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How Molecular is Molecular Developmental Biology? A Reply to Alex Rosenberg's Reductionism Redux: Computing the Embryo

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Abstract. This paper argues in defense of the anti-reductionist consensus in the philosophy of biology. More specifically, it takes issues with Alex Rosenberg's recent challenge of this position. We argue that the results of modern developmental genetics rather than eliminating the need for functional kinds in explanations of development actually reinforce their importance.

Key words: functional kinds, molecular developmental biology, physicalist antireductionism

Introduction

According to Alex Rosenberg (1997), physicalist anti-reductionism as the consensus view among philosophers of biology is threatened by the program, the promise, and the results of molecular developmental biology. Should this threat be real, philosophers of biology would face far-reaching consequences.

Rosenberg characterizes the consensus of physicalist anti-reductionism by the following two principles:

(1) The principle of autonomous reality: The levels, units, kinds identified in functional biology are real and irreducible because they reflect the existence of objective explanatory generalizations that are autonomous from those of molecular biology.
(2) The principle of explanatory primacy: At least sometimes processes at the functional level provide the best explanation for processes at the molecular level (Rosenberg 1997: 446).

In Rosenberg's view, new discoveries such as the homeobox system or the *Pax-6* pathway challenge the received model of explanation in developmental biology. Traditionally, philosophers of biology have taken the phenomena of developmental biology to support the consensus view of physicalist anti-reductionism. Now, Rosenberg argues that explanation within the program of physicalist anti-reductionism implies a commitment to "downward causation" of the form "that functional states of biological systems cause molecular processes, and do not do so simply owing to their molecular composition and properties" (p. 464). For biological kinds to be real and irreducible according to Principle 1, they must have causal powers of their own or a causal agency that is distinct from the causal powers of molecular kinds. In other words, biological kinds must have emergent properties and, due to these emergent properties, must follow their own set of causal laws that cannot be found at the level of their molecular components. And, according to Principle 2, functional (or biological as opposed to molecular) properties must also provide the best explanation for the specific molecular properties of a system and must do so not as matter of convenience because they are heuristically easier to trace but as matter of principle because they reflect the causal structure of the world. Implicit in both these claims is a commitment to the idea that true explanation has to follow the direction of causality. In Rosenberg's opinion, the physicalism of molecular developmental biology as represented by the statement that "all biological properties are realized by combinations – sometimes vastly complex combinations – of molecular properties" (p. 464) is at odds with both principles of anti-reductionism. In his interpretation the results of molecular developmental biology support this physicalist ontology in that even the most complex biological objects such as the eye can be explained in strictly molecular terms. If so, the consensus view of physicalist anti-reductionism would be in trouble. The only way it could still be applied to molecular developmental biology would be by greatly reducing its philosophical force. According to Rosenberg such a position "requires two controversial 'moves' in the philosophy of science" (p. 466). First, causation as a relation among states, events and processes would have to be accepted as conceptually dependent on explanation; and second, explanation itself would have to be seen as heavily pragmatic. In Rosenberg's view, physicalist anti-reductionism would no longer be a philosophical position that represents the ontology of nature but rather one that reflects the particular interest of a group of scientists. Thus, in Rosenberg's view, the standard account of physicalist anti-reductionism can only be upheld if it is interpreted as a thesis about the interests of biologists rather than a thesis about the ontology of biology. In other words, physicalist anti-reductionists would have to accept that their position, at least with respect to molecular developmental biology, could only be salvaged if they are willing to put the pragmatic before the real. But this would mean that they commit a deadly sin. Viewing explanation as prior to causation would in fact be tantamount to renouncing membership among the physicalists and to rub elbows with the enemy – indeed even to invite the “unspeakable one” in the form of social constructivism. The stakes are high. If we want to keep our comfortable consensus position as physicalist anti-reductionists and still maintain our scientific integrity, we must meet Rosenberg’s objections and face the challenge of molecular developmental biology.

