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From molecules to systems: the importance of looking both ways

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ABSTRACT

Although molecular biology has meant different things at different times, the term is often associated with a tendency to view cellular causation as conforming to simple linear schemas in which macro-scale effects are specified by micro-scale structures. The early achievements of molecular biologists were important for the formation of such an outlook, one to which the discovery of recombinant DNA techniques, and a number of other findings, gave new life even after the complexity of genotype–phenotype relations had become apparent. Against this background we outline how a range of scientific developments and conceptual considerations can be regarded as enabling and perhaps necessitating contemporary systems approaches. We suggest that philosophical ideas have a valuable part to play in making sense of complex scientific and disciplinary issues.

1. Introduction

Our central concern is with the development and status of molecular perspectives in cellular and organismic biology since the middle of the twentieth century. The topic can be approached by way of a variety of questions. In particular, what are we to make of the claims made at various times that molecular biology is, or is not, a reductionist enterprise? And does recent interest in systemic approaches to biology, and widespread talk of complexity and emergent phenomena, reflect the demise of reductionism?

We consider these and related questions in terms of two major themes. One addresses the development and accomplishments of molecular biology, which unquestionably occupies a central place in late twentieth-century biology. After outlining some of the complexities of its disciplinary history we describe some of its distinctive characteristics and the nature of its early achievements. We go on to consider how it is that, starting from a consensus in the 1980s that a molecular perspective was the most likely to deliver ultimate biological insight, biologists are now looking to new approaches for gaining predictive knowledge—albeit often by drawing on the resources of longstanding scientific traditions. Our second major theme, then, is a set of issues associated with the growing prominence of systems perspectives in biology (O'Malley & Dupré, 2005). These perspectives often incorporate a significant philosophical component, relating to the nature of causation and the possibility of emergent properties. We examine these and related ideas, and conclude that they have a valuable part to play in shaping how we should view biological systems and the appropriateness of taking reductionist positions towards them.

2. Biology goes molecular

The twentieth century witnessed the transformation of biology from a largely descriptive and classificatory science to one that highlighted the link between explanation and experimental intervention. Some of the impetus for this change came from the development in the first half of the century of new physical techniques such as X-ray crystallography, chromatography, and centrifugation. Significant elements of this work were funded by the Rockefeller Foundation as part of its programme of philanthropic social engineering (Kay, 1993).[1] Out of these developments

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[1] In this brief overview it is not possible to do full justice to the complexity of molecular biology's disciplinary identity or the contested nature of its history; our aim is to provide a 'low resolution' account. The importance of Rockefeller funding has been much debated (Kohler, 1976; see also the series of articles that appeared in 1984 in *Social Studies of Science*, *14*). An extensive literature looks at the nature of molecular biology's relationship with biochemistry: despite apparent tensions (see for example Gilbert, 1982; Cohen, 1984; Brenner, in Wolpert & Richards, 1988; Abir-Am, 1992), collaborations were numerous and highly productive (de Chadarevian, 1992; see also de Chadarevian, 2002). Notable too are the differences between molecular biology's disciplinary formation, in terms of institutions, professional bodies, and journals, in different national settings (Krige, 2002; Strasser, 2002).

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came new capacities to isolate physically the components of biological systems and to characterise their structures at a molecular scale. By the 1950s a new discipline was consolidating around these capacities, allied to new-found abilities to manipulate the genetic processes of microorganisms, and by the early 1960s it had a name: molecular biology (Olby, 1974; Judson, 1996; Morange, 2000).

Molecular biology can be conceived in several quite distinct ways. On one reading, it is just a way of referring to biology done through a predominant focus on the details of molecular processes; or, better perhaps, it is research that looks to the molecular scale for answers to biological questions posed at any scale. On another reading, it refers to a particular historical research programme that aimed at elucidating fundamental genetic processes, and so gave rise to molecular genetics. This programme gained a coherent identity through the employment of specific techniques, tools, and resources, and the development of a distinctive research ethos. We are referring here, of course, to the several streams of research that followed the solution by James Watson and Francis Crick in 1953 of the structure of DNA. That key event was followed in remarkably short order by the working out of the nature of the genetic code and the principles of protein synthesis, and by the discovery of some of the ways in which molecular mechanisms are regulated to realise, in an apparently teleological way, certain metabolic capacities. The detailed elaboration of the process by which particular sequences of nucleotides in DNA are 'transcribed' into messenger RNAs, which are then 'translated' into polypeptide chains led to the development of the 'central dogma' that has structured most subsequent research in molecular biology. The dogma is generally understood to assert that causal determination runs from DNA to RNA to proteins, but never in reverse, although Crick in his original formulation speaks in terms of information flow (Crick, 1958, 1970a).[2]

These two interpretations of molecular biology, as a focus on molecular detail and as a historical programme, are not unconnected, of course. The historical programme gave rise to a variety of new genetic manipulation techniques and tools that have been adopted by other biological disciplines, with those disciplines sometimes individuated on biological or functional criteria with no direct reference to physical scale (for example immunology or oncology). It can be argued that the export of these techniques led molecular biology to lose much of its original disciplinary identity. At the same time, that part of the historical programme in which methods for determining macromolecular structures were developed and refined tended to consolidate under the banners of structural biology or molecular biophysics. The separation of the structural from the genetic was not total, however. Genetic engineering techniques gave rise to possibilities for 'site-directed mutagenesis', and in the 1980s structuralists and biotechnologists began to talk of 'protein engineering' (see for example Oxender & Fox, 1987) as a way of intervening in natural proteins, and even of designing novel ones, in order to investigate structural and functional fundamentals and to realise new functional properties. By around the same time, physical chemists had brought nuclear magnetic resonance spectroscopy (NMR) to a state where it too could be applied to biological macromolecules.[3] The technique is usefully complementary to X-ray crystallography since it can be used to study molecules in solution rather than in crystalline form, and hence is capable of illuminating aspects of dynamic behaviour. Meanwhile the invention by Kary Mullis in the 1980s of the polymerase chain reaction, and the further development and automation of nucleotide sequencing techniques (the descendants of those developed by Fred Sanger and others in the early days of molecular biology), culminated in the sequencing of the entire human genome. Indeed the evolution of sequencing technology constitutes one of the clearest links between molecular biology as a historical programme and present-day genomic and post-genomic biology. This continuity yields a third sense of molecular biology, as the expanding set of genetic technologies and methods available to biologists today.

In summary, it is helpful to think of molecular biology's pre-1953 period as the formative coming together of a number of different strands of research. (Mutual interaction would substantially modify the strands but not result in the complete loss of identity.) Then, in a phase that lasted until the mid-to-late 1960s, came the working-out of the programme implicit in the central dogma, involving the elucidation of gene-protein relations in terms of coding, transcription, translation, and regulation. A subsequent broadening of scope, in which the new knowledge and methods were applied to problems in cell and developmental biology, was paralleled by the development of recombinant DNA technologies. The latter reshaped molecular genetics and almost every other field of biological enquiry, and of course gave birth to the modern biotechnology industry. It is important, in any discussion of whether molecular biology was or is reductionist, not to lose sight of these different interpretations of the term.

