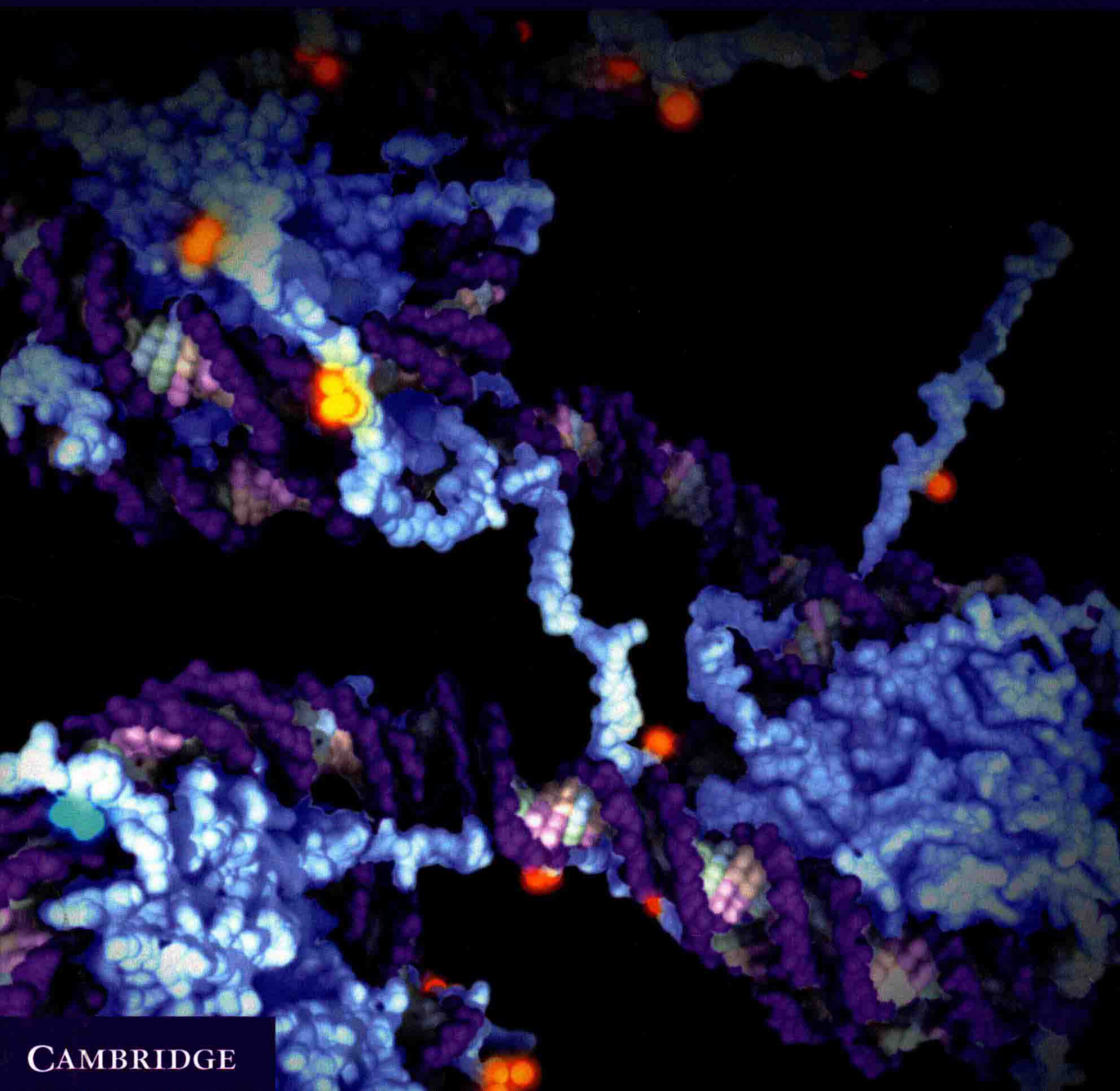
Paul Griffiths and Karola Stotz

Genetics and Philosophy

An Introduction



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Genetics and Philosophy

In the past century, nearly all of the biological sciences have been directly affected by discoveries and developments in genetics, a fast-evolving subject with important theoretical dimensions. In this rich and accessible book, Paul Griffiths and Karola Stotz show how the concept of the gene has evolved and diversified across the many fields that make up modern biology. By examining the molecular biology of the 'environment', they situate genetics in the developmental biology of whole organisms, and reveal how the molecular biosciences have undermined the nature/nurture distinction. Their discussion gives full weight to the revolutionary impacts of molecular biology, while rejecting 'genocentrism' and 'reductionism', and brings the topic right up to date with the philosophical implications of the most recent developments in genetics. Their book will be invaluable for those studying the philosophy of biology, genetics, and other life sciences.