But is Rosenberg right about molecular developmental biology? We do not think so and here we intend to question his characterization of molecular developmental biology. We will argue that the agenda of developmental biology, molecular or otherwise, is not adequately represented by Rosenberg’s interpretation of a handful of quotes and results. To that end we will present recent results in developmental biology that contradict Rosenberg’s reductionist manifesto. We will argue that rather than eliminating the role of functional kinds in explanations within developmental biology these results actually emphasize their importance. One of our central arguments will be that the relevant context or reference system for all explanations in developmental biology is either the cell or the spatial, regulatory, and dynamical properties of developing systems, rather than the physico-chemical properties of the involved molecules (Laubichler and Wagner 2000; Wagner and Laubichler 2000). Furthermore we take issue with Rosenberg’s use of the term “molecular” and the ways in which he employs “molecular” in order to justify the reduction of developmental processes to the action of molecules. What is interesting about developmental modules, such as the *hedgehog* or *engrailed* pathways is that they are repeatedly deployed in different functional contexts. For example, the *engrailed* pathway is involved in establishing the anterior-posterior compartment boundary in *Drosophila* and butterfly wings but is also employed in establishing the eye-spot organizer in butterfly wings (Keys et al. 1999; Carroll et al. 2000). Similar molecular interactions, such as the binding of specific transcription factors to similar stretches of DNA thus lead to quite different phenotypic results. Any explanatory generalization that can account why particular modules and regulatory pathways are employed in the development of certain kinds of phenotypic patterns will have to include the systemic properties (spatial, regulatory, dynamical) of higher level (cellular, organismal) biological entities as well as their evolutionary history. It is bad science and questionable ideology to preclude *a priori*, as Rosenberg does, the possibility of explanatory generalizations in developmental biology, even more so when the empirical evidence clearly suggests otherwise. As a consequence, we will argue that molecular developmental biology does not threaten physicalist anti-reductionism.

What's in a name?

The careful reader of Rosenberg's paper will be puzzled by a remarkable rhetorical shift. Rosenberg starts out by identifying molecular developmental biology as the problem for physicalist anti-reductionism. *Molecular developmental biology* is introduced as the research program that will provide a molecular account of developmental processes. But as soon as Rosenberg describes the work of his two star witnesses, Lewis Wolpert and Walter Gehring, he describes their work as *developmental molecular biology* and continues to do so through most of the paper. However, in his conclusion it is again molecular developmental biology whose results challenge physicalist anti-reductionism. What are we to make of these subtle changes in the way Rosenberg refers to modern developmental biology? Are they mere stylistic alterations or do they signify some underlying conceptual differences?

Rosenberg is too good a philosopher to miss the changes in meaning implicit in these two terms. Basically, the subject of molecular developmental biology is development and it is studied at the molecular level. This means that while techniques of molecular biology are employed, the questions that are asked are defined within the context of developmental biology. In the case of developmental molecular biology the situation is reversed. Here the focus is on molecular biology, that is the study of biologically interesting molecules and their properties, and it is only secondarily applied to questions of development. In other words, as applied to the problem of development, the two different disciplines ask radically different questions. Molecular developmental biology is concerned with general principles of development and the question of their molecular realization, whereas developmental molecular biology studies the action of single molecules in a developmental context. Whereas the goal of one discipline is to find general principles that are characteristic for a class of phenomena, the other aims at specificity or the detailed analysis of molecular interactions.

Rosenberg conflates the agenda of molecular developmental biology with developmental molecular biology when he states that the goal of the former is to trace the "developmental pathway from maternal messenger RNA all the way to the adult fly in one batch of fertilized eggs" (p. 462). The conflation is enhanced when he identifies the aim of developmental molecular biology as finding "an existence proof for one or a small number of purely molecular pathways to a biological system" (p. 462) rather than establishing generalizations or laws of its own. For Rosenberg, developmental molecular biology merely applies “other nomothetic sciences to tracing out singular causal chains” (p. 462). He denies *a priori* that such generalizations can be made and also describe causally relevant processes in development. For him, explanation in developmental molecular biology therefore “places literal truth ahead of idealized models that unify” (p. 463). The discovery of one specific molecular causal pathway is allegedly all that matters. Inasmuch as explanation follows causation, the discovery of one such causal pathway would then imply that the problem of development has found an explanation, at least for the one species analyzed. And, by analogy, that way of proceeding also opens up the possibility that other biological systems can be described as purely chemical processes as well.