3. Reductionism and molecular biology

The identification of reductionist tendencies within various biological programmes has a long history, and in relation to molecular biology there has been considerable variety to the specific claims made. It is worth briefly reviewing some of the term's different senses, to serve as a basis for orientation and comparison. First, the everyday use of 'reduce' and its cognates to connote quantitative diminution should be noted. A common but slightly more technical sense of reduction is to denote explanatory practices that emphasise the role of a single factor (Dupré, 1993, p. 87); this could be referred to as unifactorialism. (Here the quantity that is diminished is the number of parameters in the explanatory model.) A second sense is mereological reductionism: the idea that structural wholes can be decomposed into parts, and that the properties of wholes can be accounted for in terms of those of the parts. When conjoined with metaphysical monism about the material substrate of the universe one obtains a view that dominated philosophy of science for much of the past fifty years. This is the view formulated, famously, by Paul Oppenheim and Hilary Putnam (1958), who conceived of nature as being constituted by a hierarchy of objects that, in turn, defined a hierarchy of distinct sciences. At each level above the root level the objects are structures composed of objects from the next lower level. Thus elementary particles combine to form atoms, and atoms combine to form molecules; so the hierarchy ascends through living cells, multicellular organisms, and social groups. The sciences are individuated on the basis of the ontological level with which they deal, and scientific reduction, on this model, consists in relating the laws pertaining to the objects at one level with those of the next lower level via bridge principles that identify the objects at any level with the set of lower-level objects of which they are composed.

Oppenheim and Putnam contended that such theoretical reductions might well be possible. Since these reductions were thought of as involving deductive derivation they would be transitive, and hence they implied that biology, say, might ultimately be reduced to physics by a process that can be thought of as a collapsing of

[2] We do not intend in this paper to add to the extensive literature on the possible application of the concept of information in contemporary molecular biology. We do however mention the significance attached to the ideas of coding and information by the historical programme's leading proponents, since it was one of its most distinctive disciplinary features.

[3] Richard Ernst was awarded a Nobel Prize for his part in the development of NMR methods in 1991; Kurt Wüthrich was a recipient in 2002 for his work on applying the technique to proteins. Felix Bloch and Edward Purcell, who discovered and developed the technique's physical underpinnings, became Nobel Laureates in 1952.

ontological levels. We shall refer to this variant as ontological level reductionism. Modern philosophical treatments of reduction tend to resolve the concept into separate aspects that distinguish between methodological and theoretical concerns, and between ontological and epistemological issues. Another tactic has been to recognise a distinction between reduction as it might describe actual scientific practice and as it pertains to metascientific philosophical analyses of the conceptual structures of science. (Sarkar, 2005, provides a useful overview of these different issues.)[4]

What Crick meant when, in the script for his 1966 Cherwell-Simon Lecture, he wrote that molecular biology just is 'explaining anything biological in terms of physics and chemistry' is not entirely clear. Later on he baldly states that 'physics can explain everything, chemistry and biology included'.[5] Certainly the words suggest a belief in some kind of disciplinary annexation by physics of chemistry and biology, something like ontological level reductionism. There is an obvious parallel here with J. D. Bernal on chemistry: a 'slight imagination and plenty of donkey-work, and chemistry will emerge as a branch of physics' (quoted in Brown, 2005, p. 39). But Crick may have been talking more about the methods most likely to yield knowledge than about the objects to which ontological priority should be accorded. He also stressed the value of theoretical conjecture and the making and testing of hypotheses (a characteristic shared with Max Delbrück), and it is tempting to associate an attachment to the role of theory with their backgrounds in physics. The drive to theory manifested itself especially in the concepts of coding and information; Crick 'formalized the information discourse as a way of imposing thematic order and rhetorical imperatives on the central problem of protein synthesis, reproduction, and the disciplinary turf of molecular biology' (Kay, 2000, p. 29). Sydney Brenner stresses how different this perspective was from that of biochemists:

> ... in the early days of molecular biology, it was an evangelical movement. Most people were against us. Most of the biochemists didn't understand the nature of the problems that we thought were interesting and important. They had a completely different set of attitudes ... I can remember meetings at which it was impossible to get across to people the idea that the most important thing in protein synthesis was how the order of the amino acids got established. They said, 'That's not the important problem. The important problem is, where does the energy come from to join the amino acids?' Well, we have written, on many occasions, that the sequence is the important thing, and never mind the energy, it'll look after itself. And really, this is what this part of molecular biology brought. It said that the flow of information can be studied at the chemical level. I don't think biochemists actually understood the importance of information at that level. It wasn't information theory, it was the flow of messages, and we tried to seek for explanation in terms of the molecules. (Brenner, in Wolpert & Richards, 1988, pp. 101–102)

It is hard to deny the fruitfulness of information concepts as a way of framing the discipline's core problems in ways that could motivate and guide research. However, it is not obvious how best to relate such concepts to claims about reductionism. Rather than being reductionist devices burdened with ontological implication they look more like functional attributions that might usefully be regarded as epistemic tools: templates projected onto the phenomena in order to generate predictions, direct attention, and give coherence to findings. As such their role might be considered in relation to the integrative aspirations to which Gannon has drawn attention:

> In the 1950s, a new sect of biologists entered the laboratories. In an exaggerated form they worked with the molecules of life, but aimed to integrate them into the biology from whence they came. If the biochemists stressed the inanimate chemistry in the molecules they obtained from living sources, the molecular biologists tried to put the puzzle back together by demonstrating their consequences for life. (Gannon, 2002, p. 101)

There was distinctiveness too in the ways in which theory was connected with experimental practice. Both Delbrück and (for a time) Crick were notable for the elegance of their genetic experiments, in which they strove for simplicity and standardisation.[6] This approach, although often involving work with complete microorganisms, endorsed reductionism to the extent that it seemed to reflect a faith that the properties determined in artificial laboratory set-ups carried over in some straightforward way to native states. Yet Delbrück was also (like Gunther Stent[7]) partially anti-reductionist, in that one of his prime motivations in turning from physics to biology was the belief that in biology might lie laws that were complementary to, but distinct from, those of physics (Delbrück, 1949).

