

Flies, weeds, atom bombs and computers

Why models are the future of biology

'To say that a man is made up of certain chemical elements is a satisfactory description only for those who intend to use him as a fertilizer.'

These words are attributed to geneticist Herman Joseph Muller, who received the Nobel Prize for Medicine and Physiology for work implying a link between exposure to radiation and mutation. The Prize, awarded in 1946, could hardly have been more timely or its subject more topical. The previous August, American President Harry Truman had authorised the release of atomic bombs over the Japanese cities Hiroshima and Nagasaki. 80 000 people were estimated to have been killed directly from the Hiroshima blast. By the end of the year conservative estimates suggested another 10 000 people had died from the effects of radiation.

In the following decades, bomb survivors saw a far higher rate of diseases such as cancer and cardiovascular disease. The survivors of Hiroshima and Nagasaki were a terrible illustration of what Muller had been saying for twenty years: that radiation exposure caused a significant increase in mutations in individuals.



Herman J Muller in his laboratory. Each flask contains scores of drosophila (fruit flies).

How had Muller discovered this? As a student at Columbia University, Muller had been part of Thomas Hunt Morgan's fruit fly lab. Morgan was a pioneer in research with model organisms in the 1910's and 1920's, believing that by breeding and studying fruit flies he could discover more about the genetics of the entire animal kingdom. He argued that it was only by studying phenotype (the outward appearance of the organism) that you could begin to understand the genotype (the sequence of base pairs which is unique to one particular individual) of an individual.

Muller used irradiated fruit flies, which showed a significant increase in altered appearance, to hypothesise that there was a link between the radiation and the changes the fruit flies displayed. He believed that the radiation was changing the flies' genes.

Key words

biomodels
computer modelling
genotype
phenotype



Normal and mutant fruit flies of the species *Drosophila melanogaster*. From the left: the natural or wild type, known as Oregon R, with red compound eye; sepia ebony mutant with sepia eyes and ebony body; yellow bodied mutant; vestigial with greatly reduced wings. *D. melanogaster* has been used for many years in genetic studies because it is easy to raise in large numbers, reproduces rapidly, and many of its mutations are easy to spot under a low-powered light microscope. The adult flies are 2-3 mm long.

Fruit fly

The success of Muller's work is at least partly due to his use of *Drosophila melanogaster*, the fruit fly, in his work. Today, *Drosophila* is one of a host of model organisms used by biologists, including both animals and plants, to make discoveries about genetics and how it links to an organism's development and response to its environment. The success of work with these models has highlighted Muller's statement: that an organism cannot be considered by its chemical composition alone, but must be studied as an integrated whole. Over the past century it has become clear that all biological systems must be viewed in this way, from metabolic pathways to cellular interactions within a tissue to the behaviour of whole ecosystems.

Model organisms are just one of the types of model used in biology. Numerical and statistical models are crucial for medics, businesses, researchers, and Governments. When forests across the US began to wither and die as a result of Sudden Oak Death, modelling was used to map the spread of the disease and predict the most vulnerable areas in the future. Models are now being used to design control plans to halt the spread of the disease, just as they are for diseases such as bird flu.



A botanist collects data during an outbreak of Sudden Oak Death. A computer model uses the data to predict how the disease may spread.

Computer models

For hundreds of years, numerical and statistical models were created by hand. However, computers now offer incredible possibilities for biologists. Computers can rapidly analyse enormous data sets, which are increasingly common as experimental technology and techniques have changed. What's more computers can integrate different data sets, from a multitude of different biological scales (from molecules to continents), see how they interact with each other - and then make predictions based on the results.

Computer modelling has transformed the ways we can understand living organisms. Molecular biology is one of the disciplines that has benefited from the ability to manipulate and model vast quantities of data. With today's rapid genome sequencing techniques, the length of time it takes to sequence a genome has declined from a matter of years to a few hours. The latest techniques mean that you can sequence 5 000 000 000 bases in a day - almost double the length of the human genome. By contrast it took two years for Fred Sanger to sequence the first genome, that of bacteriophage phi-174, which has only 5386 bases.

As molecular biology has developed, new plants and animals have been used as model organisms, which have led to breakthroughs in understandings of biological systems. Professor Elliot Meyerowitz, Director of the Sainsbury Lab, Cambridge, described sequencing the complete genome of the *Arabidopsis thaliana* plant as a "revolution" for biologists. "We now know much of the information content of a plant cell, though in a highly encoded fashion. ... These include not only the functional recipes for plant life, but also important aspects of evolutionary history, thus

forming a resource for future analysis,” wrote Professor Meyerowitz. The information this contains may help us to feed the world’s rapidly growing population, or to use plants as medicine factories producing insulin or breast-cancer treatments such as Herceptin.



Arabidopsis thaliana was the first plant whose genome was fully sequenced, a good choice because the genome is very small. It is a model system used in many studies of plant genetics.

Systems biology

There has been a conceptual shift in science in recent years, partly as a result of our increased knowledge of the links between the microscopic and the macroscopic, and how changes in one can have profound consequences for the other. This is nowhere more evident than in biology, and in particular developmental genetics. For example, a point mutation in the genome can lead to a new phenotype appearing in a population; this phenotype can alter an organism’s fitness and eventually become widespread in the population. This can then alter how the population interacts with its habitat. In response to this change in ideas, ‘systems’ biology has become a widespread academic discipline designed to look at these complex biological systems.

Computer models now allow you to combine several sets of data on different scales and see how changes in one can cause changes in the other. You can try this for yourself by logging on to the

‘ePlant’ online software, which lets scientists look at the genetic sequence of a chosen *Arabidopsis* gene, its amino acid sequence and where these genes are expressed in the plant.



A screen from ‘ePlant’ online modelling software showing the relationship between genetics and development in a model organism.

Going online

The future of modelling in science appears to be firmly rooted online. The rise of the internet has altered the way we process and exchange information. Groups such as SETI (Search for Extra Terrestrial Intelligence) are able to link up with other internet users’ computers in order to analyse huge quantities of data and modelling software like *ePlant* is now being released onto the web, fully accessible to anyone with an internet connection. Models are becoming increasingly interactive: people are now able to both contribute their own data to modellers and use the resulting models themselves. This opens up an exciting range of possibilities for both researchers and the general public. The relatively new academic discipline of systems biology, in particular, is one which is rapidly growing – and certainly one to watch over the next decade.

Freya Scoates is a third-year undergraduate student in the Department of Plant Sciences in the University of Cambridge. She researched and wrote this article as an intern at Science and Plants for Schools, www.saps.org.uk To try out ePlant for yourself, see Freya’s guide at http://www.saps.org.uk/students/supporting-materials/717