Rosenberg does not leave any room for interpretation when he states that “in developmental biology at least there are no explanatory generalizations” (p. 447) at higher levels of organizations and that “at most the non-molecular generalizations set out tasks for developmental explanation, and never provide explanations” (p. 448). This position does not allow for autonomous biological kinds to exist within developmental biology because “even if biology’s functional kinds are perfectly genuine, they lack any very satisfying or deep autonomous explanatory role in developmental biology” (p. 448). Given these assumptions and the perceived success of the program of developmental molecular biology Rosenberg concludes that “in developmental biology at least, physicalist anti-reductionism is little different from the emergentist dualism between the living and the non-living that embryology cast off even before it was invaded by molecular methods” (p. 448). So now it is out in the open: to be anything but a developmental molecular biologist is to be vitalist, holist, or some other kind of obscurantist.

How to conceptualize development, or the question of perspective

We find Rosenberg’s representation of developmental biology as developmental molecular biology highly problematic and misleading. While we welcome that philosophers participate in analyzing the conceptual structure of scientific theories and their philosophical implications, as biologists we have to insist that scientific problems should be represented in their full complexity. Here we will offer an alternative perspective on molecular developmental biology and investigate its implications for Rosenberg’s argument.

The problem of development is basically one of spatial differentiation and growth. Thus the fundamental questions of developmental biology are: (i) through what pathways does an apparently rather homogeneous cell develop into a fully differentiated organism, (ii) what are the mechanisms that guide this ‘unfolding’ in three dimensions, (iii) what are the relevant biological objects that are causally involved in these developmental processes, and (iv) what is the relation between genetic information and the phenotypic complexity that is the end-product of developmental processes?

As suggested above, Rosenberg emphasizes the role of molecules as causal agents in developmental processes. He follows Wolpert (1994) in asking whether "given a total description of the fertilized egg – the total DNA sequence and the location of all proteins and RNA – could one predict how the embryo will develop (cited in Rosenberg 1997: 449)?" In answering Rosenberg's challenge we thus have to determine the role of molecules in developmental processes. Development is essentially the establishment and differentiation of cellular and anatomical structures. And while it is true that these structures are fundamentally composed of molecules, we fail to see how this quite obvious observation leads Rosenberg to the conclusion that physicalism, the principle "that all biological properties are realized by combinations – sometimes vastly complex combinations – of molecular properties" (p. 464) is opposed to the possibility that functionally characterized biological objects can have an autonomous reality (his Principle 1 of physicalist anti-reductionism). The problem is that Rosenberg fails to acknowledge that the vastly complex combinations of molecules that make up biological objects are *organized* and *structured* and that these organizations of molecules, i.e. biological characters (sensu Wagner and Laubichler 2000), are themselves often more stable than any of their components. In addition, the developmental processes that lead to these biological objects take place in well-defined developing systems that also have a three-dimensional structure and are context-sensitive in space and time.

The importance of the spatial dimension of developing systems has long been recognized. During the heyday of embryology in the early 1900s the idea of morphogenetic fields within the embryo was ubiquitous (e.g. Boveri 1910; Gurwitsch 1922; Spemann 1921; Weiss 1939; see also Gilbert et al. 1996; Gottlieb 1992 and Haraway 1976 for a historical treatment of this issue). Morphogenetic fields designated spatially bound areas of embryological specificity. It has been shown in many experiments, in particular transplantation experiments, that these fields regulated the activity of cells within their boundaries and specified their eventual fate. As Gilbert et al. (1996) point out, the idea of a morphogenetic field was actually never disproved, but merely eclipsed by a genetic approach to development. In its interpretation as a gradient-field (Huxley and de Beer 1934) the concept of the morphogenetic field also served as the intellectual precedent for Wolpert's (1969) idea of diffusable morphogens. Rosenberg interprets Wolpert's model of diffusable morphogens as the first step towards a purely molecular interpretation of development. Encouraged by the discovery of diffusable morphogens, i.e. molecules, such as the homeobox transcription factors, whose gradients trigger the differential expression of structural genes and thus morphological differentiation, Rosenberg then announces that development can now be explained in strictly molecular terms. Consequently, no functional kinds other than molecules are part of explanations of development and the principle of autonomous reality (principle 1 of physicalist anti-reductionism) is violated.

