Toolbox Murders: Putting Genes in their Epigenetic and Ecological Contexts

Thomas Pradeu, CIRID, CNRS & University of Bordeaux,
and IHPST, CNRS & Panthéon-Sorbonne University

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Long version (final, shorter version to appear in *Biology and Philosophy*)

Abstract
Griffiths and Stotz's *Genetics and Philosophy: An Introduction* offers a very good overview of scientific and philosophical issues raised by present-day genetics. Examining, in particular, the questions of how a "gene" should be defined and what a gene does from a causal point of view, the authors explore the different domains of the life sciences in which genetics has come to play a decisive role, from Mendelian genetics to molecular genetics, behavioural genetics, and evolution. In this review, I highlight what I consider as the two main theses of the book, namely: i) genes are better conceived as *tools*; ii) genes become *causes* only in a context. I situate these two theses in the wider perspective of developmental systems theory (DST). This leads me to emphasize that Griffiths and Stotz reflect very well an on going process in genetics, which I call the "epigenetization" of genetics, i.e., the growing interest in the complex processes by which gene activation is regulated. I then make a factual objection, which is that Griffiths and Stotz have almost entirely neglected the perspective of ecological developmental biology, and more precisely recent work on developmental symbioses, and I suggest that this omission is unfortunate in so far as an examination of developmental symbioses would have considerably strengthened Griffiths and Stotz's own conclusions.

1. Introduction

Genetics and Philosophy: An Introduction (later on *GP*) is a very useful and timely book. As an introduction to genetics and the philosophy of genetics, it is a very accessible book, though it explores recent and complex data. It offers a well-informed and stimulating overview of current genetics in the so-called "post-genomic era" (Eisenberg et al. 2000) and of recent philosophical debates about genes (What is a *gene*? How to identify *one* gene? What should we do of the different and non-overlapping definitions of the term "gene" that co-exist in the biological literature? Are genes causally "special"? What is the relation between genes and the "nature/nurture" debate?) Presenting these fundamental issues in a clearly written and short book (250 pages) was a key challenge. This challenge has been met with remarkable success by Griffiths and Stotz.

Beyond, *GP* also constitutes an excellent introduction to philosophy of biology in general, as it combines (especially in chapters 4, 5 and 6, which I see as the best chapters of the book) an impressive expertise in current molecular biology with an important contribution to major philosophical issues (in particular about biological causation). Within philosophy of biology, molecular biology has been much less extensively explored than evolutionary biology, a surprising situation given the wonderful transformations of molecular biology in the last sixty years (see, for example, Morange 1998 and Sarkar 2005). This book will certainly count as one important exception to this relative neglect for molecular biology (along, of course, with a few others, for instance Rosenberg 1985, 2006; Schaffner 1993; Sarkar 1998, 2005; Beurton et al. 2000; Keller 2000, 2002; Moss 2003; Burian 2005; Weber 2005; Neuman-Held and Rehmann-Sutter 2006; Craver 2007; for an overview, see Darden and Tabery 2009).

Finally, *GP* is also exemplary in that it makes welcome excursions into the history of biology – for instance concerning the debate between the Mendelians and the biometricians about heredity (Chapter 2), or the construction of molecular genetics and the transition from an understanding of biological "specificity" based on stereochemistry to one based on *information* (Chapter 3).

The overall structure of the book is as follows. After an introductory chapter, Chapter 2 examines the birth of "Mendelian" genetics at the beginning of the twentieth century. Following Falk (1984), this chapter distinguishes between the *instrumental gene* (defined by its role in genetic analysis) and the *hypothetical material gene* (the postulated material unit of heredity), and shows that Mendelian genetics focused on the gene understood as an *instrumental* unit, indispensable to account for observed correlations between the phenotypes of parents and offspring. Chapter 3 tells the story of the quest for the *material* gene, with the definition of a "gene" as a fragment of DNA that specifies the linear order of its products (RNAs, proteins) (this is the "*classical molecular gene*"). This chapter shows that the Mendelian gene has not been *reduced* to the new molecular gene; the two concepts of the gene simply play two different roles, and these two concepts still co-exist today. Chapter 3 also recalls how the notion of biological *specificity*, initially related to the idea of stereochemistry, became an *informational* notion in the second half of the 1950s, mainly under the influence of Crick (1958). Chapter 4 starts the analysis of present-day, "post-genomic" molecular biology. It shows that informational specificity, far from being located in DNA alone, is actually *distributed* among many different factors, including regulatory RNAs and proteins, which leads the authors to reject reductionist approaches and to defend a view that they call, after Burian (2004), "*molecular epigenesis*." Chapter 5 examines the way environmental factors influence genome expression and contribute to informational specificity in Crick's sense; this analysis leads the authors to question the nature/nurture dichotomy, and to suggest the notion of a "developmental niche". Chapter 6 examines the ideas of genetic information and genetic program; though the authors confirm some of their previous critiques against genetic information, they express more sympathy with the idea that the "genetic code" can be understood as one key evolutionary innovation by which informational specificity is faithfully transmitted from one generation to the next. Chapter 7 builds on previous work by Griffiths and Tabery to examine how genetics is used in explanations of behaviour, and in particular human behaviour. The authors show the confrontation between quantitative behaviour genetics and behavioural developmental biologists on this question, and suggest that this confrontation could now be overcome on the basis of recent molecular methods and results. Finally, Chapter 8 discusses how the current conception of what genes are and what they do presented in the previous chapters impacts traditional views about evolution, with the idea that some of the assumptions of the Modern Synthesis are no longer appropriate in regard of recent molecular data.

