PERSPECTIVES

SCIENCE AND SOCIETY

Tackling the challenges of interdisciplinary bioscience

John McCarthy

Abstract | The ultimate goal for biology is to become a science that formulates our understanding of subcellular, cellular and multicellular systems in terms of quantitative, holistic models that are underpinned by the rigorous principles of the physical sciences and mathematics. This can only be achieved through interdisciplinary research that draws heavily on the expertise and technologies of the physical sciences, engineering, computation and mathematics. Here, I discuss the benefits and challenges (both intellectual and practical) of interdisciplinary bioscience.

When Goethe's Faust pondered, "*Wie alles sich zum ganzen webt, eins in dem andern wirkt und lebt*"[1] (How all things blend into the whole, each in the other works and lives), he elegantly expressed the human desire for a comprehensive understanding of the nature of life and the universe. The classic story that underpins this dramatic work had its origins in the sixteenth century, a period during which mysticism was at last being overtaken by science as the accepted means of understanding the world. The development of scientific thought and practice before the Renaissance stretched back over several millennia, and had been comparatively slow and relatively unstructured. Yet, the driving force has always remained constant: the intellectual thirst for knowledge combined with the social need for technology. As we look back at the history of scientific endeavour, it seems unlikely that such influential figures as Archimedes, Leonardo da Vinci, Galileo Galilei, Robert Hooke (BOX 1), Antoine Lavoisier, Michael Faraday or Charles Darwin (to name but a few) would have thought twice about hopping between, or straddling, diverse disciplines in the pursuit of knowledge. Indeed, many of the most innovative scientific discoveries and technological inventions have resulted from work that spans different disciplines.

So, at first sight, it might seem strange that both the value and the particular demands of interdisciplinary working are the subjects of much debate today. However, the reasons for this are not hard to find. Over the past few decades, many developments have cumulatively enhanced both the importance and the profile of research that crosses traditional borders, no more so than across the interface to biology. Interdisciplinary and multidisciplinary research strategies are becoming increasingly vital to many areas of science, and there is a general consensus that we have to create an environment in which they can prosper. Yet at the same time, it is recognized that various 'in-built' barriers function to constrain movement across discipline borders. This article discusses these issues, largely from the perspective of the UK/European research communities, and then attempts to identify the key steps that are required for future progress. The focus is mainly on interdisciplinarity, but much of what is discussed is also applicable, to various degrees, to multidisciplinarity (BOX 2). Given the space restrictions, the subject matter is addressed in general terms, using only a few detailed examples to illustrate certain points.

Perceived barriers and problems

If we are to be in a position to promote interdisciplinarity effectively, it is clearly important

Box 1 | Robert Hooke, an archetypal interdisciplinary scientist

Robert Hooke (1635–1703) was one of the key seventeenth-century figures responsible for establishing scientific method. He made significant contributions to many areas of science, including optics (he outlined a wave theory of light[19]), microscopy (he studied various biological specimens[19]; see figure), astronomy, astrophysics (he formulated a basic gravitational theory) and mechanics (Hooke's law relates spring extension to the force applied). He was a highly innovative and influential inventor of scientific instruments. Indeed, he was one of the first to realize that science could only be advanced through, "the addition of … artificial Instruments and methods"[19]. To cap all these achievements, he had a key role as City Surveyor in the rebuilding of London after the Great Fire of 1666. For all of the above, he has been called "Europe's last Renaissance man, and England's Leonardo"[20].

The figure shows the origin of the term 'cell'. Robert Hooke was the originator of the term cell, which he used in his description of the structure of cork. This illustration is taken from his ground-breaking book on microscopy that is widely referred to simply as '*Micrographia*'[19]. Figure adapted from REF. 19 © The Royal Society.

Box 2 | What do we mean by interdisciplinarity and multidisciplinarity?

