The Varieties of Molecular Explanation

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Abstract

Reductionists in biology claim that all biological events can be explained in terms of genes and macromolecules alone, while antireductionists argue that some biological events must be explained at a higher level. The literature, however, does not distinguish between different kinds of molecular explanation. The goal of this essay is to identify and analyze three such kinds. The analysis of molecular explanations herein carries an important philosophical implication; in shunning crude reductionism and extreme versions of holism, we can combine the insights of thoughtful reductionists with sophisticated antireductionism. When this is done, the question of explanatory reductionism becomes less substantial than often supposed.

1 Introduction. Two Strands of Reductionism

The debate between reductionists and antireductionists in biology hinges on two related but distinct theses. The first is *genetic reductionism*, defined by Sarkar (1998) as the claim that all phenotypic phenomena can be reduced to facts at the genotypic level. The second thesis is what I will refer to as *molecular reductionism*, the claim that the whole of biology can be reduced to molecular biology. In spite of decades of discussion, both strands of reductionism continue to remain obscure. The problem is due in part to a general lack of clarity concerning the heart of the disagreement, and in part to the difficulties of effectively subsuming the fine-grained distinctions of molecular research under overarching labels such as "holism" and "reductionism". It is time to revise some of these questions from the standpoint of contemporary experimental science.

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Reductionism is a multifarious concept that has acquired different meanings in the philosophical literature and thus requires some clarification. Following a common trend, throughout this essay reduction will be given an epistemic interpretation according to which theory T is reducible to theory T* if and only if there is an explanation of all T-events that employs solely the language and concepts of T*. As a result, genetic reductionism can be interpreted as the claim that facts at the level of the genotype, and these facts alone, can explain the regularities of biological processes. In turn, macromolecular reductionism becomes the thesis that there is an explanation of every biological fact that mentions only biochemical properties of molecules and their interactions.[1]

Philosophers often refer to the explanations given by geneticists and developmental biologists as "mechanistic" (Machamer et al. 2000; Darden 2008) or "causal-mechanical" (Schaffner 2006) but, for the most part, fail to distinguish between kinds of molecular explanation. The goal of this essay is to isolate and discuss different explanatory models in molecular biology and identify their nature, form, and characteristic features. The next three sections individuate three independent explanatory paradigms in molecular biology. It is important to stress right away that the aim is not to provide an exhaustive list, but rather to present distinct and important forms of explanation, emphasizing differences that have generally been overlooked. In the final section, these distinctions are applied to the question of reductionism. As I will argue, we can integrate the insights of thoughtful reductionists with a sophisticated form of antireductionism, while avoiding both crude reductionism and extreme versions of holism. When this point is appreciated, the debate over explanatory reductionism becomes less substantial than often supposed.

In what follows, I shall not attempt to specify general necessary or sufficient conditions for explanation, an important philosophical endeavor that, however, transcends the scope of the present work. Throughout the paper, instances of successful explanations are individuated by glossing scientific practice. More specifically, I assume that for an explanation to be adequate is for it to satisfy current scientific and philosophical standards: it must provide a satisfactory answer to questions posed by the appropriate portion of the biological community and appeal to their language, concepts, and methodology. In addition, it must also satisfy general philosophical requirements, such as being counterfactual supporting.

[1] This preliminary characterization is not intended as a precise definition of reductionism, but rather as a way to narrow the scope of the discussion. For example, in what follows we shall not be concerned with ontological theses, such as the uncontroversial fact that organisms are constituted by molecules, or the rejection of vitalism, the discredited doctrine that biological systems are governed by forces other than physico-chemical ones. Moreover, we should note that our general statement of explanatory reductionism is broader than classic formulations of theory reduction (Nagel 1961; Schaffner 1967) since here we place no constraints on the structure of theories and correspondence rules connecting them, or on the form of the explanation. For an excellent critique of the logical empiricist view of reduction applied to biology, see (Hull 1974).

2 Genetic Explanation

Drepanocytosis, a genetic disease commonly known as sickle-cell anemia (SCA), can be subsumed under an explanation that cites only genetic and biochemical facts. Why do human beings who are homozygous for the sickling allele experience crises at low levels of oxygen? The answer lies in the role of Hemoglobin, a protein contained in erythrocytes (red blood cells) that binds to oxygen in the lungs and transports it to the rest of the body. When blood reaches an organ, Hemoglobin releases oxygen, collects carbon dioxide, and brings it back to the lungs, where it is exhaled, and the cycle begins again. SCA is triggered by a point mutation, a single-base substitution in the chain of nucleotides in the *hemoglobin* gene,[2] which leads to a single amino acid substitution in the encoded molecule. This recessive mutation, under conditions of low oxygen, causes red blood cells to assume a rigid crescent shape, which reduces their flexibility and elasticity, and affects their ability to dilate capillaries to facilitate their passage. As a result, abnormal erythrocytes tend to block capillaries, thereby restricting blood flow to organs. These vaso-occlusive crises may result in potentially lethal consequences, such as strokes, decreased immune reaction, pulmonary hypertension, and chronic renal failure. In addition, the sickling allele, when homozygous, disrupts the normal asymmetrical distribution of lipids in the layers of the cell membrane, a change that leads white blood cells to attack the affected erythrocytes. This secondary effect results in a drastic reduction of the erythrocyte life (from the normal 90-120 day cycle to 10-20 days), which affects the turnover rate of bone marrow, with serious pathological consequences.