PAUL GRIFFITHS is University Professorial Research Fellow at the University of Sydney. He is the author of *What Emotions Really Are: The Problem of Psychological Categories* (1997) and *Sex and Death: An Introduction to the Philosophy of Biology* (with K. Sterelny, 1999). He is the editor of *Trees of Life: Essays in Philosophy of Biology* (1992) and *Cycles of Contingency: Developmental Systems and Evolution* (with S. Oyama and R. D. Gray, 2001).

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Cover image: The ability of a DNA molecule to act as a collection of genes depends on many other molecules. This picture shows DNA being inactivated (switched off). The DNA double helix (purple) is in the process of being coiled tightly around histone molecules (blue-white) to form 'nucleosomes'. Once this is complete the DNA cannot be used as genes until the process is reversed. Thin 'tails' project from each cluster of histone molecules. Chemical modifications to these tails (bright yellow and turquoise) are produced by interactions with other molecules in the cell. It is these changes that control the processes of activation and inactivation. *Image courtesy of Etsuko Uno and the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.*

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1 Introduction

Unlike most books which combine philosophy and genetics in their titles, this is not a discussion of the ethical, legal, and social implications of science. It is a contribution to the philosophy of science, the branch of epistemology (theory of knowledge) which sets out to understand how science works. The word 'genetics' is construed broadly to include a wide range of molecular biosciences, and the exposition of these sciences is a backdrop to our discussion of the philosophical issues of reductionism and reductive explanation, the status of theoretical entities, and the relationship between scientific representations – models – and the targets of those representations. Genetics and molecular biology have been a powerful source of philosophical insights into these issues. Recent scientific developments in this rapidly changing area hold new lessons for philosophy of biological science.

Since Aristotle philosophers and scientists have reflected on the nature of living systems and the distinctive nature of the sciences that study them. However, the emergence of the philosophy of science as a distinct academic field in the early twentieth century was marked by an almost exclusive focus on the physical sciences. When philosophers of science turned their attention to biology in the 1960s, one of the first issues to be raised was whether the new molecular biology constituted a successful reduction of earlier biological theories, and particularly earlier theories of genetics (Schaffner 1967; Schaffner 1969; Ruse 1971; Hull 1972; Hull 1974). As well as addressing general issues like reduction, philosophers of science are tasked with analysing key scientific concepts, and the concept of the gene has proved both attractive and elusive. In part this is because it is a moving target. The concept of the gene had evolved considerably in the years between the introduction of the concept at the turn of the twentieth century and the papers just cited, and it has continued to evolve during the past forty years of intense philosophical attention.

Many of the classic philosophical papers on reductionism in molecular biology date from the 1980s, or continue the debate in the terms established in that period (Kitcher 1982; Kitcher 1984; Rosenberg 1985; Wimsatt 1986a; Waters 1990; Schaffner 1993; Waters 1994). The molecular conception of the gene which figured in these debates was the temporary consensus around the 'classical molecular gene' concept, which we describe in Chapter 3. However, the 1990s and 2000s saw the discovery of far greater complexity both in how genes are structurally constituted in the genome, and in how genes function to make their products. In the 'postgenomic era', when complete genome sequences are available for an increasing range of organisms, the range of molecular actors has expanded greatly. The genome is not merely a collection of genes, but houses diverse other functional elements. Genes no longer have a single function closely related to their structure, but respond in a flexible manner to signals from a massive regulatory architecture that is, increasingly, the real focus of research in 'genetics'. One of the main aims of this book is to revisit those earlier philosophical debates against this very different scientific background.