The Introduction holds the promise of offering "new lessons for philosophy of biological science", based on recent transformations of genetics and molecular biology. This raises the issue of the extent to which *GP* offers new perspectives in philosophy of biology and in philosophy of science. In her recent review of a book by Evelyn Fox Keller (Keller 2010), Stotz (2012) has set a very high bar for qualifying as an innovating work in philosophy. Using the metaphor of Agatha Christie's *Murder on the Orient Express*, Stotz suggests that Keller's book does not deliver the fatal blow to the nature/nurture dichotomy, but is just one of the many killers. If one applies such high standards, it seems to me that *GP* will not qualify as entirely innovating, which should come as no surprise since Griffiths and Stotz have built extensively on the work of previous biologists, historians and philosophers (including their own important work), and many of the main philosophical theses defended in this book have often been expressed in the past – in particular the critique of reductionism, the idea that the word "gene" has several meanings, and, of course, the idea that the traditional nature/nurture distinction is inadequate. Yet two answers can be given to this objection that this book would not bring

strongly novel perspectives. First, *GP* presents itself as an *introductory* work (and is highly successful as such), and obviously novelty is not the principal objective of an introductory work. Second, and more importantly, this book does bring new ideas, or rather new and important arguments and data in favour of some philosophical claims already expressed in the past, but which are considerably strengthened by these new arguments and data (especially in Chapters 4, 5 and 6 with regard to biological *causality*). So, eventually, even though this book is introductory, its authors allow themselves the luxury of offering some important new insights on the much-debated problems of how to define genes and how to understand their causal role.

It would be impossible, naturally, to cover in the present review all the different aspects examined in this very rich book. I focus on what I see as some of the most important views defended by Griffiths and Stotz, with a particular emphasis on philosophical issues. The "toolbox murders" of my title is not so much a reference to Tobe Hooper, the highly acclaimed director of *The Texas Chain Saw Massacre* and *Poltergeist*, as an emphasis on what is, in my view, the main lesson of *GP*, namely that *genes are best conceived as tools*. This idea is applied differently to two very important meanings of the word "gene". First, the *Mendelian gene* is a tool in the sense that it is an instrument used by geneticists to account for and predict the results of the interbreeding between two organisms (analysed in Section 3 below), and, importantly, this gene concept still exists in some branches of today's biology. Second, the *molecular gene* is best understood not as a causally autonomous and deterministic factor in development, but rather as *a tool for the cell* (analysed in Section 4 below). So the take-home message is that genes should be seen not as much as architects, builders, or even tinkerers than as tools – though very important ones, of course.

I consider that the most convincing contribution of *GP* lies in the analysis of how current molecular genetics has been transformed due to the adoption of an increasingly "epigenetic" point of view (what I call "the epigenetization of genetics"). Indeed, recent years have witnessed the accumulation of data showing the implication of regulatory RNAs and regulatory proteins in the most fundamental genetic processes, including transcription and translation. In light of this transformation, Griffiths and Stotz explore with remarkable insight the philosophical issue of *causality* (examined in Section 5 below). The implication of many epigenetic mechanisms in "genetic" processes strengthens the idea of "distributed causality", that is, the idea that the causality of development is shared among many and interacting factors, without the possibility to single out genetic factors as causally special. This is also where Griffiths and Stotz's book is both an illustration and a continuation of Developmental Systems Theory (DST). Proponents of DST (Oyama 1985; Oyama, Griffiths and Gray 2001) have long defended the idea of a distributed and interactive causality, and *Genetics and Philosophy* constitutes an important contribution to the demonstration of this idea.

In Section 6, I explain why I think the authors should have paid more attention to the field of "ecological developmental biology", and in particular to the many instances of developmental symbioses, and I show why those examples would have been very helpful to strengthen several theses defended in this book.

2. The multiple identities of the gene

Building on previous work by many biologists, historians and philosophers (among whom Falk 1984, 1986, 2000; Portin 1993; Burian 1995, 2005; Keller 2000; Moss 2003; Gayon 2007; and also Griffiths and Neumann-Held 1999; Griffiths and Stotz 2006), Griffiths and Stotz show that the concept of a "gene" has several, non overlapping meanings. Historian of science Rafael Falk has shown that, as early as the Mendelians, the gene had two identities: first, an *instrumental identity*, according to which the gene is defined by its role in genetic analysis; second, an *hypothetical material identity*, according to which the gene is a physical entity the exact nature of which has to be discovered. Importantly, the success of the instrumental gene in genetic analysis did not depend on the elucidation of its physical nature:

presupposing "elements" or "factors", without any specification about the material nature of these "elements" or "factors", was enough to make predictions about interbreeding work. Many Mendelian geneticists hoped that this physical nature would soon be determined, but this was a desirable addition to the perspective of genetic analysis, not a necessary condition to make it work. Of course, it was later shown that genes are made of DNA, but this discovery was a complex process and it did not lead to the reduction of the instrumental Mendelian gene to the new molecular gene (see next section).

Moss (2003) contributed to this debate by distinguishing between "genes-P" (for "phenotypes", "prediction" and "preformation") and "genes-D" (for "development"). "Genes-P" are the basis used to explain phenotypes in hybridization experiments, so they are close to Falk's "instrumental genes". "Genes-D" are defined as template for the making of gene products, in particular proteins, so they are close to the "material genes" of molecular biologists.

Griffiths and Stotz use all this previous work to present an even more complex and richer picture. In present-day biology, they argue, two identities of the gene still co-exist, the *instrumental* gene and the *material* gene. The material gene used to be, until the 2000s, the *molecular* gene (that is, the linear template for the synthesis of biomolecules), also called the "classical molecular gene" (Neumann-Held 1999; Griffiths and Neumann-Held 1999). But the material gene has now become more complex and can be divided into two categories: first, the "nominal gene", that is, a structural sequence consensually annotated as a given "gene" by the scientific community (following Burian 2004; see also Fogle 2000); second, the "postgenomic gene" (Griffiths and Stotz 2006; *GP*, p. 75; Gerstein et al. 2007), that is, the collection of sequence elements that makes gene products (here a "gene" is defined in a purely functional way). **Figure 1** sums up these different definitions.