For the sake of clarity, the term multidisciplinarity is used in this article to describe collaborative research that involves specialists who each contribute expertise from only one discipline. The term interdisciplinarity, on the other hand, describes research that involves individuals who possess, and apply, expertise from more than one discipline. At present, the latter situation tends to be less common. However, interdisciplinary researchers are increasingly in demand in academia and industry because they are more likely to be able to carry out numerous tasks in complex projects, overcome communication barriers, and find the appropriate way to achieve defined objectives. In this article, the term cross-disciplinarity is used simply as a convenient umbrella term to cover both interdisciplinarity and multidisciplinarity.

to identify the perceived barriers and problems that can inhibit such activity. The word 'perceived' is used advisedly, because the degree to which such constraints apply varies significantly between research areas and is obviously strongly influenced by the environment (and culture) in which the research is carried out. For example, in universities, there tends to be a particularly high level of concern that traditional departmental structures are not conducive to the operation of interdisciplinary research. Each discipline is the custodian of a large body of specialized knowledge and expertise, and it is understandable that departments feel obliged to guard the standards of research and training within that discipline closely. However, if a department assumes a protective position in relation to its core discipline, and/or is inflexible with respect to the management of research, faculty members can feel unduly pressured not to venture too far off the carefully groomed turf. In reality, a balance between discipline-specific and cross-disciplinary research can be maintained to mutual benefit, especially if the university provides the appropriate infrastructure to enable this balance to be achieved (see below).

Coupled to this problem is the fear, especially among young academics, that interdisciplinary research activity might be undervalued, and therefore might place them at a disadvantage in terms of career progression. In the United Kingdom, such difficulties have been compounded by the introduction of the Research Assessment Exercise (RAE), which effectively scores departmental research in the nation's universities largely within single-discipline categories. The RAE tends to be used as a justification for narrowing the scope of research activities to bring them within the single 'units of assessment' that define a department's research remit. Add to this the generally acknowledged problems that are associated with obtaining suitably qualified reviewers for interdisciplinary grant applications, as well as uncertainties about publication strategy, and the resulting mix can be discouraging, especially for those who are at an early stage in their careers.

There are also practical problems associated with pursuing novel interdisciplinary science. The most significant of these is that such research frequently requires special types of infrastructure, facilities and expertise, which are rarely available in one institution, let alone under one roof. The best solution to this problem is to create a physical centre that provides the required support infrastructure and houses all of the required equipment (see below).

The benefits

It is widely recognised that, of all the sciences, biology will benefit most fundamentally from interdisciplinarity over the coming decades. This is because biology is in the process of shifting from its traditionally descriptive (and generally reductionist) bias towards more exact, quantitative investigative strategies that are mostly 'global' and systems-orientated in nature (FIG. 1). At present, the bioscience revolution is driven by key new innovations in theoretical analysis and technology. For space reasons, the discussion has been restricted to two examples — the areas of systems biology and nanoscience, which are discussed briefly below. However, other areas, such as chemical genetics[2], provide equally exciting examples.

The systems-biology approach examines the pathways and networks that underlie cellular function, with the general intention of understanding how the component parts integrate to form the whole. By combining experiment-based knowledge with computational modelling and data mining, system models can be generated, which, in turn, produce predictions that can be tested by further experiments. For example, the consequences of defined perturbations at specific points in a network of genes or metabolites can be compared with the behaviour that is predicted by an integrative model of the network. Systems approaches are often associated with the analysis of 'omics' data, which define the abundance of many or all cellular mRNAs (transcriptomics), proteins (proteomics) or metabolites (metabolomics), but they can actually make use of many sources of quantitative and qualitative data. This strategy for analysing a cell is more akin to process-control theory in engineering and complex-network theory in mathematics than to classic biology, and requires inputs from mathematics, computation and the physical sciences[3–6]. Advances in systems biology must therefore be driven by a highly interdisciplinary community.