This interpretation of the role of developmental genes is by no means universal (e.g. Oster et al. 1988; Tautz 1992; Newman and Comper 1990). Again, the question is not whether genes and molecules are important in development, but whether it is possible to assign well-defined functions to them in the developmental process without taking the specific functional context of their expression into account. Four issues need to be considered here: genetic redundancy (Tautz 1992), the causal homeostais of morphogenetic modules (Raff 1996), phenotypic plasticity, and interspecific variation of development. Below we want to discuss an example with which we are particularly familiar to illustrate these points.

A molecular or genetic explanation of a developmental phenomenon, say limb development, only makes sense if there is a strong causal relationship between particular molecular events and the phenomenon to be explained. Such a strong relation is necessary in order to assign a specific causal role to a gene or a molecule. Very often such a connection does indeed exist; otherwise developmental genetics would not be possible at all, but there are important exceptions, collectively called “genetic redundancy”. One speaks of genetic redundancy if the deletion of a gene that is clearly involved in a developmental process leading to a specific phenotype has no or only very minor effects on this character. Apparently other genes can compensate for the loss of function. For instance, the gene *Hoxa-11* is involved in the development of lower limb elements in all tetrapods investigated so far (Haack and Gruss 1993; Nelson et al. 1996; Yokouchi et al. 1991). A knockout of this gene in the mouse, however, only leads to very subtle effects on lower limb development. The reason is that there is genetic redundancy with the gene *Hoxd-11*. We know this because a double knockout mutant of *Hoxa-11* and *Hoxd-11* leads to the complete loss of the lower arm (but not the loss of the lower leg!) (Davis et al. 1995).

Clearly genes are important to development. Nobody denies this. The question we are concerned with here is whether it is meaningful or even possible to assign a particular function to a gene (such as *Hoxa-11*) without referring to the larger molecular, cellular, and organismal context within which these genes are expressed. We do not yet know the definitive answer to this question, but the current body of evidence is not encouraging. So what would an alternative explanation for our example look like? Currently the most likely account will have to include the properties of the mesenchymal cells involved in the skeletogenesis of the limb bud. In particular, we need to recognize that this class of mesenchymal cells have a tendency to aggregate and form condensations. This behavioral propensity of cells can be found in all limb buds and plays an important role in any explanation of limb formation. Again, there are of course molecules that realize these properties, but the emergent collective behavior of these cells and its invariance among all cases of limb buds is what really leads us to understand the process. What is the role of the *Hox* genes in this account? Well, they are important in tuning the cell surface properties of the mesenchymal cells, which leads to predictable effects on pattern formation (Yokouchi et al. 1995; Newman 1996). However, it is crucial to note that in this case assigning a causal role to a gene requires the definition of the cellular and systemic context (limb bud, surface properties of cells etc.) in which they are active. Ignoring the importance of the organizational context of gene action in actually defining the causal role of any molecule will not lead to any meaningful understanding of the biological phenomenon we seek to understand.

The example discussed above points to a more general problem in biological research: the decomposition problem. Organisms are organized wholes that do not have *a priori* defined “parts.” Any identification of causally relevant parts (such as cells or molecules) is an active, informed decision by the researcher that ideally reflects the context-dependent selection of objects by the biological processes themselves. Hence, we have to justify in every instance whether a particular object, such as a specific molecule or gene, actually performs a useful role in a mechanistic explanation. In many instances molecules are the relevant entities, for instance in explanations of cellular metabolism, but to *a priori* assume that they always have to be the relevant level of description is to adopt a metaphysical position contrary to proper scientific conduct (see e.g. chapter 11 in Brandon 1996). Two examples may illustrate the point.