Our initial claim that the above explanation of SCA cites only genetic and biochemical facts requires substantial clarification: a few qualifications are thus in order. First, we should emphasize right away that not all the consequences of the disease are determined by properties of genes and gene products. The effects of the abnormal Hemoglobin molecule depend on many variables, such as capillaric structure and timing of exposure to low oxygen tension in the life of the individual, which are influenced by cellular and environmental factors that are not coded in the genes. A second and related point is that not all causes of SCA occur at the genetic or molecular level. The mutated allele, by itself, is not sufficient for anemia to occur, in the absence of other cytological, physiological, and environmental background conditions. Indeed, the mutation is not even necessary since, in principle, it would be possible to trigger SCA by intervening on the structure of the Hemoglobin molecules while leaving the gene untouched. In short, the occurrence of SCA in an individual or population may have proximate (e.g. physical) as well as ultimate (e.g. evolutionary, ecological, social, political) causes, effects, and background conditions that are not captured or entailed by the aforementioned explanation.

The crucial feature of the disease, which allows the oxygen crises to be explained by focusing on the structure of the gene, is that the presence of the mutated allele, when homozygous, determines the occurrence of the disease in an otherwise healthy

[2]Throughout the essay, I shall follow the convention of italicizing gene names and capitalizing the name of proteins, in Roman typeface. Thus "*hemoglobin*" refers to the gene, while "Hemoglobin" refers to the protein coded by the gene. In a context where the distinction does not matter, "hemoglobin" (in lowercase Roman typeface) refers indifferently to either the gene or the protein.

human being, when the organism is exposed to low oxygen conditions. Now, surely this is far from a complete explanation. Processes such as the sickling of mutated cells when oxygen is scarce or the alterations in capillaric interactions are excluded from the analysis, and filling out these details requires attending to the complex secondary effects of the presence of the Hemoglobin molecule crossed with the relevant background conditions. Nevertheless, a precise account of how the genetic changes are produced or how they are reflected in the organism is unnecessary in order to effectively isolate the mutation as the difference-making cause of SCA; in doing so, phenotypic effects and environmental conditions can be effectively black-boxed.[3] The reason for this is that once we assume a set of background conditions, which are generally invariant across individuals, the structure of the *hemoglobin* gene becomes the triggering cause that determines the sickling of erythrocytes when the organism is exposed to low oxygen levels.[4] As a result, we can reliably predict whether an individual will experience anemia when oxygen is scarce by focusing solely on the sequence of nucleotides. In general, when a biological event has an actual difference-maker that can be described in genetic or molecular language,[5] we shall say that the event can be subsumed under a "genetic-molecular explanation", *genetic explanation*, for short.

While the genetic explanation of SCA is relatively straightforward, biochemical difference-makers can be extremely complex. In such cases, the importance of functional and dispositional properties of genes and molecules becomes even more prominent. This point can be appreciated by comparing SCA with another genetic pathology, Huntington's disease (HD), a neurodegenerative disorder caused by an unstable expansion of a CAG repeat within the coding region of a single gene.[6] Although SCA cannot be permanently cured, crises can be partially controlled and affected patients can be monitored to prevent devastating consequences. In contrast, despite the fact that the sequence of both the wild-type and the mutated alleles of the *huntingtin* gene and the structure of the encoded protein have been known since 1993, HD-related neurodegenerative disorders cannot yet be cured, prevented, or even effectively controlled. What explains the asymmetry? Both diseases are genetically determined (in the sense made clear above) and depend on a single mutation in a single gene. The relevant difference, I suggest, lies in the functional difference between the two encoded proteins. The mutation causing SCA occurs in a gene coding for a protein—Hemoglobin—that has a precise physiological function, and thus the mutation triggers a single major effect. Nothing changes in the

[3]The concept of "difference making" in molecular biology was developed by (Waters 2007) to defend the primacy of the causal role of genes against the "parity thesis" that downgrades DNA as only one among many causes of biological processes and events.

[4]The relevant distinction here is between *causing a trait* and *causing a difference in a trait*. Failure to keep these two concepts separated has caused much confusion in the biological literature (Keller 2010).

[5]The notion of molecular language should be intended broadly. In what follows, I shall call "molecular" any description that appeals only to properties of macromolecules (as opposed to properties of larger systems, such as cells, organisms, or the environment), whether these are categorical, dispositional, functional, or something else. This point will become central for reassessing the debates on reductionism, an endeavor to which I shall turn in the final section of the essay.

[6]For a comprehensive and up-to-date review of research on HD, see (Zuccato et al. 2010). A philosophical discussion can be found in (Kitcher 1997, 2001).

erythrocytes except the substitution of a different molecule for the one they normally contain: instead of a molecule that is able to perform the function of transporting oxygen, the mutated Hemoglobin present in the erythrocytes now causes the capillaries to be clogged when oxygen supply is low. In contrast, the Huntingtin protein has thousands of possible transcription dysfunctions and it is proving to be a daunting task to determine all the devastating effects on the organism. Hence, whereas most developmental processes can be bracketed in the case of SCA, they are required to understand differences in neural functioning.[7] Nevertheless, in both pathologies the difference-maker lies in the structure of the gene: both diseases have a genetic trigger.

3 Morphological Explanation

The examples of SCA and HD support the reductionist claim that biological events can be subsumed under genetic explanations, which cite only structural and functional properties of nucleic acids and coded proteins. But, as many scholars are quick to point out, biochemical properties are insufficient for explaining all biological facts. In order to rebut the claims of radical reductionism, developmentalists can appeal to sophisticated molecular findings, such as mechanisms of DNA editing and repair, gene splicing, or to networks of epigenetic interactions (Keller 2001). Some authors, however, have followed the antireductionist path to much more extreme forms of holism. For instance, the "dialectical approach to biology" inspired by (Lewontin and Levins 1985) and Developmental Systems Theory (Oyama 1985; Griffiths and Gray 1994; Oyama et al. 2001) reject interactionism, the conventional view that phenotypes are determined by the interaction of genotype and environment (at least when these interactions are given a narrowly molecular interpretation) and focus instead on complex systems as basic developmental units. Even if successful, the strategy of opposing genetic explanations with life-cycles is like chasing a mole out of a garden with dynamite. Crude reductionism can be undermined within the confines of molecular developmental biology. By focusing on an important class of comparative biological explanations, in this section, I shall argue for a stronger thesis, namely that biochemical details are not just insufficient; they are sometimes irrelevant for developmental explanations. Biological explananda that lack molecular difference-makers require a different kind of explanantia.