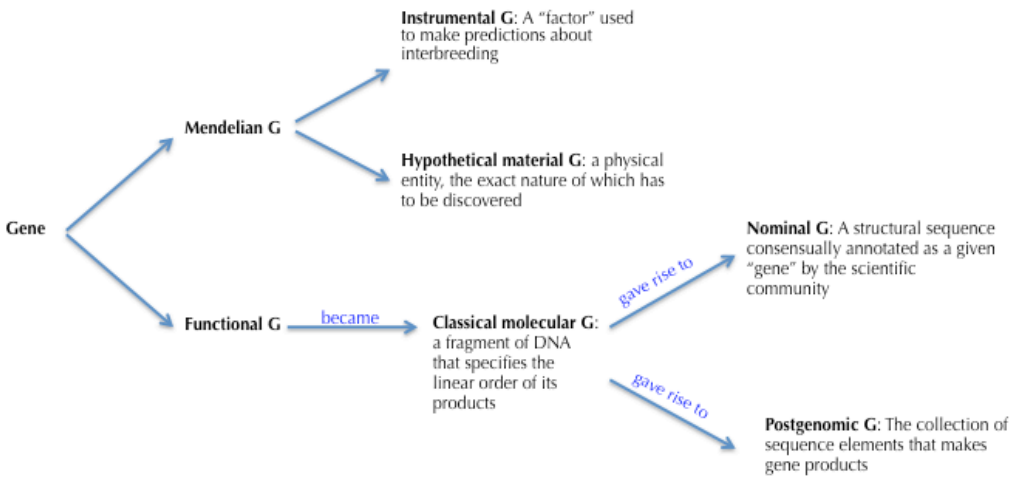

Figure 1. The different definitions of what "a gene" is. ('G' stands for 'gene').

The rest of this review will examine in detail these different definitions of the gene. It will appear clearly that Griffiths and Stotz consider that:

i) the different identities of the gene have co-existed and to a large extent still co-exist in today's biology;

ii) different definitions of a gene can be useful in different contexts;

iii) no single definition (in particular the molecular definition of the gene) has successfully "reduced" the others.

3. The failure of reductionism and the survival of the Mendelian gene

Griffiths and Stotz start with the examination of the "*Mendelian gene*", which offers the first illustration of why genes are often better understood as *tools*. This first sense concerns the domain of *classical genetics*: for a "Mendelian" biologist, the "gene" is to be understood as an instrument for predicting the result of interbreeding experiments. Faced with the results of numerous interbreeding experiments, and in particular the proportions of re-occurring characters that disappear in the first generation and reappear in the next, Mendelians found that the postulation of the transmission of "factors", and later "genes", was simply the best available explanation. Biologists were confident that their "genes" had a good explanatory power, *regardless of their material nature*, as Morgan famously emphasized in his 1933 Nobel lecture. In addition, applying the Mendelian approach made it possible to design new experiments and obtain important new results, as illustrated by the work of Morgan's group showing that in *Drosophila* females have two X chromosomes and males have one X and one Y chromosome. As Griffiths and Stotz put it: "Morgan's experiments exemplify the idea that genetic analysis was a tool of biological enquiry. Classical genetics was not a theory under test, or a theory that was simply applied to produce predictable results. It was a method of expanding biological knowledge" (p. 19). Therefore, in the context of Mendelian genetics, even if there were no straightforward physical particles corresponding to genes, genes would still be essential devices for calculation. In Falk's (1984, 1986) terms, the main identity of genes in Mendelian genetics is their *instrumental* identity, precisely because their role is to explain and predict observable results of interbreeding experiments, and to suggest new experiments.

Importantly, the subsequent story of gene was an *evolution* (new definitions were attributed to the notion of a gene), but not a *reduction*. In particular, it is simply not true, as Griffiths and Stotz argue after many others, that, with the progress made by molecular biology in the 20th century, the "Mendelian gene" has been reduced to the "molecular gene". There are two reasons for this: first, there is no straightforward matching between the Mendelian gene and the molecular gene; second, the Mendelian gene is still alive and well in some domains of contemporary biology. The first point is illustrated by the clear fact that not all segments of chromosomes that behave as Mendelian alleles count as genes under the new molecular conception (for example, untranscribed regulatory regions not immediately adjacent to the coding sequences they regulate can segregate independently of those coding sequences, and so can function as separate Mendelian alleles, but, under most definitions of a molecular gene, they are not separate molecular genes). It was initially hoped that the molecular gene would be at once the unit of *replication*, the unit of *mutation* and the unit of *function*, but the molecular gene today is not the unit of replication (this role is played by the whole DNA molecule), and it is not the unit of mutation (this role is played by a single DNA nucleotide); it is only the unit of function (namely, it plays the role of producing a gene product, typically an RNA molecule or a protein) (*GP*, p. 44). The second point is illustrated by the fact that the Mendelian gene still appears in several domains of current biology, particularly quantitative genetics.

In agreement with the quasi-consensus reached in philosophy of biology over the last forty years (e.g., Hull 1974; Kitcher 1984; Sarkar 1998; Neumann-Held 1999; Griffiths and Neumann-Held 1999; Gilbert and Sarkar 2000; Burian 2005), Griffiths and Stotz conclude that the gene does not offer a case of successful reductionism. After Sarkar (1992) and Brigandt and Love (2008), they distinguish different kinds of reductionism (methodological reductionism;

ontological reductionism, epistemic reductionism). For Griffiths and Stotz, contemporary molecular biology has been "reductionist" *methodologically*, in the sense that it has been highly successful in offering explanations situated at the low level of molecular interactions, but even this "reductive" methodology often needs to be complemented with a more "integrative" approach, as emphasized by many biologists today (e.g., Noble 2006). *Ontologically*, there is a consensus on physicalism (biological entities are, in the end, "nothing but" physicochemical entities). From an *epistemic* point of view, recent molecular biology clearly does not confirm theory reduction, nor does it support reduction understood in terms of modes of analysis, but it does illustrate a form of *explanatory reduction*, as already suggested by Sarkar (2005), Weber (2005), and Rosenberg (2006). Yet, even this "explanatory reductionism" should be conceived as both a reductive and an integrative strategy, because it is fundamental to integrate molecular details into a unified picture that takes into account all interactions and feedback loops (Gilbert and Sarkar 2000; Craver and Bechtel 2007).