This is not a history of genetics. But science is a dynamic process, and understanding it often involves understanding how concepts and theories have changed. So in some places we do give historical treatments of the emergence, development, and sometimes abandonment of ideas in genetics. In such cases, we have drawn heavily, and we hope with sufficient acknowledgment, on the many historians of science who have devoted themselves to genetics and molecular biology.

We have chosen not to deal with population genetics, the discipline whose primary focus is the algebraic consequences of Mendelian heredity and selection in populations. There are two reasons why this would take us into a very different philosophical territory from the book we have written. The first is that population genetics is a mathematical discipline centred on a few principles of high generality: the structure of population genetic theory has frequently been compared to the structure of theories in physics (Sober 1984; Brandon and McShea 2010). This is not a coincidence, since one of the creators of population genetics, Ronald Aylmer Fisher, modelled his theory on statistical thermodynamics (Depew and Weber 1995). Philosophical analyses of the molecular biosciences, in contrast, have shown that these sciences do not have a mathematical, or plausibly mathematicisable, core of highly general claims (Darden and Maull 1977; Bechtel and Richardson 1993; Schaffner

1993; Schaffner 1996; Bechtel 2006). Instead, they are organised around a cast of evolutionarily conserved parts and processes, in a way more comparable to sciences such as physiology and anatomy (Winther 2006). A second reason why a discussion of population genetics would have taken us too far afield is its close relationship to evolutionary theory. Population genetics is the mathematical core of modern evolutionary biology. A philosophical discussion of population genetics would have to engage with the philosophy of evolutionary biology, still the largest area in the philosophy of biology. This is the topic of another volume in this series, and more than deserves a book to itself. However, in Chapter 8 we do discuss some of the ways in which the developments in molecular biology outlined in this book are likely to produce, as they are more fully assimilated, changes in our understanding of evolution and how those changes may be reflected in evolutionary theory.

In Chapter 2, 'Mendel's gene', we begin our exploration with an account of the emergence of genetics at the beginning of the twentieth century. In line with much recent scholarship we argue that the important element of Mendelian genetics was not a few 'laws' of heredity, but the experimental practice known as 'genetic analysis'. We show how genetic analysis was used to solve problems in many other areas of biology. Following the historian Raphael Falk, we argue that from its very introduction the gene had two identities. The first, and initially the most prominent, was that of an instrumental unit defined by its role in genetic analysis. The second identity was that of a hypothetical material unit of heredity (Falk 1984, 1986, 2009). In their instrumental identity the existence of Mendelian genes is guaranteed by the success of genetic analysis. Hence Mendelian genes were never merely hypotheses whose confirmation awaited the discovery of the material gene. We compare the ontological status of the Mendelian gene in its instrumental identity to that of centres of mass in dynamics. Building on this approach, we argue that geneticists in the first decades of the twentieth century had two ways of thinking about – representations of – the gene. Thinking about the gene as an instrumental entity was useful in the context of genetic analysis. Thinking about the gene as a hypothetical material entity was increasingly useful as geneticists came closer to understanding the material basis of heredity.

In Chapter 3, 'The material gene', we describe how the elucidation of the structure and basic function of DNA represented the successful conclusion of the search for the gene as a material unit of heredity: the way in which DNA is passed from one cell to the next provides the physical underpinnings

for the gene's instrumental role as marker of phenotypic differences across generations. However, the causal role of the gene as it had been envisaged in classical genetics was very substantially revised in order to fit what had been discovered about the material basis of heredity. The result of the molecular revolution in genetics was not that a causal role (the Mendelian gene) was filled by a material occupant (the molecular gene). The molecular gene had a new role, very different from that of the Mendelian gene. Its primary role was to specify the linear order of elements in cellular products, initially polypeptide chains, the precursors of proteins. This explains the difficulties encountered by philosophers who have tried to explain how the Mendelian gene was reduced to molecular biology. Although the new, molecular identity of the gene was now its dominant identity, the other, instrumental identity did not simply go away. The original role of the Mendelian gene continues to define the gene in certain areas of biological research: namely, those intellectually continuous with classical genetic analysis. We give examples of contemporary research in which it is necessary to think of genes as both Mendelian alleles and molecular genes, even when those two identities do not converge on the same pieces of DNA. Reductionists are correct that the gene turned out to be grounded in DNA, but they fail to recognise that the development of genetics has left us with more than one scientifically productive way of thinking about DNA and the genes it contains. This is in large part because they have failed to recognise how the different identities of the gene are anchored in different experimental practices.

