

## 2. Regenerating Theories in Developmental Biology

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### Introduction

Developmental biology offers descriptions and explanations of the processes involved in the development of living entities. But does it formulate *theories*? If it does not, does this raise difficulties? If it does, in which ways is the formulation of theories useful? In general terms, is it important, for a given scientific field, to express theories? The dominant view among current biologists and philosophers of biology is that developmental biology does not offer theories, or at the very least is not structured by theories (Love 2008, this volume; Arthur, this volume; Gilbert and Bard, this volume; see also Goodfield 1969), and needs not to. Yet I would like to argue in this chapter that developmental biology does offer theories. The initial focus will not be on whether or not developmental biology offers a single, general, theory, though the last section will offer some thoughts about this issue.

First of all, what is ‘development?’ This apparently naïve question has in fact no straightforward answer. Delineating development from a conceptual point of view is a daunting task (Pradeu *et al.* 2011). Most of the time, in their publications and in everyday practice, developmental biologists do not define what they mean by ‘development.’ When they do, they usually insist on the fact that development refers to the *construction* of an organism (e.g., Davidson 1991; Gilbert and Raunio 1997; Gilbert 2003, 2013 (“the formation of an orderly body from relatively homogenous material”); Wolpert 2008[1991] (“the moulding of form”); see also the Minelli and Pradeu, this volume). Classically, developmental biologists have seen this construction as lasting from fertilization to the acquisition of the capacity to reproduce, while others see it as ending only with death (e.g., Gilbert 1994, 2013; see also Oyama 2000 [1985]) and/or criticize dominant adultocentric approaches to development (Bonner 1965; Minelli 2003, 2009, 2011a, this volume; see also the interpretation of the capacity to reproduce defended by Griesemer, this volume). A majority of developmental biologists would concur on the explananda of their field: cell differentiation, morphogenesis (including organogenesis), and growth as the main aspects (e.g., Bonner 1974, pp. 130-132 (though Bonner also emphasizes the possible biases of these notions); Shostak 1991; Robert 2004; Wolpert 2011; Gilbert 2013), to which many specialists of the field add the acquisition of the capacity to reproduce as well as regeneration (e.g., Wolpert *et al.* 2011; Gilbert 2013; Slack 2013), and also, for some, evolution and environmental integration (Gilbert (2013) lists those six questions as the key ones addressed by current developmental biology). Moreover, there is a consensus on the key steps of animal development, and on the need for the field of developmental biology to account for these steps: fertilization, cleavage, gastrulation, organogenesis, metamorphosis (in some species), maturity, gametogenesis (on these steps and their place in the agenda of developmental biology, see Love 2008, and this volume; these steps, however, are not all universal: see Minelli, this volume).

Here I understand development as the set of processes that leads to the construction of a novel organismal form. This definition identifies morphogenesis and organogenesis as crucial components of any developmental process. This view is broad enough to incorporate crucial mechanisms of late organogenesis, as metamorphoses, or local late development of new tissues in mammals, e.g., tertiary lymphoid organs (Eberl 2005; Pradeu 2011). Nevertheless, it is more precise than conceptions that equate ‘development’ with all forms of metabolic change from fertilization to death. Of course, other definitions of ‘development’

could be offered, but this one seems operational enough, and it will be sufficient to serve our purpose here. With this definition in mind, let us now return to the central question raised above: does developmental biology offer theories?

This chapter argues that developmental biology does indeed offer theories. This view rests on the conviction that both biologists and philosophers of biology, when they reject the idea that developmental biology could offer theories, have in mind a conception of a theory that is excessively demanding. Therefore, the path chosen here is not an easy one: my aim is to suggest a concept of a scientific theory that is demanding (in the sense that it is not trivial and it may lead to fruitful results in a given scientific field), but not *too* demanding (to avoid the often expressed idea that, for instance, quantum mechanics and evolutionary biology could offer theories, but developmental biology would not be ready yet to do so).

The structure of this chapter is as follows. The first section describes the widespread suspicion of theories in current developmental biology and philosophy of developmental biology. The second section offers a critique of this suspicion, in particular through a detailed analysis of biological fields in which people routinely speak of ‘theories’ and a historical account of the different uses of the term ‘theory’ in the past of embryology and developmental biology. The third section offers a plausible conception of what a theory may be in biology. The fourth section argues that developmental biology does offer theories of development, and it suggests some avenues for the construction of developmental theories and their articulation into a growingly unifying picture.