4. The "epigenetization" of genetics

Chapters 4, 5 and 6 are probably the most stimulating chapters of the book, because they present exciting scientific data accumulated in the last two decades and offer in addition rich philosophical insights, in particular concerning the problem of biological causality and the notion of specificity (examined in the next section). Griffiths and Stotz make a strong case for "*molecular epigenesis*", the thesis according to which development, even at the molecular level, is always the result of a complex interplay between genes, regulatory mechanisms, and the environment. The term "molecular epigenesis" was used by Burian (2004, p. 59) to describe "the revision of sequence-based information by altering molecular conformations or by action of non informational molecules", under the influence of the cellular and external environments, and then by Stotz (2006). Of course, this perspective is also in part reminiscent of Waddington, who coined the term "epigenetics" in 1942, and highlighted how genes are activated and regulated in development and also how development is always the product of the interactions of many causal factors (e.g., Waddington 1955). Here, Griffiths and Stotz offer a detailed explanation of the thesis of molecular epigenesis by systematically examining the different ways in which genes are regulated through different and interacting RNA- and protein-based mechanisms, and how these regulatory mechanisms are involved in developmental causality and specificity.

Research done in the current "postgenomic era" (namely the period starting from the publication, in 2001, of the draft human genome sequence) has led to several striking results. First, only 1.5% of the sequenced DNA corresponds to protein-coding genes; the rest includes genes for noncoding RNA, pseudogenes, introns, untranslated regions of mRNA, regulatory DNA sequences, repetitive DNA sequences, and sequences related to mobile genetic elements. Second, many RNAs are non-coding RNAs but exert key functional roles, in particular concerning the regulation of protein production. Third, there are around 20,000 to 25,000 genes in humans, but many more proteins (possibly between 250,000 and one million), so, contrary to what was thought in the 1960s, the specificity of proteins as gene products cannot be reduced to the specificity of gene sequences.

A first consequence is that the structural gene (the traditional understanding of a gene as a sequence of nucleotides giving rise to a gene product, typically a protein) has tended to become something like a "*consensual*" gene (Fogle 2000), meaning that the structural gene is often just what biologists decide to define as a gene. "Gene annotation" often rests explicitly on such consensual definitions as, for example, when geneticists decide where a gene starts and ends in the face of the widespread phenomenon of *alternative splicing* [in alternative splicing, a final mRNA transcript is obtained after the elimination of introns (i.e., non-coding sequences) from the pre-mRNA and splicing together the exons (i.e., the coding sequences) in various combinations]. Burian (2004) has talked about "*nominal genes*" to refer to structural genes understood this way, that is, as consensually defined sequences, which function as useful

devices for communicative purposes within the scientific community and sometimes beyond. (On the difficulty to define genes unambiguously when one takes into account processes such as gene regulation, split genes, and alternative splicing see also Portin 1993; Sarkar 1998, p. 157ff.; Griffiths and Neumann-Held 1999; Keller 2000, page 59ff.).

The second consequence is that, in particular because of the frequent phenomenon of gene *combination*, it seems difficult to maintain the traditional idea that the molecular gene must be at once a *structural* (a well-delineated and reasonably continuous sequence of nucleotides) and a *functional* unit (that which makes a gene product, typically a protein). One possible answer to this problem is to accept to step back from structural definitions of the gene, and to offer a purely functional definition of the gene, which is exactly what Griffiths and Stotz do with their "*postgenomic gene*" concept. According to such a definition, a *gene* is any sequence or set of sequences that can make a product, no matter how structurally complex they may be. Here the structural unity of the gene often becomes so fragmented and complex that it ceases to be an adequate focus, the only concern being to offer a functional account of what a gene produces. This is the view endorsed by Griffiths and Stotz (see also the "*molecular process gene concept*" in Griffiths and Neumann-Held 1999 and Neumann-Held 1999], and also by Gerstein et al. (2007).

Two lessons can be drawn from the adoption of this functional definition of the molecular gene: i) A "gene" is much more than just a sequence of DNA. This leads to the idea of "molecular epigenesis" defended by the authors; ii) "Genetic causality" involves much more than just DNA sequences, leading to a far-reaching re-conceptualization of biological causality. The first lesson is examined here, while the second is discussed in the next section.

Research done in genetics in the last twenty years has shown that a "gene" is much more than a sequence of DNA, because of the crucial importance of gene *activation*, *combination, and regulation*. When cells receive environmental signals (related for example to hormonal or nutritional changes), they change their gene expression via the environment-specific use of regulatory mechanisms. Such regulatory mechanisms of genome expression can *activate*, *select* and *create* sequence information, often in a causally specific way. An example of sequence *activation* mechanism is the phosphorylation of transcriptional regulators. An example of sequence *selection* is *alternative splicing*, the phenomenon by which different versions of mature mRNA transcripts can result from the cutting and joining of different combinations of exons. In alternative splicing, a single structural gene can give rise to different mature RNA transcripts, and then to different proteins. Once thought to be rare, alternative splicing is now known to be almost ubiquitous in eukaryotes, and in particular in humans (Wang et al. 2008). The production of alternatively spliced mRNAs is regulated by a system of trans-acting proteins, including splicing *activators* (which promote the usage of a particular splice site), and splicing repressors (which reduce the usage of a particular site). It is the *cellular context*, through intracellular and extracellular signals, which trigger proteins involved in alternative splicing. An important goal of current biological research is to determine exactly how proteins regulate alternative splicing, an idea sometimes presented as the quest for the "splicing code" (Barash et al. 2010; see also Matlin et al. 2005).