4. Molecular determinism's dual origins

So far we have seen how the status of classical molecular biology in relation to reductionist concepts is ambiguous; there is no unique or obvious sense in which its most distinctive features are captured by the philosophically traditional notions of reduction. Nonetheless, molecular biology did encourage a biological *Weltanschauung* that accords priority to DNA as a causal agent within the cell, and that encourages the belief that a detailed understanding of individual molecular properties may be sufficient to account fully for cellular and organismic phenomena. The first claim, about the causal priority of DNA, may be thought reductionist in at least the unifactorial sense, while the second claim appears to be about the possibility of collapsing ontological levels into the molecular. We think there are a number of reasons why this position of molecular determinism was reached, but one very significant factor is the success achieved in relating the first crystallographic structures of biological macromolecules to their biochemical properties and physiological functions.

As is well known, the structure of DNA proposed by Watson and Crick immediately appeared to answer questions about the material basis of replication and heredity, and about its mutability and stability. The early work on proteins was equally important, however, for it showed with compelling elegance how biochemical and physiological properties and functions can depend on molecular properties grounded in fine structural detail. The first enzyme structure to be determined, that of lysozyme, enabled David Phillips (its solver) to propose a mechanism that accounted for the

[4] A painstaking analysis of the merits and defects of the numerous variants of reduction would be out of place here, since one of the points we wish to make is that reduction, to the extent that the concept can be given a precise sense, fails to connect with the scientific issues. On the other hand a liberal construal of the concept, such as that of Fuerst (1982), which sees reduction in the context of molecular biology as a complex 'system of belief', seems to us to raise as many questions as it answers.

[5] Peculiarly, this assertion is written within quotation marks. Did Crick regard it as a caricature, or merely an encapsulation of a way of thinking? We favour the latter interpretation.

[6] The contrast with the research strategy of biochemist Otto Warburg, who wrote that 'Solutions usually have to be forced by carrying out innumerable experiments without much critical hesitation' (Krebs, 1981, p. 67), is marked.

[7] Stent's position appears complex. In the late 1980s he advanced the view that 'science is, by nature, reductionist, but I also believe that reductionism will not carry us all the way. One of the reasons why I think that science will eventually peter out is because you must always explain some higher level in terms of some lower level—that's what scientists have to do. But I think that when finally we get to sufficiently complex things, this will not be possible. It is precisely because I think reductionism will have to fail, that I believe that science is coming to an end' (Stent, in Wolpert & Richards, 1988, p. 119).

ability of the molecule to catalyse the cleavage of the sugar backbone of the peptidoglycans found in bacterial cell walls (Judson, 1996, pp. 557–560). Even more dramatic was the work of Max Perutz and co-workers connecting the bulk respiratory properties of blood, in terms of haemoglobin's unusual oxygen uptake–release characteristics, with the detailed structure of the molecule. It was found that the binding of oxygen to the haem group of one of the molecule's four monomers causes a structural change that is mechanically communicated to the other monomers, and that the effect of this change is to increase their affinity for oxygen. The elucidation of this cooperative mechanism was important because it accounted for certain aspects of respiratory physiology, and explained the effect of oxygenation on haemoglobin crystals observed microscopically by Felix Haurowitz and detected crystallographically by Hilary Muirhead (ibid., p. 545). Moreover, it played an instrumental role in the development by Jacques Monod of a general theory of allosteric interactions (ibid., pp. 545–555). It is not hard to see how such success in tracing the causal basis of biological function right down to microstructural details might encourage, if not necessarily justify, a faith in the capacity of molecular knowledge to explain many—perhaps all—biological phenomena.

Belief in the causal priority of DNA in the life of the cell is of course closely related to genetic determinism—the thesis that there are things called genes and that they are the key determinants of biological form and function. The two ideas are distinct, however: one can dispute the identity and existence of genes without doubting the causal primacy of DNA, for example. In practice however the two views tend to be held simultaneously: DNA has causal primacy *through* the action of genes. Again, the initial success of molecular biology in explicating fundamental mechanisms of gene action lent weight to the view that complete knowledge of molecular phenomena could be expected ultimately to furnish a full account of cellular and organismic biology.

5. Tools and data in transition

The success of molecular approaches in providing insights into fundamental biological problems might make current interest in systems perspectives and in such ideas as emergence and holism appear, prima facie, somewhat curious. Part of the explanation of this development is that molecular biology, in elucidating the details of cell function, soon revealed greater and more intractable complexity than the early successes had led many to expect. Shapere was presumably reflecting a strand of prevailing scientific thought when he wrote in 1969:

> Phenotypic characters may be determined by many non-allelic genes, and one gene may affect more than one phenotypic character. Identical genes operating in different environments may result in different phenotypes ... In regard to both heredity and development, it appears likely that at least some role is played by the cytoplasmic organelles as well as by the DNA structure in the nucleus. (Shapere, 1969, pp. 8–9)

And by the early 1970s molecular biologists themselves were beginning to see genotype–phenotype relations as being too complex to be completely captured by simple linear schemas. Work such as that carried out by Brenner and co-workers from the early 1960s on the nematode worm *Caenorhabditis elegans* was an important factor underlying this shift in perspective (de Chadarevian, 1998; Ankeny, 2001), which Stent further elaborated a little later in relation to developmental neurobiology:

> I give it as my view that development cannot be understood as a programmatic phenomenon ... its programmatic aspect is confined mainly to the assembly of polypeptide chains ... But as for the overall phenomenon, it is most unlikely—and no credible hypothesis has, as yet, been advanced how this *could* be the case—that the sequence of its events is isomorphic with the structure of any second thing, especially not with the structure of the genome ... the goal of developmental neurobiology ought not to be phrased as the understanding of how genes build nerve cells and specify the neural circuits that underlie behaviour, but as the discovery of epigenetic functional relations, or algorithms. (Stent, 1980, p. 51)

In 1970 Crick noted that 'in the long run, problems involving complex interactions can hardly be avoided, since some of the most profound aspects of biology are of this character' (Crick, 1970b, p. 615). A few years later he proposed that biologists should seek 'the intellectual satisfaction of having a single living cell completely explained', with *E. coli* K12 the suggested focus for their attentions. He foresaw practical difficulties, however, noting that it 'does not seem very probable ... that all the various proteins of the cell (which may number several thousand) will all have their amino acid sequences and stereochemical structures determined' (Crick, 1973, p. 68).

If the complexity of biological systems was increasingly recognised then why were the expectations of genomics, from the 1990s onwards and culminating in the Human Genome Project (HGP), so high? A plausible answer is that the new outlook failed to take root fully or become established as the dominant view. For in the mid 1970s recombinant DNA technologies arose out of molecular genetics, and these soon proved to be indispensable tools for investigation across the biological sciences. The development of site-directed mutagenesis techniques, in conjunction with the rapid development of molecular modelling techniques, gave rise in the 1980s to the possibility of protein engineering (Ulmer, 1983; Oxender & Fox, 1987). At the same time Christiane Nüsslein-Volhard and others were showing how the formation of organismic body plan depends on processes that involve highly conserved gene sequences. Thus by the late 1980s the climate was one in which the power of the gene, and of molecular genetic and associated techniques, appeared to be unquestionable.

