Integration in action

Sara Green & Olaf Wolkenhauer

The workshop on 'Integration in Biology and Biomedicine' was held in May 2012 at the University of Sydney. It brought together scientists and philosophers to discuss the need for, and practice of, integration in the life sciences.

The workshop on 'Integration in Biology and Biomedicine', which was jointly supported by the Sydney Centre for the Foundations of Science and Sydney University's Charles Perkins Centre and Institute for Sustainable Solutions, was convened at the University of Sydney to explore what is meant by integration, how it works, what it achieves and how it is perceived by scientists and philosophers.

Integration might be best described as a combination of activities that provide a more comprehensive and coherent picture of complex research problems, from combining data, models and methodologies, to merging explanations and establishing closer connections among disciplines. Integration of data has always been important in biology and biomedicine, but in most cases it is done on an *ad hoc* basis, often with a lack of recognition for the importance of the insights that integration makes possible. The integration of data across multiple levels of organization, from subcellular processes to cell populations or organs and whole organisms, is fuelled by powerful new technologies, with interdisciplinarity becoming an integral feature of research. The inclusion of philosophy in this process can facilitate crucial reflection on scientific practice and thereby aid conceptual development and integrative efforts in interdisciplinary collaborations. The philosopher's awareness for language and argument can also play an active role in the development of ontologies, which are central for the use of biological databases.

The need to discuss integration in biology and biomedicine is becoming more urgent, as the amount and variety of data required for understanding any given problem is steadily increasing. Without the understanding that integration can provide, the task of 'keeping up' with the latest advances

quickly becomes overwhelming. Moreover, given that many scientific questions require a range of expertise from different fields, integration across disciplinary boundaries is crucial. The expertise for particular technologies and experimental systems is rarely found in a single lab, institute, or country, and this raises the need for standards and ontologies that support the sharing and integration of data and models across labs. These efforts both facilitate reproducibility and support an integration of knowledge across levels of a system's organization. For example, although many diseases have a cellular basis, it is the combination of the cellular environment, the tissue in which the disease occurs and the physiology of the organ or organs involved that largely determines their genesis and progression. Understanding such diseases requires not only knowledge of cells and subcellular processes, but also a conceptual integration of data and models across multiple levels of structural and functional organization. This in turn requires an integration of different expertise—such as that of molecular and cell biologists, of physiologists and of clinicians.

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However, these forms of integration require a strategic effort from the scientific community and the funders of science. Without a computational infrastructure or funding mechanisms to encourage interdisciplinary and large-scale efforts, these forms of integration will not occur. To this

end, the workshop brought together scientific and philosophical perspectives on integration. The participants discussed key processes in different forms of integration, and the presentations used case studies from biology and biomedicine to illustrate the need for integration and the insight it can provide. This meeting report outlines what is meant by integration in biology and biomedicine and how it can be of value to everyday scientific practice.

Dynamics and contexts of integration

Olaf Wolkenhauer (U. Rostock, Germany) discussed the need for integration in systems medicine. He pointed out that most biomedical research projects are not able to address complex problems directly and comprehensively, and that virtually all projects—even large-scale collaborative research efforts—are forced to 'zoom in' on a specific aspect, subsystem or narrowly defined question. He offered cancer research as an example in which resistance to cell death—a research topic that receives much interest—is really only one aspect of understanding the broader issues of carcinogenesis and tumour progression. Even so, most projects address this problem by focusing on a particular molecule or pathway, using a particular technology in the context of a particular experimental system, narrowing the view even further. In practice, the integration of evidence and results into the formulation of 'theories', 'hypotheses' and 'explanatory models' can occur in leading-edge review articles, but these are few and far between. Wolkenhauer considered the two most well-known examples, the two 'influential hallmarks of cancer' review articles by Hanahan and Weinberg [1,2], in which the authors argue that all cancers have common traits or 'hallmarks' that govern the transformation of normal cells

to cancer—malignant or tumour—cells. Wolkenhauer described how the authors conducted a comprehensive survey of the literature on cancer to reduce the complexity of cancer to a small number of underlying principles that provide general and robust explanations. He argued that this form of knowledge integration, towards the identification of ‘organizing principles’, will be increasingly important in guiding the development of interdisciplinary approaches in medicine.

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Several meeting participants discussed general aspects of integration, informed by examples from biology and biomedicine. William Bechtel (U. California, San Diego, USA), for example, highlighted the importance of integrating experiments and mathematical modelling to understand chronobiology. He explained that the mechanisms responsible for the dynamic synchronization of the mouse period proteins (PERs) could not be found experimentally, and that scientists have had to rely on computational modelling to explain the temporal orchestration of circadian oscillations. Bechtel characterized the results of integration of mechanistic explanations and resources from dynamical systems theory as dynamic mechanistic explanations. He also stressed that the amount of biology that can be explained without the aid of mathematical modelling is shrinking, and that the integration of mechanistic explanations with resources from dynamical systems theory will be a key development in both the life sciences and the philosophy of biology in years to come. This insight was also evident in Ingo Brigandt’s presentation (U. Alberta, Canada): he emphasized how systems biology explains biological phenomena by integrating knowledge on molecular mechanisms with dynamic mathematical models.