Reaction-Diffusion Systems (RDSs)—mathematical models spawned from the seminal work of Turing (1952)—can be used to explain a whole array of phenomena by showing how the interaction of homogeneously distributed substances produces stable patterns. More specifically, RDSs capture how two distinct processes influence the distribution of substances within systems: chemical reactions between molecules and their diffusion in the system.[8] To illustrate, consider the action of two morphogens (sub-

[7]The fact that, in spite of substantial curative difficulties, SCA is much more tractable than HD suggests that, while explaining a phenomenon does not necessarily—or even typically—translate into a program of intervention, tractability and simplicity of explanation tend to be correlated. In general, the more complex the explanation, the harder the translation into intervention.

[8]What constitutes a "system" is an important question that deserves more attention than it has

stances that govern tissue formation by regulating cell differentiation), an activator A and a repressor R, which diffuse in an embryo and react with one another. Activator A induces the production of both A and R; R, in turn, inhibits the production of A. As predicted by Turing, if the morphogens diffuse at equal rates, spatial variation from the initial homogeneous state is eventually smoothed out and disappears. However, if the rates of diffusion are not identical and the reaction rates do not adjust quickly enough to reach equilibrium, sharp waves of concentration differences will appear and generate stable patterns.

In developmental biology, RDSs can be employed to model and explain how various organisms employ the same processes to generate different patterns. Moreover, RDSs can also be employed, at a more abstract level, to subsume a variety of related processes under a single family of models, well-instantiating Sober's (1999) remark that it is sometimes more illuminating to show that the same effect is reached by different causal pathways than to subsume different phenomena under a unified explanation. The first kind of explanation is instantiated by J.D. Murray's study of pattern formation on mammalian coats. A clear illustration of comparative explanations of the second kind is Meinhardt's work on the coiling of seashells. Let us discuss these examples, in turn.[9]

Murray (1988, 1989) shows that the formation of patterns on the coats of various mammals, such as leopard spots and zebra stripes, can be predicted and explained in terms of an RDS in which an activator induces melanocytes (cells that are responsible for the pigmentation of the epidermis) to produce melanin (pigment), and a repressor inhibits the production of that same melanin. We need not concern ourselves with the precise mathematical equations that underlie these systems. The important point, for present purposes is that, provided that Murray's models are roughly correct, a comparative explanation of coat pattern formation across organisms and species requires only a specification of basic dispositional properties of activators and inhibitors, the initial concentration of reactants together with the basic geometrical structure of the system, and the differential equations governing the diffusion of molecules. Biochemical properties, such as the structure of protein chains or the identity of genes involved, do not add anything essential to the explanation.[10] As we shall see, they only muddy the waters.

Meinhardt's (1998) study of seashells displays many similarities with Murray's work. As in the case of coat patterns, cellular interactions that govern shell coiling are modeled in terms of activator-inhibitor systems and rates of diffusion. The crucial difference is that coat patterning involves the same kind of cells (melanocytes) in most mammals. In contrast, the coiling of seashells reveals that the same family of equations can be applied

received in the literature, but which cannot be addressed in full in the present essay. In what follows, I generally assume that systems are limited, for example by the boundaries of an embryo or an organism. Some systems that count as "developmental systems", however, are not bounded this way. Whether the term "system" refers to systems of the former or the latter kind should be made clear by the context.

[9] In this section I borrow two examples discussed by Kitcher (1999) in an essay defending a multileveled picture of theorizing about development, and I elaborate on his conclusions on the role of mathematical models in molecular explanations.

[10] As a matter of fact, when Murray published the cited works, many biochemical features of melanocytes were still unknown.

to different types of molecules that instantiate activators and inhibitors in a wide array of cells, forming various patterns (e.g. patterns of pigmentation and patterns of relief) on the shell surface. In other words, while Murray shows that the same RDS explains variations of the same process in different organisms, Meinhardt shows that a single mathematical model explains similarities in patterns produced by various processes.

The important feature exhibited by both these examples is that the explanans is an RDS in which the precise identity and biochemical properties of the involved proteins are abstracted away. Molecular details, beyond basic dispositional properties of activators and inhibitors, are neither necessary nor relevant to the explanation. In order to understand why this is the case, it is important to focus on the respective explananda. In the case of Murray's models, the goal is to explain why the outcome of the pigmentation process is different across mammals (zebra stripes vs. leopard spots) in spite of the fact that they are formed through a similar process that involves the same kind of cells (melanocytes) and many of the same proteins (e.g. Tyrokinase). Given that these mammals employ the same cells and molecules in pigmenting their coats, it would be utterly surprising if differences in pattern could be explained by appealing to biochemical facts. And indeed they cannot. As Murray shows very clearly, the key difference between the coat patterns of zebras and leopards lies in the geometries of the bodies: the parameters of scale yield different equilibria for the diffusion of the same type of molecules. In short, with respect to differences in mammalian coat patterns, molecular details are largely irrelevant to the explanation. The difference maker is the geometry of the system through which the molecules diffuse. Now, surely biochemical processes constitute background conditions that are important from a causal perspective. For example, the response units must be appropriately "tuned" to morphogen signal in order for the process to yield the pattern predicted by the equations.[11] However, once these parameters are factored within the model—abstracting away from irrelevant differences across individuals and species—their specification is not required to predict the patterns, and they need not be included within the explanation.

In the case of seashells, molecular details are likewise irrelevant to the explanation, and for similar reasons. The explanandum of Meinhardt's Turing-style model is the similarity in coiling patterns, which can be described by the same family of equations despite the fact that the biochemical processes that generate them are very different from each other. Pigmentation patterns and patterns of relief (ridges and valleys) are clearly produced by different types of cells and proteins. Thus, the striking similarities in coiling emerge only once we abstract away from the precise identity of the morphogens (activators and repressors) that diffuse and interact with one another to generate the patterns. Once again, the difference-making factors that account for the relevant analogies across organisms and species are the spatial parameters that determine the geometry of the field over which the molecules diffuse.