On the other hand, biology is slowly, but surely, becoming a science that can predict the properties of cellular components on the basis of atomic and/or molecular data, which will bring it more in line with chemistry and physics. A new type of information is being provided by techniques in nanotechnology, which are revolutionizing the way in which

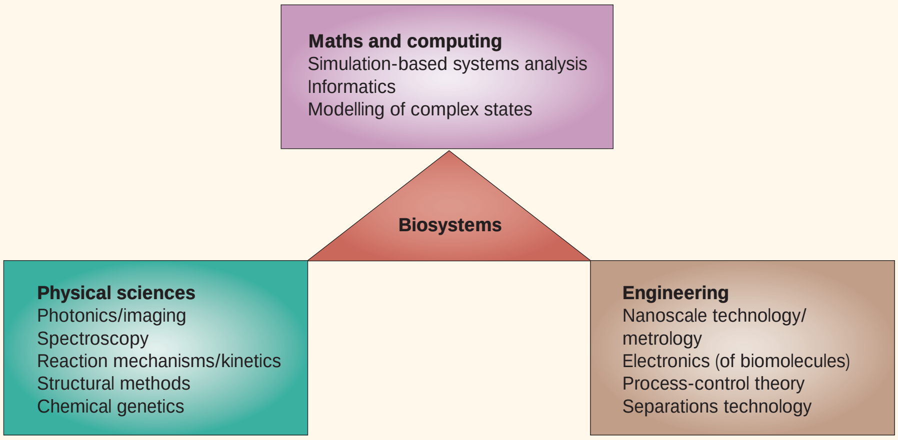
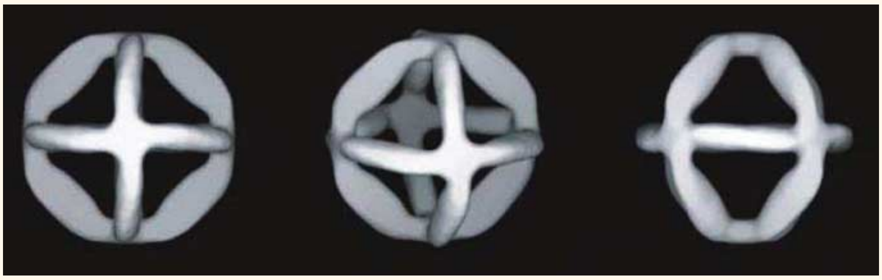


Figure 1 | **The mixture of disciplines that contribute to quantitative bioscience.** Contributions from several disciplines will have important roles in the development of quantitative bioscience over the coming years. This scheme highlights some of the key areas of expertise and technology that will feature prominently and need to be incorporated into interdisciplinary organizations and institutes.

Box 3 | Bionanotechnology



Remarkable new areas of experimentation are springing up at the interfaces between physics, chemistry, engineering and molecular cell biology. For example, by combining biomolecular complexes with nanoscale inorganic or organic systems, it is possible to generate hybrid nanodevices that can function as sensors, actuators, mechanical force transducers, catalysts or optically active components. Examples of the possible types of device that can be created include: nanopropellors that are driven by a bacterial F_1-ATPase[21]; synthetic molecular motors[22]; programmable three-dimensional nanostructures[23] made of DNA (see below and the figure); and chaperonin-encapsulated, cadmium-sulphide semiconductor nanoparticles[24]. The specific base-pairing properties of single-stranded DNA can also be used as the basis of a type of autonomous programmable computer that uses molecules to carry input and output data[25,26]. The pharmaceutical and biotechnology industries are showing increasing interest in the use of what is commonly referred to as 'nanomedicine', because nanoscale devices have potential in the areas of molecular diagnostics, drug delivery and disease therapy (see the online links box).

