robust. 'Holes' left by departing electrons are filled from the other side by an electron donor, and if the two sides are connected across an electrical load, then current flows. In nature, the hole left by a departing high-energy electron is used to oxidize water to oxygen and protons, and this opens yet another tantalizing possibility: the direct production of hydrogen in a photocatalytic reaction.

"I think in the long run you will see more photosynthetic systems making hydride or hydrogen," said Grätzel. But for economically interesting output, the photoreactive centres need to last around 20 years, surviving 100 million cycles. At present, only ruthenium complexes have

demonstrated this tenacity, but Grätzel noted that replacing magnesium ions with copper ions in chlorophyll substantially increases its stability with no reduction in photoreactivity. "We don't just have to drop biological ideas and say now we're going all silicon; we should also look into thermophilic bacteria [for more stable electron transport systems]," Grätzel pointed out. "Studying plants has always been a big inspiration for us; we all admire the plants, and we'll see more of that—research from photosynthesis has very much driven this field."

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doi:10.1038/sj.embor.7400370

minimize the number of expensive experiments and to ensure that they proceed along the right path.

For research biologists in the laboratory, or clinicians treating patients, the obvious question is to what extent they need to acquire expertise and knowledge in mathematical modelling, computation and statistical analysis and how much of it can be left to specialists. The answer is that analysis is now an integral part of biology, and it is increasingly impossible for biologists to remain ignorant of mathematics. "For biologists to know which data to gather, they need to have some idea of what modelling is," said Philip Maini, a professor at the Centre for Mathematical Biology at Oxford University, UK. He argues that experimentalists in biology have only recently started to acknowledge the relevance of theory. Before that, there was a tendency to be easily carried away by the latest techniques for making measurements without thinking sufficiently about whether they were collecting the right data, just as theoreticians may be seduced by what appears to be a beautiful model while ignoring the underlying biology. However, Maini has noticed signs of a growing appreciation on both sides of the need for greater rapport between theory and experiment. "For example, at a recent gathering the experimentalists were getting very excited about what techniques and measurements they could use when one of them said, 'But are any of these measurements going to be useful for the mathematicians?' This is the first time I have heard an experimentalist say this and it is an example of how things are changing," Maini commented.

In turn, mathematical models inform experimentalists and encourage them to explore new avenues that they might otherwise have neglected. An example of this feedback from model to experiment is a device for measuring the electrical and mechanical properties of a single myocardial (heart muscle) cell, developed by Akinori Noma, a well-known pioneer in biological simulation at Kyoto University (Japan; Hassan *et al*, 2004). His team

Laptop biology

As mathematics and computation increasingly invade laboratories, biologists need to master new skills

It is a common sight these days in the cafeterias of biological research institutes: a group of scientists sitting around a laptop computer discussing their results. Even in the laboratory, biologists now spend more time in front of a computer screen—not only to read the latest literature, but also to plan experiments or analyse results. The invasion of computers is just one visible aspect of a growing trend in the life sciences: research is becoming more analytical and multidisciplinary. This transformation from a 'soft' science based largely on experimentation, classification, observation and intuition into a 'hard' science involving mathematics and algorithms, has profound consequences on the skills required in both the laboratory and the clinic. Biologists increasingly have to master mathematical modelling, statistical analysis, image processing algorithms and 3D visualization, while mathematicians and physicists need at least graduate-level biology to engage seriously in the life sciences.

These changes have spanned at least half a century, since X-ray crystallography was first used to reveal the structure of myoglobin, a feat that required collaboration between mathematicians and physicists

(Kendrew *et al*, 1958). But it took years before such interdisciplinary cooperation became commonplace, and it is only recently that some knowledge of mathematics and computation has become essential in almost all branches of biology.