The development of the functional properties of the visual cortex in cats and primates depends on early postnatal stimulation through the visual input from the eyes. For instance, if one prevents a cat from seeing horizontal stripes after birth, the visual cortex fails to develop edge detectors for that orientation. This deficiency is a result of the interaction rules which cortical cells follow in developing and stabilizing synaptic connections. Certainly there are molecules that realize these processes of synaptic stabilization, but is this the most relevant level of description? We think not, since the anatomical organization and the cellular response to functional stimulation provide a much richer context for understanding what is happening in the cat’s brain. The reason is that the differences in the ways the cortex and the optic tectum react to external stimulation are found more in their contrasting cellular organization and cellular reaction norms than in any particular molecule that differs between these two brain regions.

The other example is a classical experiment from the developmental evolution literature (Alberch and Gale 1983, 1985). It explains the differences in the pattern of digit reduction in the limbs of newts and frogs. Newts and salamanders always lose their digits 5 and 4 first when they reduce their digit number in evolution, while frogs first lose finger 1 followed by 5 then digit 2. Alberch and Gale have shown that exactly the same pattern is produced by simply reducing the number of cells prior to skeletogenesis. The reason for the different reduction patterns between newts and frogs is the sequence of events in skeletogenesis. In frogs the last two digits that are formed are the digits 5 and 1, whereas in newts these digits are 4 and 5. Hence, any perturbation or mutation which has the effect of reducing the number of cells in a critical time during development, will have these specific effects. The level of organization that accounts for the macroscopic pattern of digit reduction is thus the level of the limb mesenchyme pattern formation. The phenotypic effect of any particular molecular change is determined by the clade-specific sequence of events at the limb bud level. We submit that this is one example where explanation does derive from the supra-cellular level of organization, because a multitude of molecular events (all those influencing cell number) will have the same effect that is ultimately determined by the sequence of condensations events. Thus an explanation of why the number of cells were reduced will not contribute anything interesting to the explanation of the particular outcome (the species specific pattern of digit reduction.)

These examples show that the fact that all biological objects are made of molecules does not imply that molecules are the most informative level of analysis. Emergent properties of supracellular entities can be more informative and thus have more explanatory force than molecules. One may try to dismiss this argument by saying that this is just a matter of heuristic convenience rather than a deep ontological statement. We, however, want to remark that this distinction may be flawed. What does it mean to uphold an ontological position that can not be transformed into actual scientific practice? In our opinion, the examples show that it might be futile to try to assign specific functions and thus specific context independent explanatory roles to particular molecules unless the systemic context favors such an assignment. It may even be that situations where a meaningful, context independent molecular explanation is possible are the exception rather than the norm.

Molecular syntax and the problem of development

For Rosenberg the task of developmental molecular biology is to provide an answer to Wolpert's question whether the egg is computable (Wolpert 1994). Rosenberg identifies the problem as:

> The thesis that the capacity to produce an indefinite variety of forms from a finite stock of units – the genes – is only explicable if the stock of units can be combined in *accordance with a syntax* – rules about switching on and off given in the case of development by natural selection – to produce the variety we know is possible (1997: 457, emphasis added).

According to this view development can be explained through the identification of the relevant molecules – DNA, RNA, maternal proteins – and their rules of interactions. The only problem that is still unresolved is understanding the full complexity of this function that maps molecular input into embryological output. Rosenberg's sources believe that this function is manageable, and if they are right, then philosophers of biology better adjust their own views about physicalist anti-reductionism. But is the situation really that clear-cut? Can we explain development based on a stock of molecular units and a syntax? We have already provided some evidence that questions this extremely reductionist view. Here we will present further arguments for the necessity of functional categories in explanations within developmental biology.

The computability thesis of development states that it is possible to predict the morphological outcome based on a molecular input and a set of interaction rules for these molecules. Under this account, any references to the cellular or organismal context within which these molecular interactions take place have to disappear eventually, replaced by a strictly molecular characterization. The problem that we see with such a view is that the rules of the molecular syntax only specify how certain molecules interact with each other. They cannot tell us what the product of these interactions will be if the product is a morphological structure, since the *organization* of these molecular building blocks into morphological structures is not part of the molecular syntax based on the reaction kinetics of molecules. This is a consequence of both scale and perspective. In focusing on the molecules one simply cannot refer to the organized cellular and organismal context; all that this perspective allows one to do is to describe the biochemical reactions as they unfold in linear time. This is, after all, the meaning of syntactical rules.