### **The suspicion towards theories in developmental biology**

The idea that developmental biology might suggest theories, let alone a general theory of development, is usually seen with the most extreme suspicion. This suspicion is expressed both by biologists and philosophers (Love 2008, this volume; Arthur, this volume; Gilbert and Bard, this volume). Developmental biologists, in their current practice, seldom use the term ‘theory.’ Table 2.1 shows how frequently the term ‘theory’ appears in titles and abstracts of several of the main journals in developmental biology. This table confirms that developmental biologists do not use this term on a regular basis (Table 2.2 below will offer a comparison with other biological fields).

What could explain the scarcity of mentions of theories in today’s developmental biology? It is often claimed that theories are too abstract (*i.e.*, remote from experimental practice), too ambitious (‘grand’ theories, which pretend to explain everything, do not explain much), or too general, and therefore unable to cope with the extreme diversity, and complexity, of developmental phenomena across species (e.g., Bard and Gilbert, this volume; see also Goodfield 1969; Freeman 2002). In addition, many biologists have the feeling that if our best physical theories are seen as the archetype of what a scientific theory should be, then developmental biology cannot suggest ‘theories’ in this strong sense, since its statements are less universal, less abstract, and less likely to be expressed in a mathematical language.

Philosophers of biology, for their part, have tended to be suspicious of the notion of theory because they see it as forged in the context of a philosophy of science dominated by logical positivism and philosophy of physics (Callebaut 2013). It has often been suggested that there are no theories and laws in biology, mainly because of the historical character of this domain (e.g., Smart 1963 – an idea discussed in Hull 1974; see also Beatty 1995). In addition, many philosophers of biology consider that classic views about scientific laws and theories should be discarded as illegitimate applications to biology of problems framed in the terms of the philosophy of physics, ignorant of the specificities of biology as a science (Hull 1969; Sterelny and Griffiths 1999; this view was shared by the evolutionary biologist Ernst Mayr (1969a, 1969b)). Hull (1974) considers that biology can offer laws, but those are almost

always to be understood as accidental generalizations; moreover, biology can have theories, but, Hull argues, only evolutionary biology expresses well-articulated theories (Hull 1992), leaving all the rest of biology, including embryology, with no ‘true’ theories. In the general philosophy of science, a major debate occurred in the 1960s and continued until the 1980s between the ‘syntactic’ and the ‘semantic’ approaches to theories: the ‘syntactic’ (often dubbed ‘classic’) view sees a theory as an abstract calculus and correspondence rules that give an empirical content to this calculus (Nagel 1961), while the ‘semantic’ view sees theories as classes of models (Suppes 1967; Suppe 1977; van Fraassen 1972). This debate, as many others in the general philosophy of science, appears extremely remote from the actual questioning and practices of the life sciences. Several philosophers of biology did attempt to apply the classic debate about the syntactic and/or the semantic conceptions to ‘theories’ and reduction in molecular biology (Schaffner 1968, 1993) and to the theory of evolution by natural selection (Ruse 1973; Lloyd 1993 [1988]; Thompson 2007; see also the work of evolutionary biologist Mary Williams (1970)), but these attempts have generated no consensus and have seemingly not been of much use to biologists. In addition, many historians and philosophers have shown that, contrary to what is often believed, the dominant view of evolution, which stems from the Modern Synthesis, does not constitute a single and unified theory, but rather a set of heuristic, and to some extent heterogeneous, statements (Gayon 1998; Love 2013). Recently, lively discussions have occurred about models, modelisation, and idealization in biology (e.g., Downes 1992; Godfrey-Smith 2006; Weisberg 2006; Wimsatt 2007; see also Morrison 2007), often in the footsteps of Richard Levins (1966), but most of them have tended to set ‘theories’ aside. Overall, many philosophers of biology consider that evolution by natural selection constitutes a genuine ‘theory.’ By contrast, non-evolutionary fields would not offer bona fide theories, but rather, at best, general descriptions situated at different levels (molecular, cellular, tissue, etc.) A more recent version of this claim has been articulated by several proponents of a mechanistic framework, who suggest that molecular biology, cell biology, neurology, etc. offer ‘mechanisms’ and ‘schemata’ (i.e., aggregations of mechanisms) rather than ‘theories’ in the sense usually retained by general philosophy of science (Machamer *et al.* 2000; Darden and Tabery 2009; see also Craver 2002, but this text expresses a more balanced view on theories, and suggests the notion of ‘mechanistic theories’ for molecular biology; Griesemer (2011a, 2011b), for his part, proposes a useful distinction between ‘mechanistic’ and ‘quantitative’ theories). Among philosophers with a special interest in developmental biology, Alan Love (2008, this volume) has forcefully defended the idea that this field does not, and needs not, offer ‘theories,’ but rather is driven by the formulation of ‘research agendas’ (please note, however, that Love’s line of thought is independent of the ‘mechanistic’ trend in current philosophy of biology). As will become clear in the rest of this chapter, I agree to a very large extent with Love’s attention to scientific practices, though our conclusions diverge radically about the role theories have, or may have, in developmental biology.

