Singing life's song

Mon, Oct 06, 2008

GENETICS:A 'systems approach' to DNA could revolutionise the way we understand how our bodies work, writes Claire O'Connell

WHEN HERETICS start to make mainstream sense, you know something is afoot. And physiologist Prof Denis Noble has plenty of statements to make ears prick up. "The genome is not the book of life, and there are no genetic programmes," he says. "There's nothing privileged about genes."

Stirring words indeed from the emeritus professor of cardiovascular physiology at the University of Oxford. A decade or two ago Noble might have been ridden out of town on the proverbial rail for such pronouncements, but research is bearing out the theory that genes are not the be all and end all. Today he is invited to speak to receptive audiences around the world, from hardline geneticists in Europe to the Dalai Lama and Buddhist monks in Thailand.

A founding father of the "systems biology" approach, which uses computers and maths to understand complex interactions in living organisms, his philosophy is coming of age.

We need to move from the reductionist approach that has dominated molecular biology over the past half century to a more integrative model, according to Noble, who addressed the Conway Festival of Research at University College Dublin last month.

"Molecular biology was about understanding the components of a biological system - identify a molecule, find out what other molecules it talks to, and understand their structure. It is the molecular anatomy of a biological system, but it doesn't tell you how it works," he explains. "Systems biology addresses the question of how do the interactions between all of those elements produce the functionality that we know about at a high level.

"So how do the proteins that are involved in heart rhythm talk to each other to produce heart rhythm? Is it written in the genes? No it isn't. Is it at the level of the cell, or at a higher level? Actual normal rhythm is integrated at the level of the cell, but arrythmia or whatever kills when people have a heart attack, is a matter of looking at the heart as a whole," he says.

So the popular perception of our DNA "letters" spelling out a computer programme that dictates to our bodies what to do is now outdated, says Noble. Instead, we need to see our genes as a database - an important one of course - but still just a load of information that makes little sense unless used properly.

And instead of our genes being "selfish" individuals, vying for space in the next generation, it's becoming clear that they work together in complex patterns. "Genes are in the same boat, they have to co-operate if they are going to survive," says Noble. "What is selected for is function - that determines whether you live or die, whether you reproduce or not. And that is quite a high level. There's nothing privileged about genes."

Genes have had the limelight, not least because of the craze sparked by sequencing our very own genome in the early 2000s. It was an undoubtedly remarkable achievement by a species, but even then scientific research was showing that the true answers lay not in knowing the genetic sequence but in understanding how genes are switched on and off, particularly by the environment.

So if genes do not work like computer programmes, what is their role in the greater scheme of things? Noble provides an alternative view in his 2006 book The Music of Life - Biology Beyond Genes.

"I was struggling with the question of there being something wrong with describing the genome as the book of life - there is no genetic programme, there are no selfish genes - how do I begin to get all of that across?" he asked.

He hit on music, and it fell into place. "The genome becomes the CD, it's the basis of being able to take something that was recorded, putting into another machine and being able to be used," he says. "And the [DNA code] is not so much a book of life or a programme, this gibberish code is a bit like a score."

In action, the DNA is "played" like a polyphonic organ, with 30,000 pipes - in this case genes - which harmonise together to create an effect. "It takes people away from thinking of the genes dictating, to the idea that it is an organ that is played and asking what's playing it," explains Noble.

But how does one study such a complicated and non-linear system?

Mathematics and insight, comes the answer. As systems become more complex, it quickly becomes difficult to intuit what they will do and maths helps enormously, explains Noble, who in the 1960s came up with the first mathematical model of heart function.

He quickly jots a calculation on the back of a conference catalogue: each gene can affect up to 100 others. Taking even a highly conservative estimate that each gene in our DNA codes for a single protein (in reality it's many more) . . . that gives us up to 10,300 possible interactions. Given that there are 1,080 atoms in the known universe, the scale of the problem quickly becomes apparent. "It's mind-bogglingly large," he says.

Getting a handle on the complexity requires a concerted effort and Noble is now heavily involved in co-ordinating "physiome" projects around the world to generate standard models of how organs and systems in the body work.

Even the core reductionists are taking note. Noble recently visited the European Molecular Biology Laboratory in Heidelberg, a central hub of molecular biology in the world. He expected to be academically lynched, but was pleasantly surprised. "It's clear that we really can't manage without a systems approach, and when I lectured in Heidelberg people more or less took that for granted. I found I was preaching to the converted," he says.

"Contemplating life and the universe in a profound way leaves you to be almost speechless, so I argue for a certain degree of awe and humilty in the face of nature, which we really have to say we don't understand," says Noble.

"We are never going to work this out simply by looking at the anatomy of the [DNA] code. We have discovered the score - we now have to work out what on earth it means and how you play it."

The Music of Life - Biology Beyond Genes by Prof Denis Noble is published by Oxford University Press for £5.99 (€8)