The figure shows a DNA-based nanostructure — a DNA octahedron, as constructed by Shih and colleagues using one long DNA strand (1,669 nucleotides) and five short 'helper' strands[23]. The images are three-dimensional reconstructions of the octahedron, which were derived using single-particle cryo-electron microscopy. Each strut in this structure comprises two parallel, interlinked double helices. Nanodevices of this kind could be used to convert DNA-sequence 'blueprints' into three-dimensional arrangements of specific binding sites for various ligands. The resulting molecular frameworks could have numerous applications, including the generation of novel lattice structures for use in structural analyses and as a basis for the construction of novel molecular machines (see also REF. 22).The figure is reproduced with permission from *Nature* REF. 23 © (2004) Macmillan Magazines Ltd.

biosystems can be studied. Single biomolecules and complexes can now be both imaged and manipulated, which allows previously unobtainable information to be generated about their rates of movement, the forces they generate, and therefore about their functional mechanisms. Examples of molecular motors that have been studied in this way include kinesin[7], myosin[8], DNA-dependent motors[9], the proton-translocating membrane-bound ATPase[10], flagellar motors[11] and many others[12]. Rigorous theoretical analysis is vital to the correct interpretation of single-molecule experiments (see, for example, REFS 13,14). There are also potential applications for self-assembling systems in the creation of new types of 'nanodevice' and even in computing technology (BOX 3). Clearly, in these areas, physics and engineering are leading the way in opening up new areas of bioscience and biotechnology.

As these, and other, interdisciplinary research areas flourish, they are progressively redefining bioscience. This is evident from the increasing numbers of papers on such cutting-edge work in leading cross-disciplinary journals. Indeed, whatever short-term problems there might initially have been in gaining support for research at the interface to biology, recognition of its significance is certainly increasing now. How, then, should the scientific community develop its competence to tackle interdisciplinary challenges?

New research environments

A crucial challenge is to optimize the academic environment to facilitate interdisciplinary science. Here it is important to realize that a significant barrier to change is essentially cultural. As discussed above, science departments tend to define themselves in terms of core disciplines and/or discipline-specific professional career paths, and therefore generally do not adapt readily to interdisciplinary ways of thinking and working. What is needed is a dynamic and flexible research infrastructure that is not strictly tied to the subject definitions that dictate how science is taught to undergraduate students. Although research ultimately determines what young people are taught, the relationship between research and teaching needs to be quite elastic. There is little doubt that if university-based science is to fulfil its true potential over the coming years, some radical reorganization of university structures is required.

Because research programmes now map less well onto the contours of traditional subject areas, a continuing reassessment of the relationship between research management and teaching activities will be required. In an extreme scenario, the definition of research communities could become largely uncoupled from their affiliations to specific core disciplines, and virtual school structures could draw on the teaching expertise of staff that are spread across various research units (departments) and buildings. An intermediate — and therefore more readily achievable solution — lies somewhere between the traditional, monodisciplinary departmental structure that manages research and teaching and the uncoupled type of structure. A balance needs to be struck between maintaining core expertise in the mainstream disciplines and providing sufficient flexibility in terms of research infrastructure and organization. There is, of course, no doubt that this balance can be more easily achieved by those communities that are above average in terms of size and resources, and have the support of a well-resourced university.

A highly effective strategy to facilitate adaptation to the changing research landscape is to establish well-resourced, theme-led research centres or institutes in which new interdisciplinary communities can be created. In such centres, these communities can develop initiatives that span several different disciplines. The emergence of centres such as Bio-X (Stanford), the Bauer Institute (Harvard) and the Institute of Systems Biology (Seattle) in the USA has been well documented[15–17], and there have also been some exciting developments in the Far East[17,18] (see also the Industrial Technology Research Institute, Taiwan, in the online links box). But what of developments this side of the Atlantic? In the United Kingdom and Europe, the comparative scarcity of large-scale endowment funding and our increased dependence on national funding agencies restrict the rate at which key initiatives get off the ground. However, there has been some progress.