An appeal to spatial organization is a classic antireductionist strategy. Mayr, Bernard,

[11] Fixing diffusion rates, relative concentrations, and thresholds of morphogens and response units is no trivial matter. The determination of these parameters, necessary for the model to effectively capture the underlying cytological mechanisms, requires various trade-offs and adjustments (Murray 1989).

and Weiss' defenses of emergent properties hinge precisely on the claim that the structure of the whole is not predictable from the properties of its parts alone (see Schaffner 1993, esp. ch. 9). Kitcher (1984) notes that geometrical properties of the system play an important role in biological explanations. Along similar lines, Kincaid (1990) poses some problems for reductionism related to biochemical diversity and multiple realizability by focusing on examples such as cell communication and signal sequences that code information and determine protein transport.[12] More recently, Laublicher and Wagner (2001) have questioned the possibility of describing spatiotemporal properties of a system at the molecular level. Others reply that spatiotemporal properties of molecules alone are sufficient for describing the system (Frost-Arnold 2004) or that the notion of positional information is in itself "almost completely nonexplanatory" (Rosenberg 2006).

Is my emphasis on mathematical models a mere reprise of an old debate? My claim is slightly different and, in an important sense, stronger. This is because, even granting that the language of molecular biology has the resources to describe the geometry of developmental systems (a point that many developmentalists would not concede),[13] we still lack a molecular explanation of intra-specific differences in pattern formation. The reason is that it is geometrical—not biochemical—properties that deliver the explanation of how different patterns are reliably generated and organized within clusters of cells.

To illustrate, imagine a complete description of all the molecules that constitute the epidermis of two mammals, a leopard and a zebra, during coat pattern formation, together with their distribution within the system, i.e. the position of every molecule in the embryo, at every instant. Assuming that we have sufficient computing power, by checking all the snapshots we can predict the patterns that will form on each coat due to the interactions between activators and repressors. But do these detailed descriptions explain the relevant differences in pattern? Do we have a general explanation of why the zebra forms stripes while the leopard forms spots? The answer is negative. Even assuming that the structural properties of the two systems are predictable and computable from the molecular description, biochemical features are too fine-grained to account for general variation in pattern in a counterfactual-supporting way. As a result, when we focus on molecular properties, we obtain an explanation that is not robust.[14] Now, surely, this is not to deny that coat patterns supervene on the distribution and biochemical structure of molecules. Changes in the initial distribution of molecules in a leopard are likely to alter the spots, but the resulting coat will still be spotted, not striped. Likewise,

[12]For a discussion of multiple-realizability in biology, see also (Rosenberg 1978) and (Sober 1999).

[13]The tenability of this assumption hinges on whether geometrical properties can be reduced to their molecular basis, a controversial issue that we shall set aside for the moment and to which I shall return in the final section of the essay.

[14]Following Woodward (2010), let us say that a causal relation is "robust" if it would continue to hold in a range of potential background circumstances. In other words, a robust relation would still hold even if the background circumstances were slightly different from the actual ones. To illustrate, Ann winning the lottery is unstable because, under slightly different circumstances, a different ticket would have been drawn. In contrast, the fact that someone wins the lottery is robust because, if Ann's ticket had not been extracted, another one would have been. My considerations concerning robustness of explanation are related to Wimsatt's (1976; 1994; 1997) discussions of aggregativity, complexity, and reductive explanation.

a change in the biochemistry of reactants is likely to affect the final outcome; for instance the coat might change color tone or the spots might not form due to an alteration of reaction rates. However, the difference between spots and stripes do not depend on these characteristics (that, to emphasize, constitute important background conditions). We can make the explanation of patterns counterfactual-supporting by focusing on the geometry—the general spatial parameters of the system through which the molecules diffuse—and the equations governing diffusion. When we do this, we can explain why under normal circumstances leopards develop spotted coats while zebras have stripes, as well as more general regularities that transcend inter-specific differences. For instance, Murray shows quite elegantly that while it is possible to have spotted animals with striped tails, there cannot be striped animals with spotted tails. In short, in these comparative explanations, the molecular details do not expose the crucial explanatory facts: the factors that make a difference toward the production of an effect are geometrical, not biochemical.[15] What is necessary is an account of how regular patterns emerge from an initial distribution of molecules in a confined space.

At this point, one might object that, even if we concede that the molecular details are not strictly speaking necessary, they are nevertheless not detrimental: if anything they make the explanation more complete. Yet this response overlooks the fact that providing irrelevant details often makes an explanation unnecessarily obscure and, more importantly, in many cases it will obliterate analogies and disanalogies between different processes.[16] Unnecessary details should not be included when multiple processes have a common explanation, or when a single process is realized in various ways, a point that is related to Woodward's (2010) discussion of perspicuity of causal effects and to the fact that causes should be proportional to their effects (Yablo 1992).

The examples of coat patterning and shell coiling discussed in this section show that, just as some biological events can be subsumed under genetic explanations which abstract away from important developmental and environmental factors, such as spatial parameters and diffusion processes, others are best explained when the biochemical details are abstracted away. In these cases, the explanatory work is fulfilled by mathematical models that deliver an account of the spatial parameters that determine the geometry of the field over which the molecules diffuse, generating stable patterns. Let us call *morphological* these explanations, which lie at the opposite side of the spectrum from genetic explanations. Neither genetic nor morphological explanations, however, constitute the paradigmatic explanatory model of current molecular-developmental biology. In the following section, I shall turn to a discussion of a third kind of molecular

[15] In a recent paper, Bogen argues that mathematical equations do not directly explain biological phenomena, but rather indicate "features of the phenomena of interest which mechanist explanations should account for." (Bogen 2005, 403) Note, however, that in the example he examines—Hodgkin and Huxley's classic essay on action potentials—the equations play no role in determining the spatial parameters of the system's components. For an independent defense of the explanatory role of mathematics, see (Strevens 2008, 329-31) and (Huneman 2010).