With the advent of genome sequencing projects attention turned once again to the nature of genotype–phenotype relations. Some commentators were remarkably quick to draw attention to the gap between the amount of genomic data acquired (and the ease with which such data can be acquired) and our ability to transform it into predictive knowledge.[8] Insufficient attention to epigenetic processes, a failure to take account of the integrated nature of biological systems, and excessive commitment to genetic determinism were cited as explanations of the gap (Strohman, 1994, 1997; Huang, 2000). There was not just the quantitative embarrassment of data, but also a qualitative issue concerning what was being learnt about the richness and diversity of genomic processes. RNA processing was found to be baroque in its complexity, for example, and, while there remains an important kernel of truth to the central dogma, it has become clear that the relationship between the genome and phenome is best characterised in terms of causal interdependency. (Epigenetic factors can result in heritable patterns of base pair methylation, for instance.) Genes, like proteins, are found often to possess multiple functions, which are sometimes critically dependent on cellular context, and the specificity of enhancers for promoter sequences is often surprisingly loose (Hampf & Gossen, 2007). Moreover, the interpretation of the term 'gene' is

[8] 'How much more data do we need to add to the already more than 12,000,000 computer-searchable references represented in *PubMed* before we begin to take this task seriously?'—the task being to build 'the scientific infrastructures that will enable an integrated understanding of the function of complex organisms and chronic diseases'—was a question that the Editor-in-Chief of *Physiological Genomics* still felt compelled to ask in 2004 (Cowley, 2004, p. 285).

looking more uncertain now than ever (Griffiths & Neumann-Held, 1999; Moss, 2003).

The erosion of confidence in genetic determinism has been accompanied by a reduction in willingness to pin all scientific hopes on the other, more generic aspect of molecular determinism: the idea that molecular-level detail alone will necessarily deliver complete biological insight. Such doubt stems largely from the perception that protein engineering and rational approaches to drug design have not, so far, provided the expected return on intellectual or financial investment. Thus a motivational shift has occurred that can be characterised as an increasing readiness to look beyond narrowly molecular perspectives for answers to biological questions.

This characterisation of the interplay between scientific findings, beliefs, and motivations is only part of the story. Another part concerns what it is in disciplinary terms that connects molecular biological traditions with recent developments. How, as data and knowledge accumulated, did changing assumptions and practices play out through individual scientists, projects, and institutions such that we got to here from there? The shape of a detailed account might well be revealed by means of thorough bibliographic and bibliometric analysis: what terms were used by whom, and when? Where were those term-users based, where did they publish, and who did they cite? That is a project for another day, however. What is clear enough already is that despite the apparent discontinuities there are important connections. This is surely as we would expect: scientific disciplines presumably do not come into being, even given genuinely novel insight, *ab initio*. Of critical importance is the development of scientific computing in tandem with that of molecular biology. Their early interdependence is illustrated by the fact that to support crystallographic work at Birkbeck it was necessary for A. D. Booth, recruited by Bernal in 1945, to develop from scratch a magnetic data storage device. It apparently then became the basis of the storage system for the computer being developed at Manchester University's Computer Laboratory, where Alan Turing was employed (Brown, 2005, pp. 276–280; Hodges, 1992, p. 393).

The evolution of computing hardware, especially notable in relation to processing speed and storage capacity, has been paralleled by equally far-reaching developments in software. Programming languages such as FORTRAN (which dates from the early 1950s) enabled scientists to write their own code and, although in time the invention and analysis of algorithms would become a flourishing branch of computer science, frequently it has been scientists themselves, confronting specific research problems, who have made significant contributions (for example Dayhoff et al., 1978; Doolittle, 2000). The development of biologically useful pattern-matching techniques, for example, has been closely associated with the availability of nucleotide and amino acid sequences and an interest in finding biological meaning in them (Needleman & Wunsch, 1970). Sometimes new algorithms make the difference between mere in-principle feasibility and the practical viability of a technique: the Fast Fourier Transform is an enabling condition of modern NMR techniques, for example.

The publication of the much-cited *Numerical recipes* (Press et al., 1986) can be seen as a sign of both the maturation of scientific computing and the increasing reliance being placed on *in silico* methods. In biology the increasing possibilities offered by such methods for exploring high-dimensional parameter spaces, where analytic mathematical techniques are useless, were exploited at an early stage. Molecular dynamics techniques now form part of the standard biophysics toolset, and methods such as energy minimisation and distance geometry are important elements of the application of NMR to studies of the solution structure and dynamics of macromolecules (Wüthrich, 1995). Here we see how a fascinating *pas-de-deux* can sometimes takes place between the generation of data and the development of computational techniques for working with that data.

The elucidation of macromolecular structures and sequences stimulated the invention and adoption of specific data formats, and the storage in databases of data encoded in such formats (Bernstein et al., 1977). The development of standards-based network infrastructures, efficient tools for searching and comparing sequences, and the widespread availability of software for visualising molecular structures, were some of the conditions that gave rise in the 1990s to bioinformatics as the disciplinary companion of genomics (Hagen, 2000; Ouzonis & Valencia, 2003). Prior to their consolidation many of the techniques of bioinformatics had been referred to simply as computational biology (a flexible term of enduring utility), or sometimes as computational molecular biology (Lesk, 1988). For its part, genomics arose out of improvements to the nucleotide sequencing techniques developed by Sanger, Pehr Edman and others. And as we have seen, it has been the data delivered by genomics, and the desire to make sense of that data, that have provided much of the stimulus for systems thinking in biology.

This kind of narrative, connecting molecular biology, computing, bioinformatics, and genomics, clearly narrows the gap between the two halves of our overall story. Another aspect is harder to delineate, but scarcely less important. This is the set of ideas that owe their development to the flowering of research into deterministic chaos, complexity, and the properties of non-linear systems that took place in the 1980s and 1990s. That research is popularly associated with the work of a few key individuals, for example Mitchell Feigenbaum in relation to chaotic systems, but it has deeper roots. Ilya Prigogine won the Nobel Prize for Chemistry in 1977 for his work on the thermodynamics of non-equilibrium systems, E. N. Lorenz had worked on attractors in the early 1960s, and Robert May was applying chaos-theoretical ideas to modelling the dynamics of populations and ecosystems in the 1970s. Many of the intellectual lineages stretch back further, however, for example to the work of Alfred Lotka and Vito Volterra and beyond. Henri Poincaré and his students were interested in the properties of non-linear functions over a century ago (Simon, 1996).