In the United Kingdom, the first large-scale, purpose-built interdisciplinary bioscience institute that is located in a university will soon be completed in Manchester. It will house scientists from all four faculties of the University of Manchester (Engineering and

Physical Sciences, Life Sciences, Humanities and Medicine), and these scientists will pursue an integrated (theoretical/experimental) programme of quantitative bioscience and technology development. An important role of the Manchester Interdisciplinary Biocentre (see the online links box) will be to function as a gateway to biology for physical scientists, engineers, mathematicians and computer scientists, whether this is through new types of training for postgraduates or through the involvement of experienced scientists in the institute's research projects. In Germany, the Max-Planck-Gesellschaft (see the online links box) has generally applied its traditionally interdisciplinary philosophy in its institutes and therefore in its collaborations with universities, and it has recently established an institute in Magdeburg that is devoted to the analysis of complex systems (see Max-Planck-Institut für Dynamik komplexer technischer Systeme in the online links box). There is also a federal initiative on systems biology that involves some 25 German research groups (Systeme des Lebens — Systembiologie; see the online links box) and is initially focusing on the liver. An alternative strategy to combine quantitative bioscience with medicine has been taken in the Institut Curie in Paris, France (see the online links box), which houses chemists and physicists as well as more mainstream cancer researchers. Overall, these and other, generally smaller, initiatives signal movement in the right direction, although much more remains to be done in the European domain. It should be noted that the Manchester and Magdeburg institutes have received a special mention here because they do not restrict themselves to postgenomic systems analysis and the standard 'omics' technologies alone. Success in advancing quantitative bioscience will depend on integrating systems biology into communities that develop and apply new technologies that can provide increasingly accurate information about biosystems from the nano to the macro level (for example, information that is related to molecular structure and dynamics, force generation, reaction kinetics and transport). At the same time, initiatives that are more focused on technology will be important, and the University of Copenhagen, Denmark, has followed this strategy by establishing a Nano-Science Center (see the online links box).

A point of frequent debate is whether virtual interdisciplinary research centres, which comprise groups that are spread across various physical sites, can be successful. In certain limited areas, particularly theoretical ones, this approach might work. However, key advances in quantitative bioscience will probably only be achieved through a tight collaboration between theoretical and experimental researchers who have access to all the appropriate facilities, and this argues for cohabitation in a dedicated centre. Indeed, a more attractive option than an entirely virtual community is to establish a dedicated institute as the physical 'hub' (and scientific focus) and to have 'spokes' that extend out to components of a virtual community. This would allow researchers who are working at the associated sites to become part of an extended community, which benefits from the combination of dedicated facilities and specialist knowledge that can only be provided by a physical centre.

> "…a key challenge for the future is to integrate analytical tools, technologies and theoretical rigour from the physical sciences, engineering and mathematics into the very fabric of bioscience research."

Training

Multidisciplinary projects that are based on collaborations between scientists who have complementary expertise in distinct core disciplines have provided many success stories. However, the special demands of many types of research are best met by teams in which one or more individuals have interdisciplinary training and expertise — at least to the extent that technical language barriers can be readily overcome. It is widely acknowledged in both academia and industry that there is a shortage of scientists with such training and experience, and that an awareness of the value of interdisciplinarity needs to be enhanced through suitable courses and practical training. But at what stage do we start?

The provision of rigorous training in each core scientific discipline in schools and universities is becoming increasingly challenging as the body of knowledge that defines each subject continually grows. Accordingly, there are limits regarding what can be added to school and degree courses without compromising the rigour of core training. However, the judicious use of a limited number of specialized course units at these stages of education would provide students with at least a taste of the power and excitement of interdisciplinary approaches. In addition, it is possible that directing an increased effort towards opening young eyes to new research avenues at the interface to biology might help counteract the declining numbers of undergraduates studying (and establishing careers in) the physical sciences, mathematics and engineering.