The focus on the biochemical rules of interactions or the reaction kinetics of a molecular syntax does not include what can be called a semantic component. The concept of a "molecular semantics" refers to the context dependency of biological processes. In the case of developmental systems the context dependency of biological processes is best illustrated by the frequent phenomenon that the same biochemical pathways following the same syntactical rules can lead to different morphological outcomes in different contexts. The *wingless/hedgehog* pathway may suffice as an example. The system that involves the *wingless* protein, the zest-white 3 kinase, and the *hedgehog* protein is important in the formation of segment boundaries in the *Drosophila* embryo. During the formation of the parasegmental boundaries, the *hedgehog* protein is expressed in the posterior segment. It in turn binds to a receptor on the anterior cell, thus stimulating the expression of the *wingless* gene, which acts to inhibit the zest-white 3 kinase in the neighboring cell. Inhibition of zw3 kinase releases the *hedgehog* repressor and stabilizes the system. The biochemical interactions that are involved in this pathway constitute a molecular syntax. What cannot be inferred from an exclusive focus on the participating molecules and their rules of interaction is how the same pathway not only is involved in the formation of segment boundaries in *Drosophila*, but also specifies the proximodistal axis in the eye, leg, and wing imaginal disc (Wilder and Perrimon 1995). In addition, a similar system, involving *wnt* proteins (homologous to wingless), glycogen synthase kinase 3β (homolog to zest-white 3 kinase) and *sonic hedgehog* is also involved in the determination of the body axis and the proximo-distal patterning of limbs in vertebrates (Niswander et al. 1994; Ingham 1994; Laufer et al. 1994).

The *sonic hedgehog* protein is also a good example of a multifunctional molecular factor. It activates different proteins in different contexts or morphogenetic fields. For instance, within the limb bud (morphogenetic field of the developing limb) high levels of *sonic hedgehog* transform mesencymal cells to form the ZPA (zone of polarizing activity) which in turn secretes the *sonic hedgehog* protein onto the anterior bud mesenchyme where it triggers an induction pathway that transforms the ectoderm into the AER (apical ectodermal ridge). Sonic hedgehog is also involved in the dorsoventral organization of the nerve cord that leads to the differentiation of motor neurons (motor neuron differentiating field) and the somite formation (for details see Gerhart and Kirschner 1997).

As these examples demonstrate, unless one pays attention to the specific context of a particular developmental system, such as the insect leg or the vertebrate body axis, not even a complete account of the molecular interactions (molecular syntax) can explain how these molecular interactions are causally linked to the spatial and temporal differentiation of particular morphological structures. The specific context of a developing system (molecular semantics) determines the biological role of conserved biochemical pathways and the particular effects of transcription factors such as *sonic* *hedgehog*. Without reference to the cellular and developmental context of gene expression the simple observation that the *hedgehog* protein binds to a specific receptor does not contribute anything to an explanation of development. Neither is it possible to identify a specific region as a regulatory sequence upstream of other genes – this assertion requires reference to the functional context of gene regulation within a cell, nor is it possible to establish any functional role to this event without implicit reference to the context of the developmental system. We submit that these examples provide ample evidence for the causal role of developmental systems. They also lead us to the important issue of functional kinds in developmental biology and their role in explanatory generalizations about developmental processes. As we have seen above, Rosenberg's interpretation of developmental biology allows no place for either functionally defined kinds or for explanatory generalizations at levels of complexity higher than individual molecules. Below we will further address these issues in the context of the problem of explanation in developmental biology.

The problem of explanation in developmental biology

Rosenberg argues that there are no explanatory generalizations that are not ultimately molecular in developmental biology and that explanations involving functional kinds will eventually be substituted by a strictly molecular account. His position on explanation, causation and reduction raises many questions that philosophers of science will certainly need to address; here, by way of conclusion, we will focus on one particular issue, the way Rosenberg employs the notion "molecular". Much of Rosenberg's argument, such as the thesis that the principle of autonomous reality of biological kinds is violated by the program of molecular developmental biology, boils down to the question of how we understand "molecular".