Even if some of the connections with contemporary systems approaches to biology are tenuous or indirect, such research undoubtedly reinforced the idea that complexity and non-linearity are ubiquitous features of nature, and this was a notable stimulus to the exploration of new biological paradigms (Kauffman, 1993). Moreover, such ideas meet, in at least some of systems biology's various manifestations, the substantial scientific resources provided by research traditions that have focused on reaction kinetics, reaction networks, and metabolism—involving such figures as Cyril Hinshelwood, Henrik Kacser, and Manfred Eigen—and the not unrelated one concentrating on pattern formation and morphogenesis with which Turing and Brian Goodwin, for example, are associated.

By the time the HGP delivered on its immediate goals, then, there were strong grounds for doubting whether merely obtaining the complete 'parts lists' of a biological system (cell, organism, ecosystem) would suffice to explain the behaviour and properties of the whole (Bains, 2001). The power and portability of computational techniques, and the rapid development and assimilation of ideas from complexity studies and elsewhere, has made it easier to articulate the bases for such doubts and to develop scientific responses to them.[9] Furthermore, and crucially, this diverse array of scientific and technological resources can now be brought to bear on the vast quantities of'omics data provided by microarray and other technologies. But perhaps what are needed in addition are new theoretical paradigms that can help us overcome some of our biases about the ways in which causal processes operate and that

[9] Strohman, describing the epigenetic system, writes of 'a determinative chaotic system open to new approaches that combine linear genetic with non-linear complex system (epigenetic) analysis' (Strohman, 1994, p. 157).

can guide us towards questions that address the deepest biological puzzles. Some maintain that the concept of emergence is destined to be associated with systems thinking in much the same way that reductionism has come to be regarded as molecular biology's philosophical counterpart (Van Regenmortel, 2004; Morange, 2006). However, just as it is unclear exactly what has been meant by some of the reductionist attributions made in relation to molecular biology, so it is not always obvious what precisely is being claimed when a phenomenon is described as emergent.

6. Emergence

One traditional idea of emergence is that a whole is in some sense 'more than the sum of its parts', but what does that mean? Among the most influential modern philosophical accounts is that of C. D. Broad (1925). His focus is on synchronic emergence, or the dependencies that pertain simultaneously between structures at different scales. This concept is to be distinguished from diachronic emergence, which deals with the ways in which phenomena develop over time. Broad frames his account in these terms:

> Put in abstract terms the emergent theory asserts that there are certain wholes, composed (say) of constituents A, B, and C in relation R to each other; that all wholes composed of constituents of the same kind as A, B, and C in relations of the same kind as R have certain characteristic properties; that A, B, and C are capable of occurring in other kinds of complex where the relation is not the same kind as R; and that the characteristic properties of the whole R(A,B,C) cannot, even in theory, be deduced from the most complete knowledge of the properties of A, B, and C in isolation or in other wholes which are not of the form R(A,B,C). (Ibid., p. 61)

He illustrates these ideas with some rather unconvincing examples from chemistry. The properties of, say, salt, are emergent to the extent that they cannot be predicted, or deduced, from those of sodium and chlorine ions, he argues. Nowadays we are inclined to suppose that in principle, given enough computational power, we could apply quantum mechanical theories to derive the properties of compounds from those of their constituents. But what if the amount of computing power needed were unattainable by many orders of magnitude? Where and how should we draw the lines between 'in practice' and 'in principle'? (Humphreys, 2004, p. 52; Dupré, 1993, pp. 95–96). It is a perennial problem for accounts of emergence that emphasise deducibility or predictability that the claims made in their name must be assessed in light of the trend of increasing predictive capability associated with advances in computer modelling and simulation. To declare a phenomenon unpredictable 'in principle', as opposed to in practice given our cognitive limitations and/or current computational capabilities, seems to make an almost unwarrantably strong claim. Some accounts distinguish epistemological (or weak) emergence, in which it is the intractability of a system—for example on account of the multiplicity of the entities composing it and/or the complexity of the rules governing their interactions—that puts prediction out of range, from ontological (or strong) emergence (Bedau, 1997). Emergence of the latter kind, involving claims of unpredictability in principle, of obstacles to prediction somehow inherent in the nature of things, is often seen as philosophically mysterious. Indeed, some dispute whether there are any good candidates for it at all, apart perhaps from certain quantum mechanical phenomena (to do with paradoxical non-local interactions between particles) and, according to some, consciousness. But such topics take us a long way from central biological concerns.

When we look at how the term 'emergence' and its cognates are used in biology we sometimes find that they simply provide a way of stressing the importance, when explaining a phenomenon, of taking into account features of the context within which the relevant parts are situated. Sometimes the aim is merely to draw a contrast, implicitly or explicitly, with the (methodologically reductionist) isolation of parts and their characterisation as independent entities. These kinds of emergence talk can be seen as reactions to the perceived over-emphasis on the explanatory power of analytic approaches when they are divorced from more synthetic modes of understanding. S. F. Gilbert and S. Sarkar connect the concept of emergence with 'organicism' (a term they adopt in order to avoid what they see as the association of the term 'holism' with vitalist ideas):

> One of the principles of organicism is that the properties at one level of complexity (for instance, tissues) cannot be ascribed directly to their component parts but arise only because of the interactions among the parts. Such properties that are not those of any part but that arise through the interactions of parts are called *emergent properties*. (Gilbert and Sarkar, 2000, p. 2)

Such a rendering might be taken to suggest that emergence is widespread—perhaps so widespread as to make its attribution rather unenlightening. Other authors take the element of unexpectedness associated with the appearance of certain phenomena to be one of the central unifying features of emergent phenomena. J. L. Casti (1994), for example, speaks of 'the science of surprise'. Considered in this way emergence sounds like a way of 'black boxing' our current ignorance of the underlying causal structure of a phenomenon. When faced with the claim that a system property is emergent, however, it is hard not to think that we *ought* to be able to provide an account of its appearance. Why these phenomena and not others? We think that there is important philosophical work to be done in honing the concept of emergence in such a way as to deflect, as far as possible, the charges of metaphysical excess that have often been directed against it. One crucial issue is the relationship between emergence and causation.

It is clear that emergence is frequently associated with causal complexity, or with processes for which the causal basis is difficult to analyse. This prompts the thought that if we had a better philosophical grip on causal processes we might succeed in distinguishing between different senses of emergence. Some discussions are framed in terms of the appearance of self-organising patterns (across space or time or both) that arise in particular contexts or media as a result of the local interactions of multiple entities.[10] Cellular automata like J. H. Conway's 'Game of Life' algorithm are often seen as providing a compelling *in silico* model of the phenomenon (Bedau, 1997). Paradigmatic physical cases include the Belousov–Zhabotinsky reaction, in which the existence of alternative reaction pathways gives rise to spatial patterns that are analogous to the wave-like growth patterns exhibited in certain circumstances by the slime mould *Dictyostelium discoideum*. Andy Clark discusses emergence in terms of the causal interplay between agents and environment modelled in some artificial life research (Clark, 1996), while John Holland looks at the emergence of organisation in complex adaptive systems consisting of *in silico* agents endowed with rudimentary 'genetic' capacities (Holland, 1995).