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Experiments and observations remain at the core of biological research, but they now intersect more closely with theory—a situation that mirrors the development of physics a century ago. "I see biologists becoming rather like particle physicists," said Denis Noble, Professor of Physiology at Oxford University, UK, who specializes in computer models of biological organs. Noble argues that, more and more, experiments in biology are being conducted only after models to predict their outcome have been developed, as is the case in particle physics. This is necessary to

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constructed a set of micro-columns made of polydimethylsiloxane, arranged like a miniature line of posts. A single myocardial cell can be attached to the grid by suction, and then stimulated via electrical impulses from tiny electrodes within each miniature post. This causes the cell to move, and the displacement can be measured accurately by detecting the displacements of the posts. Noble

describes the device as a tour de force, exemplifying how the desire for accurate data on the part of theoretical modellers can stimulate experimental work.

But mathematical models are not confined to research and simulation. They also feature prominently in drug and vaccine development, and can save time by cutting down on laboratory work. In some cases, the time saved is measured not just in money but also in human health. An example of this is influenza vaccine development. Flu vaccines must be updated every year because the virus constantly mutates as part of its strategy to evade the host immune system through antigenic shifts of surface glycoproteins. But if information about the current flu strains reaches vaccine manufacturers too late or is incorrect, the vaccine would arrive too late for that year's flu victims. Until now, the World Health Organization has relied on surveillance and expert knowledge to predict antigenic shifts. In an attempt to improve on this practice, mathematical models are now being considered, in particular one developed by Neil Ferguson, Professor of Mathematical Biology at Imperial College, London, UK.

Ferguson's model simulates evolution of the flu virus and the transmission of each viral strain within a constant population of 12 million individuals who are distributed across multiple zones (Ferguson *et al*, 2003). The model takes into account

each individual's immune history and age, and expresses the possibility of transmission of a given strain between individuals as a combination of whether they are in the same zone and, if so, how far apart they are. The 'air travel effect' is also factored in by incorporating a small chance of transmission between individuals in different zones. The aim is to predict not just what mutations will occur, but also which ones will spread successfully within the human population.

The model has already made a significant contribution to understanding human immunity to flu. Although a flu virus needs to mutate to survive, about 95% of new strains fail to infect more than 100 people in the real world. What was not known is exactly why so few novel strains fail to gain a foothold in the general population. But Ferguson, with the help of his model, concluded that there are two types of flu immunity: one that provides permanent defence against a specific flu virus that will probably never be encountered again, and one that provides temporary defence for up to a year against a broad group of flu viruses. His model enabled this pattern to be established much more readily than could be done through experimentation.

Ferguson was initially trained as a theoretical physicist, and brings strong analytical skills to the field of biology. But not every biologist has the luxury of having a mathematician around. It is therefore

imperative that some researchers acquire sufficient knowledge of mathematical models to determine what kind of analysis is most appropriate for their data. The maximum likelihood method, for instance, has become a common tool for determining the most probable evolutionary history of a particular protein or gene (Hillis *et al*, 1994), thus helping to identify the function of a particular protein.

But the maximum likelihood method may not always be the best method. It is complex and computationally intensive, produces different answers according to the model used and can easily give erroneous answers if used naively.

Mathematicians and physicists cannot make significant contributions to biological research without at least a graduate-level knowledge of biology...

These caveats also apply to the use of advanced mathematical concepts, such as nonlinear systems, partial differential equations, the degrees of freedom within a model, Eigen values and Fourier transforms. These enable biologists to analyse complex systems that depend on several varying factors, such as temperature and concentration of different reactants. When finding the solution that best fits their data, biologists also need to understand the general problems that are involved in optimization. In simulating protein folding, for example, the aim is to find the native tertiary conformation of a protein sequence, which is assumed to be the form that requires minimum energy. But if a protein-folding algorithm becomes trapped in local energy minima, it will never calculate the correct native form no matter how powerful the algorithm.