Though sequence activation and selection are very important phenomena, the most challenging process with regard to classical conceptions is sequence *creation*, by which the linear sequence of the final product is extensively scrambled, modified or created by a series of co- or post-transcriptional regulatory mechanisms. An example of sequence creation is *trans*-splicing phenomena, which are inconsistent with Crick's sequence hypothesis "because *they change in a regulated way the linear order of the elements in the product with respect to the order of the elements in the DNA from which those elements are derived*" (*GP*, p. 93). A second example is RNA editing: RNA editing changes the primary sequence of mRNA during or after its transcription via the site-specific insertion, deletion, or substitution of one of the four nucleotides. A third example is translational recoding, where the message is recoded through frameshifting, programmed slippage or bypassing, or codon redefinition.

Griffiths and Stotz do an impressive job in presenting these phenomena in a clear and convincing way (the three columns of Figure 4.5 are particularly useful from that point of view), despite their complexity. One can regret, nonetheless, that, probably because they wanted to remain as accessible as possible, they do not discuss some recent data that would contribute to strengthen their claims. For example, Griffiths and Stotz emphasize that a major aim of current molecular biology is to decipher the "splicing code", that is, to uncover and predict how different mRNAs can be generated from a single piece of DNA, but, surprisingly, they do not mention the recent and striking progresses that have been made in this area. In particular, in a paper featured on the front cover of *Nature* under the heading "Cracking the splicing code: Alternative splicing patterns predicted from RNA sequences", Barash et al. (2010) have used computer tools to develop a "splicing code" that enabled to predict how hundreds of RNA features work together to regulate tissue-dependent alternative splicing for thousands of exons. This "code" has been used to shed light on new biological mechanisms and to predict how alternative splicing is involved in different processes, including major developmental processes, and many of these predictions have proved correct (Fu and Ares 2014). An analysis of recent progresses made concerning the functioning of the proteome would have also been extremely interesting (see, for example, Cox and Mann 2011; Altelaar, Munoz and Heck 2013; for a recent attempt to "map" the human proteome, see Kim et al. 2014). It would also have been helpful to provide a discussion of prokaryote genetics, which is mentioned only "negatively", meaning that it is contrasted with eukaryote genetics. This, of course, is related to the fact that gene regulation is not as complex in prokaryotes as in eukaryotes, but a discussion about how genes are regulated in prokaryotes and how gene regulation has evolved would have been useful. Naturally, a short book cannot cover all the aspects of today's genetics, but it would have been sensible to bring up some recent results that make Griffiths and Stotz's arguments even stronger.

Griffiths and Stotz gather the phenomena of gene activation, combination, and regulation under the label "*molecular epigenesis*" (following Burian 2004). "Epigenesis" has had historically several different meanings, but one of them is the antithesis of "preformationism" in the context of the embryology of the 18th century, and beyond: while preformationists considered that the final adult form is already contained in the egg (or sperm), epigeneticists asserted that the final adult form does not "pre-exist", but is constructed progressively through interactions among all egg components and with the environment (Maienschein 2005). While many have criticized the recent resurgence of "preformationist" ideas in developmental biology (e.g., Oyama 1985; Griffiths and Knight 1998; Griffiths and Neumann-Held 1999; Lewontin 2000), some have suggested that a minimalist sense of "preformationism" was valid at the molecular level, in so far as, in virtue of the "genetic code", the sequence of nucleotides on the DNA largely "mirrors" the sequence of amino acids on the protein (e.g., Godfrey-Smith 2000, 2001). In this context, the thesis of the "molecular epigenesis" defended by Griffiths and Stotz can be seen as a radicalization and extension of the anti-preformationist critique, with the explicit idea that preformationism is wrong *even at the molecular level*. Indeed, the different molecular mechanisms that regulate gene activity (through activation, selection and creation) show that the correspondence between nucleotides and amino acids is, at the very least, much more indirect and "scrambled" than it was thought thirty years ago. Molecular "information" is not contained in any single molecule; on the contrary it is constructed through multiple interactions in processes regulated by the larger system at the level of the cell, the tissue or even the organism. Therefore, recent developmental and molecular biology suggest the validity of "epigenesis" at all levels, from molecules to individual traits.

This view constitutes indeed an extension of Burian's (2004) "molecular epigenesis". Building himself on Gilbert (2003), Burian writes:

> alternative splicing, systematic silencing of DNA by methylation and various modifications of histones, have thoroughly disrupted the notion that the DNA encodes

> information or contains a program that can be read out in any simple way. A cellular context is required for DNA to function, and different cellular contexts extract different information from the same DNA sequence. (Burian 2004: p. 63).

In that paper, Burian explores important regulatory mechanisms that illustrate and give a precise content to a new conception of epigenesis that had been emerging since the beginning of the 2000s, and which was summed up by Van de Vijver, Van Speybroeck, and De Waele in 2002 in the following way: "instead of containing the core program or the basic instructions of the living, the genome is viewed as a regulatory system that actively responds to internal and external fluctuations of various kinds and that is embedded in a variety of contexts that can selectively determine its expression." (2002, p. 4). The defence of "molecular epigenesis" by Griffiths and Stotz is thus perfectly in line with this general framework, to which they contribute by their examination of recent molecular data, as they have already done in the past (e.g., Stotz 2006b; Stotz, Bostanci, Griffiths 2006).

The perspective of Griffiths and Stotz also reflects very well the current move in genetics, which we can call the "*epigenetization*" of genetics. The focus on the mechanisms of gene regulation by RNAs and proteins has shown that there was no molecular genetics without molecular epigenetics, because to understand what genes are and what they do presupposes to untangle the complex mechanisms of that regulation. This is also the reason why genetics is in close and permanent interaction with the emerging fields of "transcriptomics" (the study of the complete set of RNA transcripts that are produced by the genome, under specific circumstances or in a specific cell) and "proteomics" (the study of the entire set of proteins expressed by a genome, cell, tissue or organism at a given time), the results of which are often published in journals specialized in genetics (e.g., Wang, Gerstein and Snyder 2009; Altelaar, Munoz and Heck 2013).