Perhaps further work will demonstrate the feasibility of situating these sorts of cases within a unified framework that encompasses the interactions of numerous, individually rather simple, entities at one extreme, and the complex interactions of a small number of highly structured, adaptive agents with a structurally and dynamically rich environment at the other. It may still be, however, that the kinds of process to which the term

[10] The emergent patterns might amount just to the statistical generalisations that become apparent only when the rule-determined outcomes are analysed; then we might tend to think in terms of emergent laws, as opposed, say, to emergent structures or patterns.

emergence is applied in biology are too diverse to be collectively subsumed by any *single* account. Perhaps we will need separate accounts to deal adequately with the play of historical contingency that over time gives rise to the increasingly differentiated and complex structures generated by evolutionary processes, the constancies and repetitions of metabolism, and the canalised unfolding of form seen in morphogenesis.

7. Downward causation

Garland Allen, writing over thirty years ago, saw no need to eschew the use of the term 'holism' that Gilbert and Sarkar appeared keen to avoid. Allen clearly took that term to mean what nowadays would be thought of as emergence, characterising it as the view that 'what is important is not simply the sum total of the individual parts, but how they interact. Holistic materialists maintain that one of the characteristics of parts is the nature of their interaction with other parts in the whole, and that, in fact, one cannot know about the part without knowing about its interactions, because they, too, help define its character' (Allen, 1978, p. xxii). The value of this idea is that it confronts a widespread epistemic bias towards seeking reductive accounts for phenomena by looking for explanatory factors exclusively at lower rather than higher levels. The emphasis on the importance of interactions in influencing parts seems promising. The properties of biological objects are contingent on their structures: it is those structures that give rise to the causal capacities that interactions make manifest. This much is, presumably, uncontroversial. The idea of downward causation, however, which is a thesis about the capacity of wholes to influence their parts, is often seen as more controversial.

A widespread intuition about material causation is that it operates in an exclusively bottom-up way, from the microscopic to the macroscopic. To many it seems just self-evident that events and processes at the smallest scales are what give rise to those at larger scales. Adherents of such a view often express perplexity at the idea that determination might ever run in the reverse direction. This perplexity is generally grounded on the assumption that microscopic entities conform to a uniform and comprehensive set of laws that fully determines their behaviour, and hence, it seems to follow, the behaviour of any more complex object of which they are the only constituents. If this is so then it might seem that the causal powers attributed to complex entities must be, at best, redundant—consequences, that is, of the causal powers of their constituents.[11] Some emergentists will reply that the strong reasons for believing in downward causation are, *ipso facto*, reasons for denying that the microphysical laws are sufficient to determine the behaviour even of microphysical objects (Dupré, 1993). Here we encounter a fundamental clash of intuitions that we cannot hope to resolve here. We will suggest, however, that much in contemporary molecular biology, perhaps surprisingly, provides strong support for the anti-reductionist side of the debate.

Concrete examples from molecular biology nicely highlight some of the problems associated with denying that larger-scale phenomena can influence smaller-scale phenomena. Think about a protein's conformation, as represented by way of a 'Ramachandran plot' (Ramakrishnan & Ramachandran, 1965) in which each amino acid residue is plotted according to its phi and psi values, the angles of rotation around the two (per residue) rotatable main-chain bonds. G. N. Ramachandran used hard-sphere atomic models of the individual amino acids to derive the sterically allowable phi/psi combinations for each residue type. When the crystal structure of a protein is analysed to produce a Ramachandran plot, most of its residues are found to fall within the allowed areas—but there is considerable variation amongst the precise phi/psi values, even amongst residues of the same type. Whilst some of the variation can be attributed to imperfections of crystallographic structure refinement (Kleywegt & Jones, 1996), for most residues local steric factors of course leave considerable latitude as to the exact conformation adopted. So what determines the actual phi/psi values that obtain in the context of a specific protein? One surely has to say: downward causation. To a first approximation, in the context of the folded structure any single residue is subject to the sum of the forces exerted on it by the other residues, and these will compel it to adopt that configuration which is energetically accessible and in which the overall energy of the molecule is minimised—even if as a result the individual residue is distorted into a conformation it would not, 'in isolation', frequently adopt. Proteins thus illustrate in microcosm how wholes can determine the properties of their parts.

When we attempt to generalise our thoughts about downward causation one idea that results is this: the influences, or causal potentials, that act at a particular location or region can come from multiple directions and distances, and the way the influences sum and act, together with the nature of whatever exists at that location, is determinative of what happens there. (By influences we typically mean forces arising from fields, whether acting over long or short ranges. At different scales, different fields predominate.) Certain sorts of effect depend for their realisation on the attainment of a minimum local concentration of causal potential, and sometimes this can only be brought about by a summation of the individual causal potentials of multiple parts. (Think of light being focused onto a small region so as to heat it to its ignition point.) Conversely, parts are compatible—in the sense that they can retain their integrity or identity—only with particular contexts, within bounds beyond which they are changed. The conditions under which, and the manner in which, they are changed depend in complex ways on energetic and other factors. Highly non-linear behaviours can thus be generated: if a causal threshold is met, X happens; if it is not met, X does not happen.

Biological causes may be highly dispersed too. Extracellularly, fluid media such as the bloodstream can be used to broadcast a wide variety of signals to different cellular targets with varying degrees of specificity. Intracellularly, causes may similarly be distributed, taking advantage of the properties of the intracellular environment in order to exert their effects. Should these kinds of contingently acting, message-based phenomena be grouped under the heading of downward causation? Arguably not, to the extent that we can think of the messages and their targets as lying at the same structural level, i.e. the molecular. On the other hand one might argue that such cases go some way towards undermining the concept of levels altogether. In an animal, for example, signalling molecules—a hormone, say—might originate from the cells of one organ, such as the pituitary gland, and travel around the body to the cells of other organs where—if those cells bear the relevant receptors—they set in train molecular processes that might ultimately result in the expression of a particular gene. The pituitary gland cells may have been stimulated to secrete the hormone as a result of the collective activity of neurons distributed across a variety of cortical levels, including those associated with higher (more abstract) cognitive skills—neuronal activity that could well have been triggered by the organism finding itself in a particular kind of environment. It is hard to see how thinking in terms of levels helps much in these and many other cases; more helpful is to try to track the flows of causal influence and see how they propagate and act through space and time.[12]

[11] The *locus classicus* for this line of thought is a series of papers and books by Jaegwon Kim. See, for example, Kim (1998).

[12] Craver & Bechtel (2007) express a point of view that seems broadly congenial to our own.

