Making an impact in biology

Physicists are increasingly contributing to solutions to problems in biology, but **Robert G Endres** argues that further funding for fundamental research is needed to reap the rewards of such work

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Endless possibilities Physicists have made major contributions to biology, for example work on protein folding.

In late June a group of physicists from around the world came together at University College London in the UK to talk about the "physical cell". This month a similar conference at Oxford University is being held to discuss "physics meets biology", while another related meeting takes place in Cambridge to look at the "physics of living matter".

What are these meetings about: a secret society or a new exotic field of physics? Are these people like those working on chaos theory in the 1960s, who were so eloquently described in the book *Chaos* by the journalist James Gleick?

No, on the contrary, biological physics is a major field of physics, which aims to understand the workings of living biological matter, just as traditional physics has so successfully explained common non-living matter. In fact, biological physics is a major research field in Germany, France and the US, with biological physics being the fastest growing division of the American Physical Society. So why is biological physics not bigger in the UK?

Historically speaking, physicists have made major contributions to molecular biology, and could even be described as the subject's founding fathers. Indeed, in the 1940s the German biophysicist Max Delbrück, far ahead of his time, described molecular genetics even before the structure of DNA had been discovered. This won him a share of the 1969 Nobel Prize for Physiology or Medicine.

This impact of physics in molecular biology was also felt in the UK. Inspired by Erwin Schrödinger's book *What is Life?* Francis Crick finally transformed the largely descriptive field of molecular biology into a quantitative science. In 1954 he described how the genetic code is reflected in the structure of DNA . Similarly, the British biophysicists Alan Hodgkin and Andrew Huxley, together with neurophysiologist Sir John Eccles, were awarded the 1963 Nobel Prize for Physiology or Medicine for their use of experiments and mathematical tools to explain the operation of "action potentials" – short events in which the electrical membrane potential of a cell rapidly rises and falls.

Major contributions

Despite these milestones, contributions by physicists to biology have been rather scarce as biology has not been fully ripe for quantitative explanation. Nevertheless, some physicists recognized the great potential that physics can offer biology; after all, the distinction between living and non-living matter is blurry and somewhat artificial. A lot of the early work was hypothetical, but brilliant. For example, in 1969 the US molecular biologist Cyrus Levinthal came up with what is now known as Levinthal's paradox, which tells us how amino-acid sequences should not be able to fold into proteins and thus guided future experiments towards its resolution. In 1983, meanwhile, Harvard University biophysicist Howard Berg wrote *Random Walks in Biology*, which examines how cells experience their low-Reynolds-number environment and is still an enjoyable and educational read.

At a more philosophical level, in 1972 the physicist and Nobel laureate Philip Anderson wrote a now famous essay entitled "More is different" for *Science*, which explained that higher-level properties of complex matter cannot generally be derived from first principles and that a reductionist approach must ultimately fail. These ideas are very much alive today and apply directly to biology. For example, bistability and hysteresis are emergent properties utterly independent of molecular details – genetic networks and a simple ferromagnet can produce both these types of behaviour.

In 2004 the Dutch biophysicist Alexander van Oudenaarden of the Massachusetts Institute of Technology in the US showed that hysteresis in the bacterial gene expression is the result of a type of network – positive feedback with co-operativity – that is used by the cells for nutrient uptake. However, the foundation for this astonishing result was already laid out by the biologist and Nobel laureate Jacques Monod in 1941. These examples show that physics can contribute more to biology than just making better microscopes, and claims such as "mathematics is biology's next microscope" by the mathematical biologist Joel Cohen of Rockefeller University have quickly became famous.

Over the last 15 years or so, major, non-trivial contributions to biology have been made by physicists, demonstrating the vast insight physics can deliver. (Of course, all this was made possible by an explosion of biological high-throughput data and the discovery of the green fluorescent protein for imaging proteins in live cells.) My favourites among these contributions by physicists are that protein designability explains why only a small number of protein folds are used by biology despite the infinite number of possibilities, and also that biological networks are not fine-tuned but robust to some system parameters such as variations in gene expression or temperature. Additional studies have shown that, surprisingly, cells with identical genetic material can look and behave completely differently. This can be attributed to the small number of molecules in a cell. Random molecular collisions lead to chemical reactions or not, and hence determine the fate of the cell. But there is a more fundmental connection between biology and physics – both are natural sciences, so making a merger of the two disciplines is obvious.