The defence of "molecular epigenesis" is related to the second sense in which the gene can be considered as a *tool* – this time in the domain of *molecular genetics* (and not Mendelian genetics, as examined in the previous section). Here the gene is a tool not for the scientist, but for the cell, or even for the whole organism. *GP* (p. 75) indeed describes the way genes function as resources for the cell or the organism: "genes are ways in which cells utilize available template resources to create the biomolecules that are needed in a specific place at a specific time: genes are things an organism can do with its genome!" (see also Griffiths and Neumann-Held 1999, p. 658-659; Stotz, Bostanci, and Griffiths 2006). Alternative splicing, in particular, makes it clear that the molecular gene is now "a modular structure that can be used in different ways to make different products" (p. 56). This conception of the molecular gene as a "tool", rather than a "determinant", an "architect" or a "programmer" (to mention only some of the metaphors that have traditionally been used to describe gene action) is in part reminiscent of Noble's claim that genes, far from being the "controllers" of the organism, may rather be seen as "prisoners" of the rest of the organism: "Indeed, it might be more helpful to avoid saying that genes do anything at all; it is more that genes are used" (Noble 2006: 105). It also echoes Enrico Coen's idea that it would be more appropriate, in many circumstances, to speak of "master proteins" rather than "master genes" (Coen 1999, p. 87-88). More generally, the idea that genes are tools used by cells and organisms according to the spatial and temporal context is now widely shared among molecular biologists (e.g., Dillon 2003; Gerstein et al. 2007; Chen and Manley 2009; Chanock 2012; Fu and Ares 2014), developmental biologists (interestingly, the title of Chapter 4, "The reactive genome", is borrowed from a paper by Gilbert (2003)), systems biologists (e.g., Strange 2005; Jaeger, Irons and Monk 2008), and philosophers (e.g., Oyama 1985; Laubichler and Wagner 2001; Robert 2004, who talks about "constitutive epigenesis"). In fact, this idea has been adopted by a majority of biologists for more than fifteen years, and what should be surprising is that many philosophers still seem to neglect the vast amount of data that support it. Here is what an editor of *Science* wrote in 2001, in a special issue devoted to epigenetics:

> Some of the weirdest genetic phenomena have very little to do with the genes themselves. True, as the units of DNA that define the proteins needed for life, genes have played biology's center stage for decades. But whereas the genes always seem to get star billing, work over the past few years suggests that they are little more than puppets. An assortment of proteins and, sometimes, RNAs, pull the strings, telling the genes when and where to turn on or off. (Pennisi 2001: 1064).

Thus, one can only hope that *Genetics and Philosophy* will contribute to convince philosophers of biology and, perhaps even more importantly, generalist philosophers that genes in the organism are not so much *activators* as they are *activated*, and that today's genetics is interested in precisely how this activation is regulated.

5. Re-thinking developmental causality

On the basis of the above arguments concerning gene regulation, Griffiths and Stotz offer a rich reflection on biological causality and specificity, which constitutes certainly the most important philosophical contribution of the book. They defend that biological causality is both *distributed* and *interactive*. The emphasis here is on *developmental* causality. In fact, Griffiths and Stotz's discussion about causality makes it clear that the main focus of the book is biological development, and more precisely how genetic and non-genetic mechanisms interact in making the development of an organism possible. A key question for several decades now has been to determine whether or not genes are *causally special*, in particular in development, and Griffiths and Stotz offer here their answer to this question.

To understand what *GP* brings to the debate over developmental causality, it is useful to step back, and say a few words about developmental systems theory (DST) in general (Oyama 1985; Oyama, Griffiths and Gray 2001; Griffiths and Gray 1994, 2005; analysed in Barberousse, Merlin and Pradeu 2010). A key DST thesis is that many factors are involved in development, and these factors interact in complex ways. One crucial consequence is that a developmental resource *becomes a cause* only in a given *context*, in which many other factors are involved. For instance, it is true that DNA is to some extent "already there" in an egg cell, but DNA *becomes a cause* only in an adequate cellular and extracellular context, for example because an hormone interacts with a protein, which in turn will activate one or several genes, which themselves will be involved in the synthesis of a protein. This is what Oyama (1985) has called, famously, the "ontogeny of information", which means that even biological "information" itself does not just "lie" somewhere, ready to be expressed; even biological "information", in other words, is *constructed* in the course of development, through complex interactions (see also Griffiths and Neumann-Held 1999; Stotz 2006a; Noble 2006: 21). This general view is strongly supported by the different regulatory mechanisms examined in great detail by Griffiths and Stotz, and this is precisely the investigation of these mechanisms that leads them to conclude: "A set of sequences is a gene because of the way in which it is used by the cell, not because of its intrinsic nature" (p. 106) (see also Griffiths and Neumann-Held 1999, p. 658: "It is the DNA itself, not the gene, that just 'is.'"). In the same vein, Noble (2006, p. 21) says: "the DNA code of a gene is nonsense until it is interpreted functionally, first by the cell/protein machinery that initiates and controls transcription and post-transcriptional modifications, and then by the systems-level interaction between proteins that generate higher-level function. A gene can do nothing without this interpretation by the system."

In my view, this thesis about developmental causality, shared by several scientists (e.g., Lewontin 2000; Noble 2006, 2008, 2012) is important, and it is not trivial. Indeed, it is an arduous task to always keep in mind that developmental resources interact in complex ways, and that the cellular, organismic and environmental context significantly influences what genes can do in development. Research on epigenetic and environmental regulation of genes, for example, has long been seen with suspicion, even though it has been well-known for decades that the cytoplasm, the cellular context and some factors of the external environment (for example temperature) can sometimes have a strong influence on developmental outcomes

(Gilbert 2002). Some DST opponents have suggested that taking into account the intertwinement of developmental resources would just make research impossible in practice. How would it be conceivable, the objection goes, to pay attention to *all* the developmental resources and to *all* their interactions? No biologist could develop a research program based on such an encompassing view! DST would therefore be "holistic", and "impracticable", as famously suggested by Kitcher (2001). With the benefit of hindsight, Kitcher's critique seems specious. First, the idea of "causal democracy" (all causes are of equal weight) is a straw man, not to be found in the writings of Lewontin or DST proponents (see Oyama 2000; Griffiths and Gray 2005; Griffiths 2006). Second, Lewontin and DST people's view about causality reflected past empirical work ranging from genetics to developmental psychology (for example the work of Gottlieb and Lehrman: see Oyama, Griffiths and Gray 2001; Griffiths 2006). Third, research done in the last fifteen years (in particular about the epigenetic regulation of genes and about developmental symbioses, as detailed in the next section) has proved that biologists are increasingly aware of the importance of studying this intertwinement of developmental causes, and have developed remarkable tools to account for it. Thus, a general claim of DST, taken on by *GP*, is that there is no causal primacy of genes, and that genes become a cause only in a context.