The other major theme of Chapter 3 is the emergence of 'informational specificity' as the key property of the molecular gene. We describe how biological specificity (the ability of biomolecules to catalyse very specific chemical reactions) was transformed from a physical concept based on stereochemistry (the three-dimensional shape of molecules) to an informational concept based on the linear correspondence between molecules, most famously in the case of the genetic code. We introduce the term 'Crick information' to refer to the sense of 'information' introduced by Francis Crick (1958) and used to define informational specificity.

Chapter 3 introduces a philosophical model of explanation which will recur throughout the remainder of the book as the best way to capture the nature of research in the molecular biosciences. Following recent neo-mechanist philosophers we argue that mechanistic explanation includes both a reductionist phase and an integrative phase. The reductionist phase of research

identifies and characterises the constituent parts of a mechanism. The integrative phase shows how the phenomenon to be explained is produced by the specific ways in which those parts are organised so as to make up that mechanism (Bechtel and Abrahamsen 2005; Bechtel 2006; Craver and Bechtel 2007).

In Chapter 4, 'The reactive genome', we explore one dimension of the increased complexity of 'postgenomic' biology. We argue that informational specificity or Crick information – the ability to causally specify the linear sequence of a gene product – is not located solely in coding sequences of DNA, but is distributed between the coding sequences, regulatory sequences and their RNA and protein products, and the environmental signals that act via that regulatory machinery. These other factors help to determine the specificity of gene products through the activation and selection of coding sequences, and the creation of additional Crick information during post-transcriptional processing. We outline the concepts of 'distributed specificity' and 'combinatorial control' and show that they support a profoundly non-reductionist account of gene function which we refer to as 'molecular epigenesis' (Burian 2004; Stotz 2006a). The way in which genes in combination with other actors determine the activity of cells is mechanistic, but it is not reductionistic.

In Chapter 5, 'Outside the genome', we look at the sources of the environmental signals which act as drivers for genome expression and are an additional source of Crick information, and explore the new fields of 'epigenetics' and 'epigenetic inheritance' in both the narrow and wider senses of those contested terms. Genetics as the study of heredity has traditionally been aligned with the nature side of the nature/nurture dichotomy, which has in turn been regarded as 'reductionist', while scientists who have focused on nurture have been labelled as 'anti-reductionist'. Today, however, some aspects of nurture have proved to be heritable, and in addition the study of nurture has gone increasingly molecular, so that research into the role of the environment in the development and functioning of organisms is potentially as 'reductionist' – that is to say, mechanistic – as research in any other areas of the molecular biosciences. Organisms construct their life cycles through the interaction of the contents of the fertilised egg, the genome and its narrowly epigenetic surroundings, with a 'developmental niche' which is the result of epigenetic inheritance in a wider sense (to avoid confusion, we refer to this as 'exogenetic inheritance'; West and King 1987). Organisms inherit elements of their

developmental niche in much the same sense that they inherit their genome, albeit via different mechanisms of transmission. We reiterate our argument that the nature of development supports mechanistic anti-reductionism: developmental outcomes are explained by the organisation of the components which regulate gene expression, but cannot be reduced to the components taken out of the context of their causally crucial organisation. The regulatory architecture of the genome extends outside the organism into the developmental niche, partly vindicating some other traditional 'anti-reductionist' themes.