More physics in biology

Living systems are often conceptualized as networks of interacting genes and proteins, which, although useful tools, obscure the fundamental link between physics and biology. Without doubt, biological systems have evolved under the constraints of physical laws and are optimized to sense and encode physical stimuli encountered by the cell with the statistics of a given environment. Physical stimuli are traditionally thought to be soluble chemicals of the fluid environment, which bind cell-surface proteins (receptors) and activate signalling pathways inside the cell.

However, there is also another important physical aspect of the stimuli, which may affect the process of sensing. For instance, small external molecules (known as ligands) arrive at the cell surface randomly by diffusion, thus making the process of measurement highly uncertain at low ligand concentrations. Additional physical stimuli include forces and shear stresses exerted by the substrate, neighbouring cells or fluid flow. These effects are major determinants of cells and even embryonic development, and hence need to be included. Biological physics can be quite different from the systems-biology movement, which is heavily routed in computer science and the belief that molecular details really matter.

Over the last 15 years, major contributions to biology have been made by physicists

It is important to make sure that physicists have a role to play in future biological research, and how successful that is in the UK will ultimately depend on funding agencies and policymakers. And bigger is not always better. When I did research at the Oak Ridge National Laboratory in the US a few years ago, managers used to say that supercomputers should be used in the upcoming field of biology-inspired research, as this would, in retrospect, justify the lab's investment in a huge computing infrastructure. But they also worried that someone would get "lucky" and find a smaller, more tractable, model or a more efficient algorithm to solve the same problem on a laptop – making the lab's investment into such projects superfluous.

Moving to Princeton University shortly afterwards, I realized that these worries were well founded. Top researchers, by asking the right questions and using clever models, could produce high-impact research results without ever needing supercomputers. I am not saying that we should shy away from using supercomputers. Indeed, problems such as those in climate research, nuclear fusion, together with combinatorial problems such as protein folding, absolutely require them.

What I am mainly advocating is that funding agencies should provide the freedom via small grants for researchers to work on non-hypothesis driven, fundamental research. This is ultimately key for making new breakthroughs, similar to the serendipitous discoveries of penicillin or radioactivity, on which larger research consortia can build for more applied research. As Crick once wrote in *Nature* in an article entitled "Molecular biology in the year 2000", "unexpected discoveries are to be expected!".

Robert G Endres is a biophysicist at Imperial College London, UK, e-mail r.endres@imperial.ac.uk

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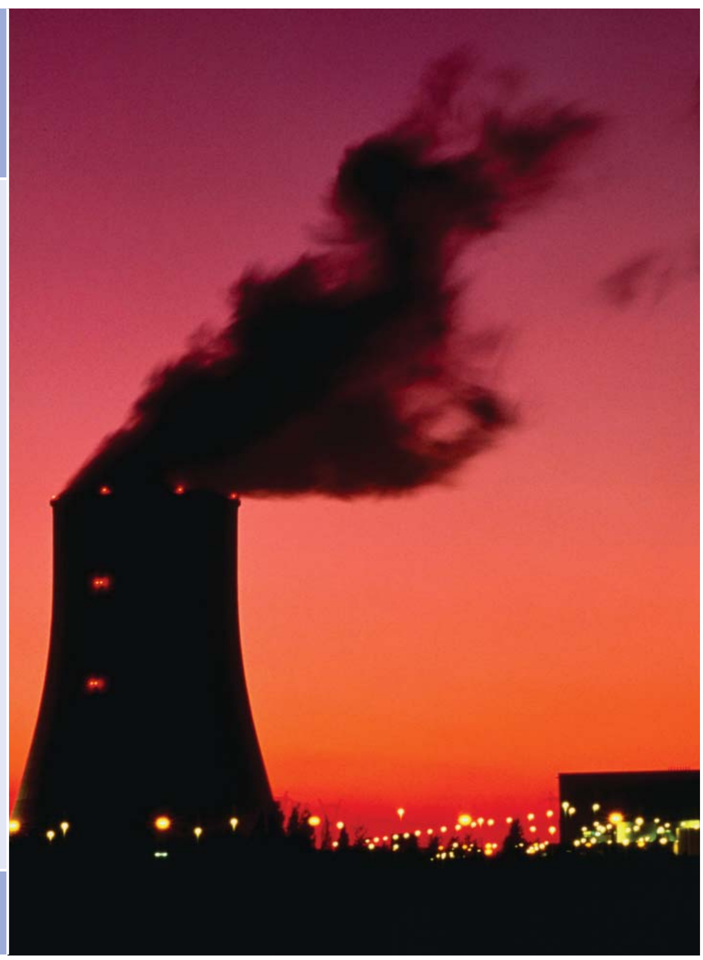

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