But the initial question, "Are genes *causally special*?", can come back under a different guise. In the last decade, a new attempt to defend that genes are causally special has been put forward by Waters (2007), and this view constitutes a new and crucial target of *GP*. Waters' (2007, 572) aim is "to identify situations in which DNA is an ontologically distinctive cause, and to clarify the nature of its causal distinctiveness in these situations." According to Waters, genes are causally special because DNA is the sole source of sequence specificity. Waters uses Woodward's (2003, 2010) manipulationist account of causation, according to which there is a causal relationship between X and Y if it is possible to manipulate the value of Y by intervening to change the value of X. Woodward insists that the most important question is not to say *if* something is a cause, but rather to distinguish *among* causal relationships, according to some appropriate characteristics. One of these characteristics is *specificity*: a cause is specific if fine-grained changes in X lead to fine-grained changes in Y. For Waters (2007: 574), DNA is a *specific* difference maker because different changes in the sequence of nucleotides in DNA would change the linear sequence in RNA molecules in many different and very specific ways (in contrast, for example, with the way RNA polymerase influences the RNA linear sequence). In response to Waters, Griffiths and Stotz explain that they perfectly accept Woodward's manipulationist account, and that from this perspective an important question is indeed to determine which causes are specific. But it is simply not true that DNA is the only specific cause. To demonstrate this, they propose to call "Crick information" (or "informational specificity") the specific determination of the linear sequence of a gene product, in line with Crick's (1958) proposal. They then show that several "epigenetic" regulatory mechanisms examined above (in particular trans-splicing, RNA editing and translational recoding) can exert a *specific* causal influence on the determination of the linear sequence of gene products. In other words, specificity is "distributed", that is, shared among many different developmental factors. Thus, distinguishing specific causes is indeed important, but, contrary to Waters' view, genes are *not* the only specific difference makers.

One important contribution of *GP*, therefore, concerns the concept of *information*, and its relations with the concept of *causality*. This leads Griffiths and Stotz to partly reconsider some of their previous critiques of the notion of biological information (e.g., Griffiths 2001), in two senses:

i) They show that the notion of Crick information (informational specificity) is useful in the context of molecular biology. Nevertheless, one should in fact adopt an *extended informational specificity*, according to which informational specificity is distributed among many developmental resources (for an analysis of how to measure informational specificity, see Griffiths et al., submitted).

ii) They express more sympathy with the idea that the "genetic code" can be understood as one key evolutionary innovation by which informational specificity is faithfully transmitted from one generation to the next (following Shea 2007, Bergstrom and Rosvall 2009).

A difficult question, and one not addressed specifically in *GP*, concerns the *delineation of potentially relevant causal factors in development*. Griffiths and Stotz explain that "environmental" factors can influence the genes, and contribute to informational specificity. But how to draw the boundaries between meaningful and non-meaningful factors to understand development? This question takes us back to an old challenge to DST, which was to offer a convincing delineation of "developmental systems" (DS). In response to an objection made by Sterelny (the "Elvis Presley problem"), Griffiths and Gray (1994) have claimed that the original definition of a "DS" as the whole set of resources contributing to the development of an organism was too inclusive and imprecise, and that adopting an evolutionary view on DS would solve this problem: "We have tried to confront one major weakness of previous presentations of the developmental systems idea – the lack of any way of delimiting and individuating developmental systems. We suggest an etiological solution: the DS consists of the resources that produce the developmental outcomes that are stably replicated in that lineage" (p. 278). In (Pradeu 2010), I have tried to show that two traditions coexist in DST: one (best represented by Oyama 1985) focuses on understanding the causality of development and adopts the organism as its main unit of analysis; the other (best represented by Griffiths and Gray 1994) focuses on explaining the coevolution of organisms and their environments and questions the organism as an adequate unit of analysis. I also insisted that the first strategy, the developmental-organismic one, was more original and fruitful than the second one. Now, I see *GP* as a contribution to the first rather than the second strategy, in contrast then to (Griffiths and Gray 1994): *GP* is mainly about development and developmental causality, and its principal unit of analysis seems to be the organism. I even see the concept of a "developmental niche" (defined by Griffiths and Stotz, after West and King 1987, as "the set of environmental and social legacies that make possible the regulated expression of the genome during the life cycle of the organism") as a potential return to the extended and development-based notion of a "developmental system". I wonder if Griffiths and Stotz will agree on this characterization of their work. It seems consistent, anyway, with recent emphasis of Griffiths on the proximal, as opposed to ultimate, causes of development (Griffiths 2013). What has been said here, therefore, raises the following questions:

a) Is the "developmental niche" equivalent to the "DS"?

b) Does the developmental niche expose itself to the same possible objection as the "DS", namely that it is too inclusive and therefore imprecise?

c) Is development (rather than evolution) the main focus of a "developmental systems perspective"?

d) Is the organism an adequate level of analysis for this perspective?

One can regret that these questions have not been addressed in *GP*, and I look forward to seeing how Griffiths and Stotz situate their current perspective with regard to those questions.

In the last section, I turn to what I see as an important factual objection.