In Chapter 6, 'The informational gene', we discuss genetic information, the genetic programme, and the informational identity of the gene. This is the conception of genes as units of information, supplying the form to complement matter and make matter come to life. The informational identity of the gene provides the underlying rationale for the view that genes retain a unique importance in development despite all evidence of the impact of other factors. Attitudes to the idea that biology is an 'information science' differ profoundly: some regard it as the greatest insight of twentieth-century biology, others as no more than a muddle caused by taking metaphors too seriously. Our position is somewhere in between. We argue strongly against *semantic* conceptions of both genetic information and the genetic programme – those which seek to identify meanings and messages in molecules. However, we conclude that in reacting against these semantic approaches, critics such as ourselves have mistakenly dismissed less overblown but very important informational ideas in biology. While we and other critics have insisted on restricting talk of the 'genetic code' to the actual triplet code which translates nucleic acid into protein (Godfrey-Smith 2000a; Griffiths 2001), there is more to say about this than we had supposed. We now propose that the code is a means to transfer information in the sense defined by Francis Crick (Crick 1958, 1970): namely, sequence specificity, or Crick information. Crick information is not contained solely in nucleic acid sequence, as the previous chapters will establish. However, despite the existence of other mechanisms of inheritance the ability of organisms to transfer sequence specificity between generations is crucially dependent on the invention of nucleic acid-based heredity. Nucleic acid-based heredity is an evolutionary 'key innovation' because it allows secure and efficient transfer of specificity between cells (similar emphases exist in the accounts of Moss 2003 and Sarkar 2005). We also take on board the criticism that philosophers like ourselves have not appreciated the theoretical value of treating heredity as

a formal coding problem using the mathematical theory of communication (Bergstrom and Rosvall 2009). We argue that the information whose transmission is being optimised here is, once again, Crick information. Finally, we argue that the concept of a genetic programme can and should be divorced from the traditional idea of the genome as a 'blueprint' for the organism (Mayr 1961). The genetic programme as it figures in contemporary molecular developmental biology is best understood as a form of mechanistic explanation corresponding to the concepts of distributed specificity and combinatorial control described in Chapter 4.

In Chapter 7, 'The behavioural gene', we look at the use of genetics to explain behaviour, including human behaviour. This chapter draws on earlier, collaborative research with James Tabery. We briefly revisit the well-trodden ground of the interpretation of heritability coefficients and the other results of traditional statistical behaviour genetics. Our primary concern, however, is to explain how genes and gene action were conceptualised by traditional, quantitative behaviour geneticists and by their critics from the science of behavioural development. Behaviour geneticists and their critics focus on two different identities of the gene. Whereas behaviour geneticists use a Mendelian representation of the gene, their critics think in terms of what we call 'abstract developmental genes'. These two representations of the gene feature in two very different styles of genetic explanation of phenotypes. We show how the substantial scientific disagreements between these two groups were grounded in these differences. Chapter 7 also shows how the integration of molecular methods into both behaviour genetics and its traditional adversary developmental psychobiology has created common ground on which their differences can be resolved through research rather than polemic.

Finally, in Chapter 8, 'The genome in evolution', we discuss how evolutionary theory may be affected by the research discussed in the preceding chapters. The message here is that some of the assumptions underlying the 'Modern Synthesis' are based on an outmoded conception of the genome, and are significantly challenged by new developments in the molecular biosciences.

We have no illusions that this book will be the last contribution to the forty-year philosophical discussion of the gene, but we do believe that our conclusions move that discussion forward. Briefly, we argue that the gene today has several identities, identities which have accumulated as the molecular biosciences have developed and diversified. It is still an instrumental unit

for genetic analysis, and it is also a reasonably clearly defined structural unit used in annotating genomes. The gene is also a unit of Crick information, but the relationship between this identity of the gene and its conventional structural definition has become increasingly vexed in recent years. It also has less prominent identities: in Chapter 7 we show that some 'genes' are no more than hypothesized anchors for the parameters of developmental models. Each of these identities plays a productive role in some forms of biological research. Scientists are adept at thinking about genes in whichever way best suits their work, and at switching between these different representations of the gene as the nature of their work changes. The concept of the gene is therefore best conceived as a set of contextually activated representations.

Our other conclusion is that recent developments in the molecular biosciences have considerably undermined the idea that genes, however understood, are the prime movers in all biological processes. Despite the key role of nucleic acid inheritance in making it possible to move biological specificity between the generations, there is much more to heredity than the inheritance of nuclear DNA. Although all biomolecules are ultimately synthesised from a nucleic acid template, that template is only one source of the specificity of those biomolecules. Finally, despite the importance of gene control networks in the regulatory architecture of the cell, the complete regulatory apparatus includes a much wider 'developmental niche'. The specific roles played by the gene in its several identities are more than enough to explain its central place in biology. There is no need for anything more grandiose.