[16] Consider a related example from a different area of science. In quantum mechanics, the structural differences between photons and electrons are not just irrelevant in describing the results of the "double slit experiment". More importantly, they are misleading, since they potentially obscure the fact that the wave-particle duality applies to both light and matter.

explanation that combines genetic and molecular details with mathematical models to provide an accurate and robust account of the development of organisms.

4 Morphogenetic Explanation

The interplay of molecular details and mathematical structures is well illustrated by the standard textbook explanation of axis formation in *Drosophila*. The choice of this example is motivated by two considerations. First, the development of the fruit fly has been studied to a greater extent than any other biological organism and, as a result, we are in an ideal position to assess the depth of the presented explanation. Second, some philosophers employ the development of the early *Drosophila* to support reductionism (e.g. Rosenberg 1997, 2006), while others take it to vindicate antireductionist conclusions (e.g. Laublicher and Wagner 2001)). In the course of the following analysis, I shall attempt to capture the protean nature of this case study.

In the early stages of development, embryos specialize their cells, orienting them towards different fates. In dipterans like *Drosophila*, the differentiation of cells occurs through a process called *syncytial specification*. In short, cell division is not completed: instead of being embedded in individual membranes, nuclei are divided directly within the egg cytoplasm. The result is one large *oocyte* (immature egg cell), called a *syncytium*, containing many nuclei that develop into various types of cells depending on their position within the syncytium. This is possible thanks to the presence of morphogens that, once synthesized in specific sites, diffuse throughout the embryo and form concentration gradients that break the uniformity of the oocyte cytoplasm. The relative concentration of morphogens provides a signal that determines the fate of the nuclei according to their position relative to the source of the morphogen: the lower the morphogen concentration, the farther the nucleus is from the source.[17] The signals provided by various morphogen concentrations interact to form a fine-grained coordinate system that specifies the position of nuclei and selectively triggers the activation of the genes that govern the fate of the cell.[18]

[17]The relation between signals and position requires some clarification. From a causal perspective, the determination of the cell fate depends primarily on the signal it receives and secondarily, on its position within the embryo. This is because, if we vary the signal received by a nucleus without altering its position, the fate of the cell will change. In contrast, if we vary the position of the nucleus within the embryo without altering the signal, the cell will not develop differently. However, in normal (i.e. non-experimental) conditions, the diffusion of morphogens and the formation of gradients in the embryo are fixed: a change in signal never occurs without a corresponding change in position; the two parameters co-vary. Thus, I shall treat signals and position, indifferently, as primary causes of cellular specification.

[18]I should stress that this form of cellular differentiation cannot be generalized and applied to all insects, let alone all organisms. Dipterans (long germ band insects) are unusual in forming a syncytium. Invertebrates typically employ a form of *autonomous specification*, in which morphogenetic determinants are apportioned to the cells as the embryo divides. As a result, cell specification is independent of their position in the embryo, giving rise to a pattern of embryogenesis called *mosaic development*. In contrast, short germ band insects (e.g. grasshoppers), intermediate germ band insects (e.g. crickets), and most arthropods develop complete cells before specification begins and thus the fate of their cells is determined through a process called *conditional specification*, giving rise to a pattern of embryogenesis

A concrete example should make the process clearer. In order to account for the segmentation of the *Drosophila* larva, two processes need to be explained: the specification of concentration gradients and the differentiation of cells along the axes. Let us consider them in turn.[19] The localized production of morphogenetic signals that specify positional information occurs before the moment of fertilization, at a stage called *oogenesis* in which the oocyte is formed. The fruit fly oocyte develops within a cyst of 16 germline cells, surrounded by an epithelium (a sheet or tube) or somatic follicle cells, which secrete the eggshell. Each 16-cell cyst derives from a single cell, the *cytoblast*, through four division cycles (with incomplete cytokinesis). One of the cells, located at the future posterior end of the embryo, becomes the oocyte precursor, while the other 15 cells become nurse cells, which supply essential components to the oocyte. Initially, the nurse cells are non-differentiated, in the sense that each of them can potentially acquire the same fate. The first task of the oocyte precursor is thus to differentiate the instructions for the development of these nurse cells.

The preliminary organization of the cytoskeleton is determined by two distinct signals governed by the same gene, *gurken*. The gurken message is synthesized within the nurse cells, but is transported inside the oocyte nucleus through cytoplasmic channels, microtubules that connect nurse cells to each other and to the oocyte, allowing cytoplasmic material to pass from one cell to the other. Inside the nucleus (more specifically, between the nucleus and the cell membrane) this message is translated into the Gurken protein. Since, as said, at this time the oocyte nucleus is located at the posterior end of the follicle, the nurse cells located at that position receive the gurken signal (through a receptor coded by the *torpedo* gene) and, as a consequence, undergo a process called "posteriorization". In turn, these nurse cells, which are provided with posterior identity, send a feedback signal to the oocyte that reorients its cytoskeleton, establishing a preliminary anteroposterior polarity in the oocyte. While the cytoskeleton is rearranging its structure, cytoplasmic components—which include maternal messengers such as bicoid and nanos mRNAs that, as we shall see, play a central role in the segmentation process—are carried by motor proteins along the microtubules from the nurse cells into the oocyte, at specific sites. At the end of oogenesis, after emptying their contents into the oocyte, the nurse cells die. In short, the localized production of morphogens and the resulting formation of concentration gradients is established by gene products that govern interactions between the syncytium and follicle cells altering the oocyte's cytoskeleton and organizing the distribution of maternal mRNAs in the early embryo.