8. Mechanisms and networks

Discussion along these lines of causal influences and how they bring about biological activities leads to the issue of how we might best conceive of cellular processes. One view is that such processes depend on structures that are analogous to artificial macroscopic mechanisms, in which the coordinated operation of a set of relatively stable components, having a particular spatial configuration, results in the performance of some function. In such mechanisms what is important is the synchronisation and tight causal coupling amongst the parts. The design of a mechanism is such that in their normal configuration, the parts are 'sympathetic' to highly specific modes of interaction, and collectively they constrain each other to interact in those 'standard' modes and not others. In macroscopic mechanical devices the parts are aggregations of solid matter, and the standard modes of interaction are the relative motions between parts that are enabled by the existence of various articulation points, lines, and surfaces.[13] The energy barriers to non-standard modes of interaction are very high compared to those associated with the standard modes. Hence it is harder to deform a part than it is to move it relative to other parts in accordance with a standard mode.

What is important about mechanisms is the way in which concentrated and consistent patterns of causation propagate through them. Indeed, such concentrations of causal influence are constitutive of them. In macroscopic mechanical devices this causal influence is in terms of the directed transmission of force from matter aggregate to matter aggregate, sometimes mediated by the properties of particular physical states or exploiting the effects of state changes. With a change of physical scale to the molecular comes a different, richer, set of causal possibilities. Now we are dealing not with bulk—averaged—material properties but with molecules having specific chemical properties arising from their shape, from the way in which charge is distributed over their surfaces to create fields of electrostatic potential with which other charged entities can interact,[14] and from the possibilities for interaction with other molecules presented by particular chemical groups. Such interaction will sometimes result in a chemical reaction that transforms one or more of the interacting species. And this points to another crucial difference between cells and machines: whereas the latter undergo only gradual degradation of their parts, in the former we find a constant production, transformation, and dissolution of parts. But despite such differences we do see, as in macroscopic mechanisms, concentrated and consistent patterns of causation at work. Enzymes, for example, function by bringing absolutely specific chemical groups into a precise spatial configuration that, when brought to bear on a molecule within a particular target class, results in the exertion of chemical forces that catalyse its conversion to a new species.

The classical mechanistic paradigm is of a set of tightly causally connected parts having rigid spatial relations, and behaviour that is largely independent of their environment. Biological systems, in contrast, have much more loosely coupled components and typically exhibit sensitivity to a range of features of their environment. Though we can see these two cases as lying on a continuum, the differences along the continuum can be as salient as the commonalities. Components organised in the former way can be identified with the performance of particular discrete functions: we can say that component C_1 performs function F_1, component C_2 performs function F_2, and so on. Stable aggregations can give rise to structural and functional hierarchies (Simon, 1996). In such systems the material and functional decompositions are aligned with each other, and it is this alignment, grounded in patterns of causal interconnection, to which the idea of decomposability refers.

It is clear that many, presumably most, cellular processes depend on the operation of often highly sophisticated macromolecular mechanisms. A good example is the proteasome complex, a barrel-shaped multi-enzyme complex that digests a range of endogenous proteins including transcription factors and misfolded proteins (Ciechanover & Schwartz, 1998). The identification of such mechanisms has led to the cell being described as a 'collection of protein machines' (Alberts, 1998). But it is not obvious that the existence of discrete mechanisms is enough to guarantee the decomposability of all cellular functions. The work on emergent processes mentioned earlier shows how the combined actions of apparently independent mechanisms (agents) can give rise to collective behaviours that are apparently unanalysable in terms of the operations of the individual mechanisms. Hence although there is detailed knowledge of many of the cell's individual mechanisms at the macromolecular level, it does not follow that we have a good sense of how such mechanisms collectively give rise to fundamental cellular activities such as chromosomal replication and cell division. This is so despite the impressive progress that has been made in unravelling the intricacies of the cell cycle (Nurse, 2000).

One factor that hampers our understanding is the fact that many components—whether genes or proteins—are associated with multiple functions, cellular context playing a significant part in determining what role a component plays in the causal economy of the cell. An additional complication is that, as noted above, many cell components exist only transiently, with their expression, import or synthesis, and their degradation or export, being contingent on complex sets of conditions. The structural constancies exhibited by living systems, certainly at the cellular and sub-cellular level, are often merely apparent. As thermodynamically far-from-equilibrium systems they must consume quantities of energy just to remain in the same organisational place, and the metabolic processes by which they do so involve the turnover of matter at a wide variety of rates.

The issue of whether biological systems are decomposable has acquired particular significance with the recent rise of synthetic biology (O'Malley et al., 2008). The proponents of this emerging discipline sometimes express the belief that biological systems *are* decomposable and because of this will prove amenable to modification, reconfiguration, and construction by the application of engineering principles. Others are more sceptical of such claims (for example Brent, 2004), which, it might be argued, are in some tension with the appeals that have been made by, for example, computer scientists, that we look to biological systems in order to learn how to make systems that are robust and capable of 'graceful degradation'. This was one of the motivations in the 1980s and 1990s for research on artificial neural networks (Rumelhart et al., 1986).

An important feature of most current interpretations of systems and synthetic biology is the adoption of a network perspective on the cell, which focuses on the dynamics and topology of genetic regulatory circuits and interaction networks rather than on structural details (Barabási & Oltvai, 2004; Weiss, 2005). The proponents of network approaches argue that cellular networks, in drawing on a finite set of functional motifs that in many cases appear to be connected together in ways that ensure they do not interfere with each other, can be expected to be complicated but not insuperably complex (Alon, 2007). The molecular mechanistic and network-oriented perspectives involve different and complementary epistemic trade-offs, and taken together they may compensate for each other. Currently, however, both conceptions face the possibility that contextual and biophysical aspects of the intracellular environment constitute significant causal influences on the way in which cellular processes play out.

[13] Similar in spirit is Gregory's discussion of mechanistic causation in terms of the limitation of the number of degrees of freedom in a system (Gregory, 1993, Ch. 3). See also Dupré (2001), pp. 170–174.

[14] Electrostatic complementarity and 'steering' effects appear to be important for a variety of molecular recognition processes.

Cellular spaces are populated and dynamically structured in ways that increasingly make the presumption of simple liquid properties look implausible. Compartments are densely packed with heterogeneous populations of molecules that vary greatly in size, chemical properties, and copy number (the number of tokens of a given molecular type that are present at a given time); some can wander freely, subject to the moment-by-moment constraints imposed by other wandering molecules, while others are associated more or less tightly and persistently with cell or compartment membrane structures. The cytoplasm has been estimated to represent a 70% solution of macromolecular species. Only recently have biologists begun to develop a feel for what the effects of this macromolecular crowding on *in vivo* activities might be (Ellis, 2001; Hall & Minton, 2003; Schnell & Turner, 2004; Golding & Cox, 2006). Protein folding and stability, enzyme activity, DNA condensation, intracellular signalling, and pattern formation, for example, are all known to be potentially affected (Bray, 1998; Weiss, 2003; Weiss et al., 2004), and it is clear that our conceptions of cellular causality need to take some account of this.

