process, though, are the genes, as they control which proteins are made – including some proteins that activate specific genes. It is essential that there is this control over which cells continue to divide, and of mechanisms to pattern the embryo so that different cells develop into different structures, such as the brain or limbs.

There is a huge incentive to understand these processes and so be able to work out the development of an embryo given only its genome. This ability could pave the way for regenerative medicine by allowing scientists to program stem cells to become structures that could replace damaged parts of the body.

To win the bet, we will have to be able to predict the behaviour of almost all the cells in the embryo. In a small worm, say the nematode *Caenorhabditis elegans*, there are 959 cells, making it the ideal model to solve this problem. It is a major challenge, but advances in cell biology, systems biology and computing will take us there.

“One of the nematode worms, with just 959 cells, is the ideal model to solve this problem”

Lewis Wolpert is emeritus professor of biology at University College London. His latest book is *How We Live and Why We Die: The secret lives of cells* (Faber and Faber, 2009)
A BRIEF HISTORY OF WAGERS

Scientific wagers date back to Greece in the 5th or 6th century BC and were often a rhetorical device for thinking about a subject. In their current form, they can also help stimulate fresh thinking.

One of the famous wagers of the more modern era was announced by Christopher Wren in 1684. He would give a book worth 40 shillings to anyone who could deduce Kepler’s laws from the inverse-square law. Isaac Newton took this seriously and his deliberations eventually became his Principia — but too late to claim the prize.

In 1959, physicist Richard Feynman bet $1000 that it was impossible to build a motor no bigger than 1/4s of an inch on each side. He lost: electrical engineer Bill McElhaney succeeded. Feynman was said to be disappointed because he hoped his bet would stimulate new technology, but McElhaney’s motor used existing techniques.

In 1975, Stephen Hawking bet fellow cosmologist Kip Thorne a magazine subscription that Cygnus X-1 was not a black hole. Hawking lost, which is just as well since so much of his work depends on... black holes.

Rupert Sheldrake

LEWIS WOLPERT’s faith in the predictive power of the genome is misplaced. Genes enable organisms to make proteins, but do not contain programs or blueprints, or explain the development of embryos.

The problems begin with proteins. Genes code for the linear sequences of amino acids in proteins, which then fold up into complex three-dimensional forms. Wolpert’s wager presupposes that the folding of proteins can be computed from first principles, given the sequence of amino acids specified by the gene. So far, this has proved impossible.

In all bottom-up calculations, there is a combinatorial explosion. For example, by random folding, the amino-acid chain of the enzyme ribonuclease, a small protein, could adopt more than 1060 different shapes, which would take billions of years to explore. In fact, it folds into its habitual form in 2 minutes.

Even if we could solve protein-folding, the next stage would be to predict the structure of cells on the basis of the interactions of millions of proteins and other molecules. This would unleash a far worse combinatorial explosion, with more possible arrangements than all the atoms in the universe.

Random molecular permutations simply cannot explain how organisms work. Instead, cells, tissues and organs develop in a modular manner, shaped by morphogenetic fields, first recognised by developmental biologists in the 1920s. Wolpert himself acknowledges the importance of such fields. Among biologists, he is best known for “positional information”, by which cells “know” where they are within the field of a developing organ, such as a limb. But he believes morphogenetic fields can be reduced to standard chemistry and physics. I disagree. I believe these fields have organising abilities, or systems properties, that involve new scientific principles.

The Human Genome Project has itself set back the hopes it engendered. First, our genome contains only between 20,000 and 25,000 genes, far fewer than the 100,000 expected. In contrast, sea urchins have about 26,000, and rice plants 38,000. Moreover, our genome differs very little from the chimpanzee’s genome, the sequencing of which was completed in 2005. As Svante Pääbo, director of the Chimpanzee Genome Project, commented: “We cannot see in this why we are so different from chimpanzees.”

“We cannot see in the chimpanzee genome why we are so different from chimps”

Second, in practice, the predictive value of human genomes turns out to be low. Everyone knows tall parents tend to have tall children, and recent studies on the genomes of 30,000 people identified about 50 genes associated with being tall or short. Yet together these genes accounted for only about 5 per cent of the inheritance of height. This is not the only example of “missing heritability”. Steve Jones, professor of genetics at University College London says that “hubris has been replaced with concern”, and he suggests the present approach is “throwing good money after bad”.

Wolpert is not alone in believing in the predictive value of the genome. Governments, venture capitalists and medical charities have bet and are still betting billions of dollars on it. More than a case of fine port is at stake.

Rupert Sheldrake is director of the Perrott-Warrick Project for research on unexplained human and animal abilities. A revised edition of his book *A New Science of Life* is now available (Icon Books, 2009)