In the second process, the specification of syncytial cells depends on the interaction between morphogens and nuclei, which selectively regulates gene expression, according to the position of the nucleus along the axis. The differentiation of the *Drosophila* larva along the anteroposterior axis is determined by the relative concentration of two morphogens: Bicoid and Nanos.[20] During the initial organization process described

called *regulative development*, which depends on interactions between neighboring cells, as opposed to nuclei-morphogens interactions.

[19] In what follows, we shall abstract from many complex details that are largely irrelevant for present purposes. A comprehensive description can be found in Davidson (2005) and Gilbert (2006) .

[20] The determination of the dorsal-ventral axis is, likewise, established by the diffusion of morphogens

above, bicoid mRNA is transported to the anterior portion of the embryo, where the Bicoid protein is synthesized and diffused. As a result, the concentration of Bicoid is higher in the anterior part and gradually declines the further along we move towards the posterior tip. Precisely the opposite is true of nanos mRNA, which is transported to and synthesized in the posterior regions. Consequently, the concentration of Nanos protein is higher in the posterior regions and gradually reduces the closer we get to the anterior portions. Oversimplifying a bit, Bicoid and Nanos are, respectively, an activator and a repressor. Bicoid induces the action of a gene, *hunchback*, which triggers the development of the anterior segments of the embryo. In contrast, the maternal-effect gene *nanos* encodes a protein, Nanos, whose main function is to bind to sequences in the trailer region ("Nanos-response elements") of the hunchback mRNA and prevent its translation into protein.[21] As they divide, nuclei will be found in different regions of the syncytium. In nuclei located in the anterior areas of the embryo, where the concentration of Bicoid is high and the concentration of Nanos is low, the Hunchback protein activates the genes necessary for developing the head. Conversely, in posterior regions with little or no Bicoid but plenty of Nanos, Nanos inhibits the translation of the Hunchback protein, generating the abdominal structures. Finally, nuclei found in the central regions, where the Bicoid : Nanos ratio approaches, 1 : 1, the complex interactions of these morphogens with hunchback mRNA activates the genes that produce the thorax. (See Figure 1 for a graphic illustration.) This account of cellular differentiation is known as the "French Flag model" (Wolpert 1969), since the three specified regions (anterior, central, and posterior) are reminiscent of the stripes of a French flag.

The explanation of axis formation in *Drosophila* bears both important analogies and significant differences with genetic and morphological explanations discussed in the previous sections. Compare first axis formation with coat patterning and shell coiling. As in the case of Murray and Meinhardt's work, rates of diffusion, geometrical properties of the system, and dispositional properties of reactants (activators and repressors) play a fundamental role in the explanation of segment specification, as reflected by the analogies in the corresponding RDS. However, while a relatively abstract mathematical model is sufficient to explain differences in coat pattern formation across mammals and similarities in the coiling of shells, the explanation of axis formation also requires a specification of molecular details, because the identities and structural properties of genes, RNAs, and molecules (bicoid, nanos, hunchback, gurken, etc.) make a difference to the outcome of the diffusion process.

Next, compare the explanation of *Drosophila* segmentation with genetic explanations. In both types of explanation, molecular properties are important difference makers. As said, the structure of the *hemoglobin* gene determines the disposition to experience crises at low oxygen levels. Likewise, the differentiation of fruit fly cells is governed by a chemical signal that selectively activates genes depending of the nucleus' position in the

throughout the embryo, but is more complicated from a molecular perspective. Given that these complexities are not essential to the philosophical argument, in what follows, I shall focus solely on the formation of the anteroposterior axis.

[21] Hence, Nanos is a repressor not at the transcriptional, but at the translational level.

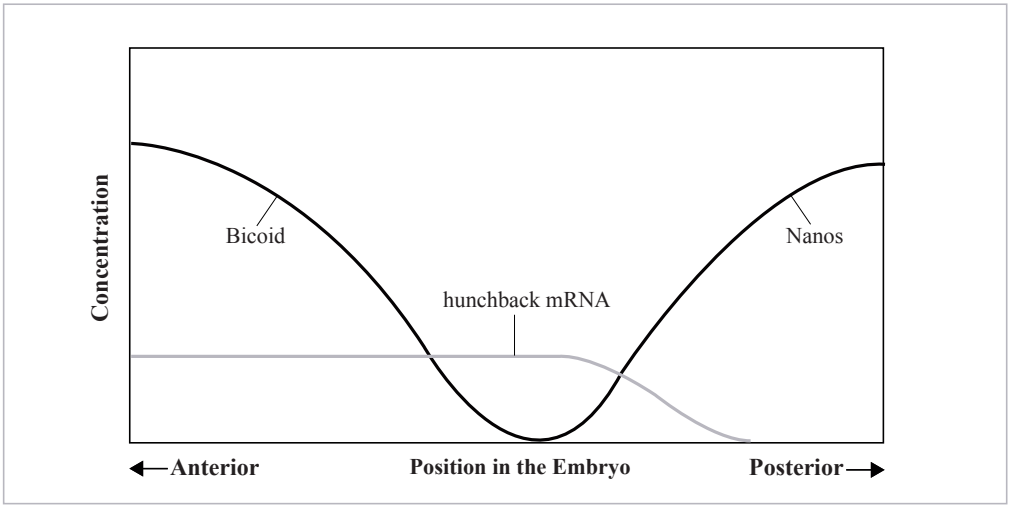

Figure 1: Bicoid, Nanos, and hunchback gradients in the *Drosophila* embryo.

embryo. However, while the structure of the *hemoglobin* gene is sufficient to determine whether or not the erythrocytes will sickle in an organism (against a background of "normal" physiological conditions), here the variable parameters that control the fate of each nucleus include both the interactions of genes and gene products and the spatial organization of the embryo that governs the concentration of morphogens in the oocyte. In short, both molecular details and geometrical properties of the system are necessary to explain the segmentation of *Drosophila*, but neither is, by itself, sufficient. To refer to explanations of this kind, where difference makers occur both at the molecular and the morphological level, I introduce the term *morphogenetic explanation.*