Such techniques have long been taught within physics degree courses, but it is only now that they are beginning to infiltrate biology courses. However, the expertise and knowledge does not flow in only one direction—towards biology from maths, physics and the information sciences. Mathematicians and physicists cannot make significant contributions to biological research without at least a graduate-level knowledge of biology, according to Kouichi Takahashi, a research associate in the Institute for Advanced Biosciences at Keio University in Tokyo, Japan. Having reached that level, they are then well placed to become computational or theoretical biologists, Takahashi commented.

... there is a broad spectrum of requirements that ranges from experimentalists to theoreticians with mathematical biologists in the middle who provide a core of true interdisciplinary expertise

Maini warned against mixing the disciplines too much and thereby diluting the skills. Theoreticians and experimentalists should preserve clearly defined skill sets even though they need a better understanding of each other's expertise in order to communicate and interact better. "More is to be gained from theoreticians and experimentalists bringing their respective skills to the table than having two mathematical biologists," said Maini. This would seem to contradict the current fashion for mathematical and computational biologists. But there is no real contradiction—there is a broad spectrum of requirements that ranges from experimentalists to theoreticians with mathematical biologists in the middle who provide a core of true interdisciplinary expertise. "Not every biologist can become a computer modeller," said Noble. "We need to train a core of scientists who are interdisciplinary so that they know the biology well, have even done some of it themselves, but whose main interest is in quantitative databasing and reconstruction."

However, the demand for cross-disciplinary skills will continue to increase, according to Ajay Royyuru, a senior manager at IBM's computational biology centre in New York,

NY, USA. A study by the Alfred P. Sloan Foundation, also in New York, concluded that, while demand for people with such core skills has actually decreased within the biotech industry due to global economic conditions, it is holding up in academia (Black & Stephan, 2004). Royyuru believes this will be further encouraged as more scientists with interdisciplinary training advance to the highest level of research. But within this interdisciplinary core, the skill sets and the boundaries between them will continue to change, making it even harder to provide all the required ingredients through formal university education. "There will be a need for more continuous education," noted Royyuru. "The more successful folks will be able to teach themselves and integrate information from different disciplines." This will be increasingly necessary, he argued, as biology moves away from the reductionist approach that dominated the science until the end of the twentieth century. "Taking the reductionist approach is not sufficient to understand the complexity of cancer, for example," Royyuru said. "You have to put all these pieces together and know everything about everything."

This is not to say that reductionism is dead. It will always have its place, and there will always be a demand for specialists in particular pathways or reaction centres in which just a few molecules are involved. Many fundamental reactions in biology boil down to pure chemistry, a good example of which is photosynthesis. This field is becoming more important, as attempts to artificially replicate the process to produce hydrogen as a source of clean energy gather pace. But even this requires a combination of skills, and brings together electrochemistry, X-ray crystallography and computation.

It is not only in research that cross-disciplinary skills are becoming essential. They also feature in clinical practice, now that growing amounts of diagnostic data can no longer be assimilated without the help of computers. But past attempts to involve computers in diagnosis have not proven to be very successful. During the 1970s and 1980s, 'expert systems' based on hierarchies of rules were developed for making diagnoses on the

basis of given sets of symptoms. However, these could never be relied on to reach reliably consistent conclusions. But now the role of computers is not so much to reach a diagnosis, but rather to refine it. "Clinicians don't want help with diagnosis, but they want help going through their entire data to find out what the exceptions are," said Royyuru.

Similarly, the massive amounts of data produced during drug trials could also be managed more effectively to reduce the lead time from concept to clinical application, which can be as long as 10 years. So far, computation has failed to achieve this goal, but as the infrastructure and the models mature, this will change, according to Russ Altman, Associate Professor of Genetics and Medicine at Stanford University (Stanford, CA, USA), and a strong proponent of computational biology. "I see the next decade of research being one in which computational modellers work much more closely with experimentalists to adjust their experiments being performed for maximum utility in modelling," he said. "There is no question that the human brain simply cannot handle the volumes of relevant information created, and so computational methods will be required not only to do things well, but to do them at all."

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doi:10.1038/sj.embor.7400358