The shift towards a network-oriented view of the cell represents a decisive move away from a narrower mechanistic perspective associated with macromolecular structures and their pairwise interactions.[15] But perhaps the positive, inherently systemic aspects of network thinking come at an uncomfortably high price if it results in the wholesale neglect of structure and morphology (see Harold, 2005). On the other hand network concepts may be destined to play the same organising role that the ideas of coding and information played in molecular biology—and possibly share their ambiguous relation to reductionism. It is probably simply too early to say whether the network perspective marks the first stage of a journey 'into a strange more abstract world, more readily analysable in terms of mathematics than our present imaginings of cells operating as a microcosm of our everyday world' (Nurse, 2000, p. 77), or whether ultimately it will come to be seen as another useful but limiting simplification. Similarly it seems too soon to judge how it should be seen in relation to calls for a new vision of biological processes, one emphasising the causal circularity of metabolism (Rosen, 1991; Cornish-Bowden & Cárdenas, 2007).

9. Conclusions

In this paper we have considered the transition from molecular to systemic perspectives by paying attention simultaneously to selected historical episodes, scientific issues, and philosophical themes and concepts. Now we are in a better position to address our initial questions: what does it mean to speak of molecular biology as a reductionistic discipline, and has reductionism had its day?

Our answer to the first question begins with the observation that molecular biology had a strong disciplinary identity perhaps only in the fifteen years or so following the discovery of the structure of DNA. Elsewhere we argue that many factors contribute towards discipline formation, but that naming is key (Powell et al., 2007). In saying that molecular biology had a strong disciplinary identity we mean that the name became, for a time at least, associated with recognisable clusters of concepts, projects, tools, institutions, and individuals. In that time it elucidated the molecular basis of fundamental genetic processes, determined the nature of the genetic code, and showed how knowledge of the details of macromolecular structure can shed light on biological function. But were those successes attributable to a commitment to reductionism? Much has been written about the possibility of reducing the laws and theories of classical, Mendelian genetics to those of molecular biology—whatever they might be (see, for example, Schaffner, 1969; Kitcher, 1984; Kincaid, 1990). We have chosen not to add to that topic's word count. The ontological collapse of level-specific theories and laws via bridge principles, as Oppenheim and Putnam envisaged, has very little relevance to the actual concerns and practices of scientists themselves (Waters, 2007). As we have seen, levels cannot be equated with scale in any straightforward way, and the dynamic and interactional complexity of biological systems is reflected in intricate patterns of causation that render such projects more or less hopeless.

In a superficial sense the isolation of the molecular components of living systems, and their characterisation as independent entities, might be said to be methodologically reductionist. But that such isolation and analysis is possible at all is just a reflection of the fact that cells do, it turns out, contain relatively stable, relatively discrete functional units at the molecular scale—up to a point. Hence sometimes it can make sense to seek explanations in terms of the properties of components. This does not mean that we must grant room for any systematic epistemological reductionism, however. Rarely can explanations be given *solely* in terms of the properties of isolated components, and perhaps they never can. Often a molecular structure provides details that are illuminating only in the light of what is already known about other entities, or about the wider context from which the molecule has been isolated. Or else a causal matrix is understood except for one part, for which a black box must do explanatory duty until knowledge of molecular structure allows the box to be unpacked. Suggestive details stimulate hypothesis-making and attempts at experimental confirmation. Typically these give rise to lengthy cycles of experimental analysis—often involving the inventive construction of material systems capable of revealing the features of interest—and knowledge synthesis. Reductionism scarcely sounds like the most appropriate term for such practices.

Perhaps to deliberate about whether molecular biology is or was reductionist or not is to miss the more scientifically (and philosophically) interesting point. This is that molecular biology showed that molecular details do count, and may be richly explanatory. This prosaic yet productive discovery becomes potentially distorting only when it is combined with a commitment towards the simple, since that commitment so easily slips into the simplistic (Dupré, 2002). Biological complexity has repeatedly confounded scientific hopes for discovery of the kind of order that makes for theoretical neatness. Illustrations include Wrinch's cyclol hypothesis about protein structure, with its emphasis on symmetry principles (Wrinch, 1937; Ferry, 1998, pp. 147–160), and the failure of Bragg and Perutz to consider a non-integral number of repeats in the alpha helix (Judson, 1996, p. 67). No doubt there have been others. At the core of all accounts of reductionism lies a seductive vision of the simplicity of phenomena, whether in terms of the nature of the relationships between theories, the ways in which material objects are constructed, the number of factors needed to explain them, or the nature of the methods needed for their investigation. What biology keeps reminding us is that things can be complex, and that coming to know about complex things can be difficult. Any one approach, or any exclusive focus on one ontological level (in so far, indeed, as there really are such things), will almost certainly be inadequate to all aspects of the task.

From the 1990s onwards we see, for reasons we have outlined, increasing recognition of the significance of complexity and context. Associated with this are the development and convergence of various scientific strands that have fuelled the rapid growth of systems approaches to biology. Even beyond the vocal core of self-declared systems biologists, however, we see a re-orientation that is being reflected in the development of new experimental

[15] In philosophy of science we see a parallel interest in more flexible conceptions of what mechanisms are, framed variously in terms of interactions and activities (Machamer et al., 2000; Glennan, 2002; Tabery, 2004).

techniques (Cavagnero & Jungbauer, 2005; Charlton & Pielak, 2006; Bax & Torchia, 2007), exploration of new theoretical avenues (Dobson, 2004), and discussion of the prospects for systems-oriented therapeutic approaches (Ahn et al., 2006; Zimmerman et al., 2007). The concepts of emergence and downward causation look set to play a part in the further genesis of such work, if only as an essential corrective to misleading philosophical assumptions grounded in traditions of reductionist thought.

But there may also be more positive benefits to be derived from the application of these ideas. Emergence concepts remain relatively undeveloped, and it may even be that some of their utility stems from their ambiguity. However, the development of more nuanced accounts of emergence may prove valuable in characterising the kinds of causal processes that occur in biological systems. In contrast, downward causation already fulfils an important role. Monolithically molecular perspectives amount to a claim about the *grain*, or level of resolution, at which explanatory insight is most effectively gleaned. The success of molecular biology in providing mechanistic explanations can lead, if viewed through an excessively reductionist lens, to the distorted idea that insight is gained only by looking 'downwards' and inwards at the constitution of isolated entities. Recognition of not just the possibility but the pervasiveness of downward causation reminds us of the importance of looking both ways. We must retain a high level of resolution, because the details matter, but must extend the *scope* outwards, 'upwards', because sometimes the biologically interesting causal powers are grounded not in the internal structures of the entities we analytically distinguish, but in the relations between them.

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