Several presentations illustrated how integration has many faces. Sabina Leonelli (U. Exeter, UK) drew on case studies in model organism biology, biofuel research and plant pathogens to distinguish three context-related types of integration:

(i) inter-level integration that combines fields to obtain an understanding of living systems that cut across levels of organization; (ii) cross-species integration, in which the biology of one species is understood by referencing existing knowledge of another; and (iii) translational integration, in which existing biological knowledge is used to devise interventions to improve human health. These differences are important because the process of integration depends on the context in which it is undertaken, and the challenges that arise differ accordingly.

Inter-level integration, for example, merges phenomena from different fields. As such, it requires a collaborative network in which scientific standards for accuracy, validation of data and differences in epistemic goals are evaluated. Cross-species integration instead draws heavily on assumptions about genetic conservation and homology. Finally, translational integration is primarily seen in projects in which research on model organisms is conducted to gain knowledge that can be used in clinical applications, and to develop well-informed interventions for specific ecosystems. In the two latter types, the differences and similarities both between organisms and between data sets must be evaluated to facilitate integration.

Integration as a process

The types of integration discussed at the workshop differed from past concepts of integration derived from philosophical accounts of the reduction of one science or theory to another to create one unified scientific theory. Philosopher Todd Grantham (College of Charleston, USA) presented an overview of the changes in the concept of integration, from the notion of theory reduction to the current consensus among philosophers. Various accounts embrace a non-reductionistic pluralism stressing that there is more to integration than integration of theories. This insight was illustrated by the notion of ‘integrative pluralism’, a term coined by Sandra Mitchell (U. Pittsburgh, USA). Her presentation illustrated how coordination among partial representations does not lead to theory unification by reduction, but to an integration of multiple contributions. Mitchell examined the contemporary sciences investigating protein folding, exploring how the integration of both methods and explanations from structural chemistry, physics and biology contributes to our understanding of the process. She also stressed that

integration is a continuing process of interaction among scientists when, for example, the *in vitro* experimental results of structural chemists are used to modify *in silico* physical models of protein folding, or where *in vivo* detection by biologists of co-expression of multiple proteins in the cell influences conditions for *in vitro* investigations.

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Integration often leads to new ways of thinking about a subject. John Crawford (Charles Perkin’s Centre, U. Sydney, Australia) stressed the importance of the shift towards a systems perspective for the study of soil systems. He demonstrated how an integrated perspective, from human networks to microorganisms, can be crucial for understanding soil organization and recovery. Crawford argued that for many complex systems this means that what is linked to what, and how, is more important than the details of the links. This gives some hope that a system-wide understanding of environmental health systems can be reached by developing models that abstract away from many of the details and instead describe the overall dynamics of the system. The example illustrates that integration often involves a new level of understanding that transcends the previous perspective and explains why integration is not straightforward.

Facilitating integration

The workshop also touched on evaluating interventions to facilitate integrative research. A well-known problem for the initiation of interdisciplinary collaborations is the finding of a ‘common ground’ for the formulation of a joint research problem, hypothesis development, data analysis, interpretation and application. Leonelli and David James (Garvan Institute of Medical Research, Sydney, Australia) stressed the complexity of the process of integrating data, as data have evidential value in relation to specific standards that can differ with research contexts. Therefore, reuse of data in a new research context necessitates an examination of the relevant information about its production, including the methods used, models used, explanations

assumed and so on. Each of these, they argued, needs to be addressed by online databases that serve to transfer data across research contexts.

The workshop illustrated how interactions among scientists, social scientists and philosophers contribute to the goal of understanding the challenges faced in biology and biomedicine, and how greater integration might address them. A specific example of the benefit of combining resources from philosophy, social sciences and the natural sciences is the 'Toolbox Project' [3], as presented by Michael O'Rourke (U. Idaho, USA) and Stephen Crowley (Boise State U., USA). Given that many of the challenges encountered in cross-disciplinary projects include conceptual and epistemic differences, the questionnaires distributed to the participants of a 'Toolbox Project' workshop are designed to draw out a scientist's views on

philosophical aspects of his or her work. The resulting dialogue among scientists in different specialities, facilitated by philosophers, enables researchers to immerse themselves in the language, culture and knowledge of their collaborators, and thereby aids integration across disciplines.

In summary, the workshop offered insights into the nature of integration as a productive process. Integration is not the straightforward addition of knowledge derived from different disciplines, but rather requires the effort of a collaborative dialogue that, if successful, generates a new level of understanding. By reflecting on the different types of integration that occur in science, it is possible to gain deeper insight into large-scale scientific endeavours, which might ultimately influence how we conceive of the dynamics of science and the activities of integration themselves.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Sara Green is at the Department of Physics and Astronomy, the Centre for Science Studies, Aarhus, Denmark.

E-mail: sarag@ivs.au.dk

Olaf Wolkenhauer is at the Department of Systems Biology and Bioinformatics, Rostock University, Rostock, Germany.

E-mail: olaf.wolkenhauer@uni-rostock.de

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