The expression "morphogenetic explanation" alludes to the old concept of the *morphogenetic field*: a group of cells responding to discrete localized biochemical signals that govern the development of morphological structures. Once a prominent postulate of embryology, morphogenetic fields were later set aside with the development of molecular genetics. The reason is that the discovery of the structure and causal role of genes led many scientists to believe that all developmental processes could be explained in terms of genetic or cytological mechanisms. Progress in the study of gene regulation and expression, however, has made it clear that this is not the case. In particular, the discovery that many developmental processes are regulated by signals that diffuse throughout the embryo, interact with cells, and assign them a position within coordinate systems revived interest in patterns formed by spatially coordinated and temporally synchronized patterns of cells. Interestingly, these clusters often coincide with the embryonic fields identified and studied in the first part of the 20^{th} century (e.g. the limb field, the eye field, and the otic field). Seventy years after the golden age of embryology, morphogenetic fields have reemerged as a valuable scientific concept, albeit with a remarkable difference. Whereas the original embryonic fields were defined anatomically or cytoplasmically, cel-

lular interactions are now known to be regulated by gene action. In other words, the old field concept was completely independent of genes. In contrast, the epithelial units of current developmental biology are governed and determined by sequences of nucleotides and their products, which constitute a regulative and responsive cytological apparatus involving complex forms of redundant controls and negative and positive feedback loops that modulate the response of the received signals. The anatomically-defined fields of Spemann, Needham, and Weiss have thus been "molecularized", i.e. transformed into a network of cells whose time evolution is governed by the partial differential equations of diffusion processes regulating gene networks (Gilbert et al. 1996). In a sense, this transformation is just a matter of recovering an older concept and attuning it with contemporary molecular findings. Nonetheless, as Wolpert and Nüsslein-Volhardt understood long ago, these redescriptions play an important explanatory role in scientific practice.

5 Reframing reductionism

Let us take stock. I identified three paradigms of molecular explanation: genetic, morphological, and morphogenetic. Genetic explanations, where genes and gene products do all the explanatory work, are possible when the difference-maker(s) occur at the biochemical level, broadly construed, so as to include functional and dispositional properties of nucleotides and proteins. As noted in the discussion of sickle-cell anemia and Huntington's disease, the genetic explanans does not necessarily—or even commonly—capture all the causes and effects of the disease. However, when biochemical difference-makers determine the occurrence of an event against a set of fixed background conditions, we can provide a relatively straightforward genetic explanation that abstracts away from further causes and effects. In the second paradigm, morphological explanation, the difference-makers that explain a phenomenon occur at the level of the geometrical structure of the system and its patterns of variation. Mathematical models that largely abstract from molecular details are especially useful when comparing processes across organisms and species, because they provide an effective means to explain similarities in the outcome of different molecular processes and variety in patterns that are generated by analogous biochemical apparatuses. Finally, when the parameters that make a difference to the outcome of a process occur both at the biochemical and the geometrical level, we have morphogenetic explanations, where genes and molecules are brought together in a morphogenetic field so as to account for the formation of biological traits. This third paradigm of explanation is the most widely adopted in current molecular-developmental biology, where it is applicable to a broad range of explananda. However, the importance of morphogenetic explanations should not obscure the significance of the two other paradigms, which play an important role in areas of the life sciences and clinical research such as genetics, genomics, evolutionary-developmental biology, and systems biology. The boundaries, limits and characteristic features of these paradigms, as well as

their relations,[22] deserve to be investigated more thoroughly and systematically than has been done here and, perhaps, further varieties of molecular explanation can be isolated. The explicit aim of the above discussion was not to provide an exhaustive list but, much more modestly, to emphasize important distinctions between models of explanation that should not be obliterated.

With all of this in mind, we can now return to the two strands of reductionism mentioned at the outset. Despite their superficial perspicuity, substantial issues in both theses are obscured by ambiguities of scope and terminology. Consider, first, genetic reductionism, the claim that the genetic program alone is able to explain the regularities of development. What is, precisely, the "genetic program"? Antireductionists often adopt—more or less explicitly—a restrictive definition that makes the genetic program coextensive with sequences of nucleotides. If we adopt this narrow definition, then the answer to the reductionist challenge is clearly negative: DNA alone cannot explain development. But is this really a victory for antireductionism? Does any biologist worth her salt believe that DNA is the complete, all-determining program for the construction of an organism, or that genes are the only important developmental resource? In contrast, reductionists tend to attribute a much broader scope to the genetic program and include in its domain RNAs, proteins, and other macromolecules (Rosenberg 2006). If we accept this extended genotype, genetic reductionism becomes a much more plausible thesis.[23] However, once we endow sequences of nucleotides with epigenetic processes, cytoplasmic molecules, and other gears of the cellular machinery, genetic reductionism turns out to be coextensive with molecular reductionism, the thesis that every biological event can be explained in terms of biochemical facts alone. In short, the plausibility of genetic reductionism and its autonomy from its molecular counterpart are jeopardized by ambiguity: the thesis teeters on a false claim or, alternatively, tends to overlap with molecular reductionism, depending on how rich we allow the genetic program to be.

The crucial issue for settling the debate thus becomes the tenability of molecular reductionism, which hinges on the range of phenomena that can be described and explained by molecular biology in purely biochemical terms. The problem is that the expressions "molecular biology" and "purely biochemical language" are, in and of themselves, dangerously ambiguous; precise, uncontroversial definitions have seldom (if ever) been articulated. As a result, even in the case of genetic explanation—which constitutes the form of explanation closest to the molecular-reductionist framework—the claim that only pure biochemical facts figure in the explanans can be questioned. Genetic ex-

[22]Indeed, explanations occurring at different levels can be mutually relevant and can be jointly employed to narrow the gaps in our understanding of development. While a fuller account of the relation between types of molecular explanation must be left for another occasion, these interactive modes of investigation can be fruitfully described in terms of "exploration, iterativity, and kludging" (O'Malley 2011).