In a trivial sense all biological entities are molecular, and so is everything else on this planet. A corollary of this observation is that biological entities qua their nature of being molecular do not violate the laws of physics and chemistry. This is obviously an uninteresting assertion, unless one is still concerned with the hidden danger of vitalism. We take Rosenberg's frequent references to vitalism or emergentist dualism throughout his paper to be more of a philosopher's preoccupation with logical possibilities than a reflection of any serious biological position. The theoretically more interesting way in which molecular properties can relate to biological (i.e. functional) ones is a 'nothing-but' relation. All biological properties are nothing but combinations of molecular properties. This is a statement about the properties of biological objects and not just about their material composition. And it is a classical reduction statement: the properties of one class of objects – biological objects – are nothing but a combination of the properties of another class of objects – molecules. Before we can assess the evidence whether or not this statement can be substantiated, which is ultimately an empirical problem, we have to first clarify what we mean by biological and by molecular properties.

Nowhere in his paper does Rosenberg ever explicitly define ‘molecular’. He talks about the “molecular biology of nucleic acids and their immediate protein products” (p. 455) or the “molecularly characterized properties of molecular assemblages.” And in his account of molecular developmental biology the molecular as opposed to the cellular refers to descriptions in terms of DNA, RNA, and proteins without any reference to cellular structures (other than that they are ultimately composed of molecules as well.) It thus seems fair to say that the ‘molecular’ in Rosenberg’s account refers to the chemical properties of molecules, their three-dimensional structure, their potential to react with each other, and their reaction kinetics. This characterization entails a molecule-centered perspective. Focusing on molecules this way, the only effects that can be observed are linear sequences of chemical reactions that transform the involved molecules according to their chemical properties. There is no room for the spatial dimension or the organized structure of developing systems to play any role in these descriptions of molecular interactions. The existence and the potential causal effects of biological kinds other than molecules are thus ruled out *a priori*. The same logic, when applied to physical phenomena, would also rule out statistical thermodynamics. Temperature cannot be described within such a molecule-centered perspective; rather it is an emergent property of an ensemble of molecules dependent on the statistical distribution of their velocities.

We think that Rosenberg’s approach is flawed because it ignores a fundamental property of developmental processes, namely the fact that developmental processes often vary more profoundly than the characters that develop from them. A particular stunning example is the role of the gene *bicoid*, which in *Drosophila* is essential for the development of the anterior-posterior body axis. In Drosophila the chain of molecular events that leads from maternal gene expression to the activation of the developmental program are well understood. In other dipteran species, however, the gene for *bicoid* does not even exist, even if body axis determination is an essential step in early embryogenesis for all of them. Obviously the functional role of *bicoid* is played by other genes in closely similar (but not closely related!) species. Axis determination is certainly older than *bicoid* function, since all ancestors of the fly down to the flatworm-like animals had an anterior posterior body axis. Hence, the role of axis determination can be played by different molecular mechanisms and the players can actually change while the functions are performed. In what sense, then, is *bicoid* function a "deep" (Rosenberg's term) explanation of axis formation, if its purview is so limited? Similar stories exist for the "segmentation genes" which differ fundamentally among orders of insects. What do we learn from these examples? Let us take a short detour into the structure of human organizations. A university does not change its function as a university by changing its top administrators. To understand the functioning of such an organization, isn't it more interesting to know how information flows and how decisions are made under what the structural constraints than to ask about the personal motivation of the individual agents? We think that in developmental biology we face a similar problem: how much do we learn from knowing the players, and how much do we learn from understanding the process in which they partake? For each particular model system we need to know – down to the molecule – how the system is working. But ultimately we want to know more. We want to understand the structural commonalties among different model systems, and these are most likely not the molecules themselves but the functional context in which they are expressed. This is where really "deep" explanations will emerge, and the recent success in analyzing model species is an important, but by no means the final step in this direction.

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