Overall, the suspicion about scientific theories expressed in biology and in philosophy of biology rests on a double assumption. The first assumption is that traditional debates in the general philosophy of science (in particular the ‘syntactic’ vs. ‘semantic’ debate) would have given us an adequate conception of what a theory is. The second assumption is that physics (or, rather, physics as seen by biologists) would offer the archetype of what a scientific theory should be. But it is very likely that these assumptions are inadequate. The next section offers three reasons to cast doubts on the idea that developmental biology would not offer theories.

### **Critique of this suspicion**

The first reason for being sceptical on the dominant view presented in the previous section is that several biological fields routinely offer theories. Indeed, it is perfectly usual to talk about theories in evolutionary biology (e.g., Gould 2002; Wilson 1997), ecology (Scheiner and Willig 2008), genetics (e.g., Morgan 1917), biochemistry (Weber 2002 gives important examples), molecular biology (Culp and Kitcher 1989 give important examples), immunology (e.g., Burnet 1959; Bretscher and Cohn 1970; Jerne 1974), neurology (e.g., Dayan and Abbott 2001), etc. (Several examples of biological theories are analysed in Krakauer *et al.* 2011).

It is often claimed that theories are found in evolutionary biology, but not in the ‘mechanistic’ fields of the life sciences, that is, molecular biology, cellular biology, physiology, developmental biology, etc. (together, these domains are often described as ‘experimental biology,’ but this label is problematic, as evolutionary biology can also perfectly be experimental). Table 2.2 shows, for each biological domain, the number and percentage of papers published in the *Proceedings of the National Academy of Sciences of the United States of America* that have the word ‘theory’ in their titles and/or abstracts (*PNAS* was chosen because it is representative of a high profile scientific journal covering all scientific fields). It appears that evolution and ecology mention theories more often than other domains, but several key areas of mechanistic biology do mention theories relatively often, in particular biophysics and computational biology, systems biology and neurosciences. (It should also be emphasized, for the sake of comparison, that physics, probably the most theoretically oriented of all fields in experimental sciences, has 206 occurrences of ‘theory’ in the titles and abstracts of a total of 1765 papers in the same journal, that is, 11.67% - much less, probably, than many people, and especially philosophers of science, would have expected). As far as it is concerned, developmental biology has only five occurrences, none of them in the article title, and none of them specific to developmental biology (for instance, it is in fact the theory of evolution that is mentioned).

So, it seems that some biological domains (evolution, ecology, systems biology, etc.) routinely mention theories, while others (immunology, neurosciences, etc.) do not really talk routinely of theories, but have nonetheless well-identified and commonly discussed theories. Developmental biology, in contrast, seems to mention very few theories, and none of them seems properly specific to development. What could explain that developmental biology does not formulate theories? Several criteria could be envisioned, including the level of generality (a theory is often supposed to have an extensive domain, that is, to apply widely across diverse entities), the level of abstraction, the complexity of the subject, the use of models or idealizations, or the role played by mathematics. But none of these criteria resists a close examination. Let us take the example of the clonal selection theory in immunology (Burnet 1959): it has a limited domain (it applies only to jawed vertebrates), it is not formulated in mathematical terms, it is not highly abstract, it is not characterized by a particular use of models and idealizations, and its subject (the generation of lymphocytes) is certainly complex, but not necessarily more so than the explanation of limb development. And yet it is recognized by virtually everyone in the field as a ‘theory.’ Many theories in neurosciences, physiology or biochemistry are in a similar situation. Therefore, it is likely that, if current developmental biologists fear to speak about theories in their field, it is just a contingent fact, related to the impression they have that a theory is such a demanding notion that their field cannot fit its requirements.