[23]This applies only to modest reductionist frameworks that place no restrictions on the form of the reduction. Rosenberg (1997) advocates a more ambitious project that integrates into reductionism a "simplicity requirement" according to which development must be explained by a small number of genes and molecules. Given that such a desideratum can hardly be fulfilled (Frost-Arnold 2004; Franklin-Hall 2008), Rosenberg (2006) subsequently articulated a less radical version of reductionism that drops simplicity.

planations in current biological practice constantly appeal to dispositional properties, such as flexibility or elasticity, and terms like "transcription factor" that involve an implicit appeal to function, which would be extremely hard, if not impossible, to specify in structural terms. And once we move away from genetic explanations and focus on morphological and morphogenetic models, the need for enriching a strictly biochemical language becomes even more evident. Even a cursory glance at current molecular research reveals that structural properties of genes and gene products, functional and dispositional features of reactants, spatial and geometrical parameters of systems, and diffusion processes all play a central role in developmental explanations. Thus, unless the reductionist is willing to hedge her bets and argue that, in principle, we can dispose of this whole explanatory apparatus,[24] the standard reductionist move is to acknowledge the explanatory importance of all this extra stuff, but also to contend that it all part of molecular biology and its language.[25] In turn, antireductionists, with the exception, perhaps, of radical holists, accept the primacy of this explanatory apparatus, but contend that it transcends the molecular realm since the constant appeal to teleological concepts renders the molecular language not "fully molecular" (Culp and Kitcher 1989; Kincaid 1990; Franklin-Hall 2008).

So, who wins, the reductionist or the antireductionist? Some readers might view the paradigms of molecular explanation isolated above as a rephrasing of the reductionist framework. Granted, the explicit acknowledgment of the importance of functional-dispositional concepts and positional information makes the reduction of developmental processes to a molecular basis less brutal, but it is still reduction after all. Others might interpret my emphasis on the interaction of biochemical details with spatial properties of the system as providing (another!) defense of antireductionism, albeit in a softer form. In a sense, both parties are right. The three paradigms of molecular explanation isolated here are inconsistent with both radical reductionism—the thesis that everything can be explained in terms of biochemical properties and fundamental laws—and, radical holism, according to which complete developmental explanations must focus on macro-systems involving organisms embedded in their environments for entire life-cycles. Once we set these extreme views aside, however, it becomes apparent that modest reductionism substantially overlaps with sophisticated forms of antireductionism.[26] Thus, if there is substantial agreement among both parties concerning the range of explananda and the required explanantia, then perhaps the dispute is less substantive and more verbal than many disputants are likely to admit. Whether the paradigms of molecular explanation isolated here are better classified as falling under reductionism or antireductionism is

[24]Perhaps philosophers of science who believe that all scientific explanations can be provided at the level of fundamental physics would sympathize with this view. To the best of my knowledge, very few (if any) students of biology, however, would be willing to endorse and defend such a radical form of reductionism, which runs contrary to the theory and practice of current molecular biology.

[25]This more modest approach seems to be the path followed by most philosophers of biology with reductionist inclinations (e.g. Rosenberg 2006; Schaffner 2006).

[26]The modest (anti)reductionism articulated here bears significant analogies to Wimsatt's view of reductionism and holism as complementary perspectives (see the essays collected in Wimsatt 2007), *explanatory extensions* (Kitcher 1984), *interfield theory* (Darden and Maull 1977; Maull 1977), and *partial reductions* (Schaffner 2006).

ultimately an issue that depends more on terminological convention than metaphysical or methodological distinctions.

Should we conclude, then, that the whole reductionist-antireductionist debate ought to be abandoned? This might be too strong. Perhaps there are other ways of reconstructing the dispute to make it more substantive by focusing on issues other than the extent of the explanatory basis such as, for example, *causality*.[27] The above discussion suggests that one way to reconstruct the opposition is to concentrate on *difference-making*, a concept that is central to many biological explanations and deserves more attention that has been accorded so far. Waters (2007) is right to point out that, in many biological contexts, genes are the causes that make an (actual) difference. As a result, there is an important subclass of causal explanations in biology—those that we identified here as genetic explanations—where genes play a more prominent causal role than other processes and background conditions. However, as shown in this essay, in other biological contexts the difference-making role is fulfilled by morphological properties (morphological explanations) or by a combination of molecular-genetic and geometrical properties (morphogenetic explanations). In this respect, the reductionist might claim that all biological difference-makers are reducible to the causal properties of genes and molecules. This would involve, for example, showing that geometrical and morphological features of developmental systems inherit their causal powers from their fundamental constituents. The antireductionist, in turn, could respond that causal relations occurring at a higher-level cannot always be reduced to a lower level, and defend some form of "downward causation", according to which developmental systems (or other supra-molecular units) are causally efficacious in ways that cannot be given a strictly molecular analysis.

These considerations raise some deep and substantial philosophical issues (What is a cause? What assigns causes to different levels? What is the relation between causation and explanation?) that cannot be addressed in full in the present essay. The moral that we ought to draw from the discussion above is that "reductionism" and "antireductionism" are not the right categories for classifying explanation because these frameworks, as they are currently intended, are too coarse-grained and ambiguous. Presenting the dispute as hinging on the claim that there is an explanation of every biological event in a purely molecular language obscures subtle but significant distinctions among the varieties of molecular explanation.

[27] Some passages in the literature suggest that this is what many philosophers have in mind: "What reductionism denies is that there are distinct causal properties of [items such as cells] that are not open to identification in macromolecular terms." (Rosenberg 2006, 84). (See also Kincaid 1990; Sober 1999; Schaffner 2006).

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