Once students have reached the postgraduate level, multidisciplinary and interdisciplinary training can be more readily diversified and intensified, providing a strong platform for continued learning in a range of disciplines through later years. This can be achieved by integrating suitable theoretical and practical training courses into Ph.D. programmes. Purpose-built interdisciplinary institutes will increasingly have a key role as sites for this type of training, not only at the postgraduate and postdoctoral levels, but also through courses and visiting arrangements that are tailored to the needs of more experienced scientists from academia and industry.

Conclusions

Today, mainstream biology remains largely qualitative and descriptive, and a key challenge for the future is to integrate analytical tools, technologies and theoretical rigour from the physical sciences, engineering and mathematics into the very fabric of bioscience research (FIG. 1). A combination of changes will be required if we are to realize this ambitious aim. One key requirement is the need to create research environments and infrastructures that are tailored to the needs of interdisciplinary communities. At the same time, universities will need to adapt their policies on research and education. Degree courses must convey the excitement and importance of quantitative bioscience research to students from across the sciences, engineering and mathematics.

None of the above will be achievable without partnerships between universities, governments, funding agencies, industry and learned societies, and it is reassuring to observe that a broad consensus on many of the points that have been touched on in this article is beginning to emerge. For example, in the United Kingdom, it is particularly pleasing to see the research councils and charities that support bioscience talking to bodies that represent the physical sciences, engineering and mathematics about research at the interface to biology (for information on a number of the bodies that are involved in these discussions, see the online links box). Such interactions will lead to better-informed strategies and policies in many key areas, including university research infrastructure, research funding and training.

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Competing interests statement

The author declares no competing financial interests.

Online links

FURTHER INFORMATION
Biotechnology and Biological Sciences Research Council: http://www.bbsrc.ac.uk/
Engineering and Physical Sciences Research Council: http://www.epsrc.ac.uk/
European Science Foundation: http://www.esf.org/
Foresight Institute — preparing for nanotechnology: http://www.foresight.org/Nanomedicine/
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Nanobiotechnology Center: http://www.nbtc.cornell.edu/
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TIMELINE

Happy Hollidays: 40th anniversary of the Holliday junction

Yilun Liu and Stephen C. West

In 1964, the geneticist Robin Holliday proposed a mechanism of DNA-strand exchange that attempted to explain gene-conversion events that occur during meiosis in fungi. His proposal marked the birthday of the now famous cross-stranded DNA structure, or Holliday junction. To understand the importance of the Holliday model we must look back in the history of science beyond the last 40 years, to a time when theories of heredity were being proposed by Gregor Johann Mendel.

Gregor Mendel, an Augustinian monk who taught natural science, was a man who paid attention to detail. In 1866 (TIMELINE), on the basis of his studies with pea plants, Mendel published a series of observations describing how characters or traits (now known as genes) are passed from parents to their offspring. One important conclusion from his study was that hereditary factors do not combine, but are passed intact to the offspring, and that each member of the parental generation transmits only half of its hereditary factors to each offspring (with some factors being dominant over others). His work became the foundation for modern genetics; we now interpret it as showing that a parental cell with a pair of heterozygous (that is, different) alleles will produce gametes with a 2:2 ratio, such that each allele is represented equally in the haploid gametes (FIG. 1). However, although Mendel's law of segregation was mostly shown to hold true, subsequent studies indicated that this was not always the case. Deviations from the expected 2:2 ratio were first reported by the German scientist Hans Winkler who, in 1930, introduced the term gene conversion to define the aberrant 3:1 ratio that had been observed in yeast tetrads. That is, during the process of segregation of the gametes, a gene-conversion event takes place that converts one allele to the other, so that the ratio of the alleles in the haploid gametes changes from 2:2 to 3:1.

How does gene conversion work? In 1964, Robin Holliday (FIG. 2) from the John Innes

> "The structure at the point of strand exchange later became known as a Holliday junction, and is embedded in history as a central intermediate in the process of homologous recombination."