6. The missing final blow: developmental symbioses

Griffiths and Stotz examine, in Chapter 5, how environmental signals can influence the development of the organism, and, more precisely, how they impact gene regulation (on this topic, see also van der Weele 1999). They are also interested in how environmentally induced changes can influence the next generation. Examples discussed by Griffiths and Stotz are mainly related to the field of "epigenetics" understood in a broad way, and include genomic imprinting, cytoplasmic inheritance, and the role of some regulatory RNAs. Griffiths and Stotz also describe what they label "exogenetic inheritance", including the inheritance of chromatin modification (Jablonka and Raz 2009). They also mention several research programs about

environment-development interactions, including "ecological developmental biology" (Gilbert and Epel 2009), but only in passing (p. 130).

However, Griffiths and Stotz do not analyse in detail the phenomenon of developmental symbiosis, which is arguably the most innovating and convincing aspect of recent work done on how the environment influences development, and in particular on environmental regulation of genes (McFall-Ngai 2002; Gilbert 2005; Gilbert and Epel 2009; Gilbert 2014; Pennisi 2013; McFall-Ngai et al. 2013; strikingly, as early as 2002, in a special issue devoted to epigenetics, Gilbert (2002) was already insisting on the crucial importance of this phenomenon). This recent work illustrates what can be called the ongoing "symbiotization" of genetics, parallel to the "epigenetization" of genetics described above. For example, it has been shown in mice that a bacterial component of normal intestinal microflora modulates expression of host genes involved in key processes such as the maturation of the intestine and angiogenesis (formation of blood vessels) (Hooper et al. 2001; Stappenbeck, Hooper and Gordon 2002), and that bacteria-induced postnatal organogenesis was frequent in the gut (Eberl 2005). Many other examples of how microbes decisively influence host oogenesis, organogenesis and morphogenesis have been documented across species (reviewed in Pradeu 2011). Several arguments make of developmental symbioses an extraordinarily convincing example to show that the environment can play a decisive role in development and how gene activation often depends on environmental factors. First, while some people might resist the idea that epigenetic regulation of gene activation in trans-splicing and similar examples is a form of *environmental* regulation, very few people would deny it in the case of microbe-dependent regulation. Incidentally, as Griffiths and Stotz note, some people are tempted to say that even epigenetic regulations can always be described as ultimately coming from the host *genome*, but this view is invalid in the case of microbe-regulated development. Second, the phenomenon of microbe-dependent development seems to be ubiquitous in nature, in plants, invertebrates and vertebrates (Gilbert and Epel 2009). Third, from an evolutionary point of view, some people deny that epigenetic regulations are important because they are rarely transmitted over many generations; I agree with Griffiths and Stotz that this is not a sound argument, as an influence over a single generation can perfectly be evolutionarily significant, but another striking feature of developmental symbioses is that they often involve microbes that are transmissible over many generations, with long-lasting effects, especially in arthropods (McFall-Ngai 2002), which makes the "multigeneration objection" invalid. Fourth, the effects of microbes on host development can be *causally specific*, in Woodward's sense: in many cases, fine-grained changes in the composition of the microbiota can be related to fine-grained changes in host's development or metabolism (e.g., Shin et al. 2011). For all these reasons, developmental symbiosis constitutes a major phenomenon to demonstrate the importance of environmental regulation of development, and in particular of the regulation of gene activation by environmental factors. It seems to me to be one of the most convincing examples of environmentally regulated "molecular epigenesis", and one that obliges us to question the traditional boundaries of biological entities (Pradeu 2011, 2012). In my view, Griffiths and Stotz should have discussed in some detail this example, which seems so useful to strengthen their most fundamental claims.

7. Conclusion

GP is a very good and clearly written book. One minor difficulty lies in the many anticipations and reminders, with some pieces of information scattered in different places in the book. For example, detailed explanations about regulated recruitment and combinatorial control are scattered throughout Chapters 3 and 4, which forces the reader to go back and forth between these different sections. Another example concerns the description of epigenetic mechanisms, which leads the authors to mention in Chapter 3 (page 53) Figure 5.1 of Chapter 5, a figure that indeed becomes fully understandable only in Chapter 5. Typos are very rare in the book, except perhaps for a minor confusion on page 68 between *Science* and *Nature* (Elizabeth

Pennisi is a well-known editor of *Science*), a mistake (page 65) concerning the date of publication of Craver's *Explaining the Brain* (2007, not 2009), and a misspelling of Denis Noble's name (page 102).

To sum up, *GP* defends the key idea that genes should be seen as "tools", and that genes act as causes only in an epigenetic and environmental context. To make this claim, the book uses in an exemplary way various fascinating data coming from recent molecular biology. This leads Griffiths and Stotz to take up philosophical theses that have often been defended in the recent past, but which are considerably strengthened by the rigorous analysis of molecular data offered by the authors. I will conclude by recapitulating my questions/objections to GS:

i) The inclusion of some recent data on the local and environmental regulation of development (especially symbiosis) would have been helpful, all the more so as these data would have considerably strengthened Griffiths and Stotz's point of view, in particular concerning molecular epigenesis and distributed specificity. Among other important advantages, these data confirm that an investigation of how different developmental causes are intertwined has become reality in today's biology, against the "impracticality" objection of Kitcher (2001) and others.

ii) Precisely because data in molecular biology change very quickly, up-to-date philosophy of molecular biology needs to change more quickly than other branches of philosophy of biology. It would be highly desirable, then, that Griffiths and Stotz plan updated editions of their book in the future and create a website with updated references and data (as done by Godfrey-Smith 2013, for instance).

iii) It would have been extremely helpful, from a philosophical point of view, if Griffiths and Stotz had spelled out in more details what their main unit of analysis is: is it the organism? The "OE" (namely, the "organism-environment association": Griffiths and Gray 1994)? The developmental system? If the later, what is the exact articulation between the "developmental system" and the "developmental niche"? This issue about the unit of analysis is related to an important debate, the respective role of the ultimate and proximate explanations in biology, and whether this distinction is legitimate. In my view, *GP* is about development and more generally about proximate rather than ultimate causes and it focuses on the organism as a major unit of analysis, but perhaps Griffiths and Stotz will disagree, and in any case I think that it would have been helpful to address these issues in this stimulating book.

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