The second reason for putting into question the view that developmental biology could not offer theories, is a straightforward historical one: in the past, developmental biology and its ‘ancestor,’ embryology (much can be said about the differences between embryology and developmental biology: see for instance Burian and Thieffry (2000) and Gilbert (1998), but the idea that embryology has been transformed into developmental biology is undisputed) have undoubtedly formulated ‘theories.’ Without going back to the long controversy between

preformation and epigenesis (see, e.g., van Speybroeck *et al.* 2002; Robert 2004), this is particularly true of 19<sup>th</sup> century embryology. Some of these embryological theories are comparative, and later on evolutionary, in nature. An important example is offered by Karl von Baer, who formulated the ‘germ-layer theory’ and a ‘law,’ articulated in four parts, about the development of metazoans (Brauckmann 2008; on this theory, its influence and its opposition to the ‘recapitulation theory,’ see Ospovat 1976). The germ-layer theory states that: a) during the development of animals, the cells that come from the egg cell constitute embryonic layers (the ectoderm, the mesoderm and the endoderm), and b) in every animal species, the same organs or structures develop from the same layers (von Baer 1828). Other embryological theories are related to the idea of ‘recapitulation,’ that is, to the idea that development of advanced species passes through stages represented by adult organisms of more primitive species. This view is often attributed to Haeckel (1867), but was in fact diversely expressed by several authors. This view was later criticized, but it probably played a significant role in the promotion of comparative embryology and in the conviction that it was crucial, in establishing phylogenies, to pay attention to embryonic stages (for a historical analysis, see Rinard 1981; Hoßfeld and Olsson 2003). Other theories in 19<sup>th</sup> century embryology are mechanistic in nature. For the *Entwicklungsmechanik* trend, in particular, the task of embryology was to uncover the laws followed by all ontogenetic processes across species (Roux 1895). In other words, it sought to discover *general mechanisms* of development, that is, mechanisms that could be observed in all metazoans. Two key general concepts, which have been discussed ever since, are the *gradient* and the *organizer* (Gilbert *et al.* 1996). The highly general mechanistic frameworks suggested by Roux and his followers constitute theories, which must be understood within a context characterized by a particular attention to theories, vividly described by Klaus Sander (Sander 1991b; for an overall characterization of Roux’s programme for a mechanistic developmental biology, see Sander 1991a). In these different examples, we find two important components of theories that will reappear later in this chapter: *evolutionary generalizations* and *mechanistic generalizations*: what is at stake is to make comparisons across species and, if possible, to find results that hold for several species, as well as finding out some fundamental mechanisms of how development occurs.

The building of theories did not stop with the 19<sup>th</sup> century. During the second half of the 20<sup>th</sup> century, several influential theories about developmental processes have been formulated. Five of them will briefly be mentioned here. The genetic program of development constitutes a first example. Mayr (1969a), in particular, sees the genetic program, based on the Monod-Jacob model of gene regulation, as “the ‘general theory of development’ which embryologists are looking for so assiduously.” Though the idea of a developmental program has been criticized in different ways, it is still present in several contemporary texts (e.g., Wolpert 2008 [1991], 1994; Levine and Davidson 2005; for a critique see, in particular, Oyama 2000 [1985]; Minelli 2003; Robert 2004). A second example is offered by a paper by Wolpert and Lewis (1975), beautifully entitled *Towards a theory of development*. It seemed absolutely clear to these two prominent developmental biologists that it was possible to articulate a general theory of development, based on ‘general principles’ rooted in positional information and a proper understanding of the genetic program. The third example is the tradition started with Turing’s formal model of morphogenesis through reaction-diffusion (Turing 1952). This tradition has had many followers in the 1980s and 1990s. The reaction-diffusion model received recently striking experimental confirmations (Sick *et al.* 2006; Maini *et al.* 2006; Bansagi *et al.* 2011). The ‘source-sink model’ constitutes a fourth example: formulated by Crick (1970), and partially related to Wolpert’s positional information, it has given rise to experimental tests and was recently corroborated by Yu *et al.* (2009) (see Newman, this volume; Vecchi and Hernandez, this volume). Finally, one last example has

been the use of thermodynamics to suggest a ‘thermodynamic theory of growth’ (Zotin 1972, following in the footsteps of Prigogine and Wiame (1946) and Prigogine (1967); see also Zotin and Zotin 1997). These five theories were influential when they were suggested and, as we will see, some of them are still very influential in today’s developmental biology.

Again, what has changed in the field of developmental biology and might explain this shift from a ‘theory-friendly’ field (up to the end of the 1970s, approximately) to one in which it seems inappropriate to evoke theories? One might think that, starting with the 1970s, developmental biology has entered a descriptive phase, during which developmental biologists have primarily tried to offer genetic and molecular descriptions of local developmental mechanisms in a given organism, often taken from a limited number of model species (Gilbert and Tuan 2001; Gilbert 2009). Many have expressed the necessity to keep in mind the ‘big picture’ (theories, high-level concepts, comparisons with other biological fields, etc.), but also emphasized that it was difficult to find time to do it. As Bonner (2013, p. ix) said: “Many biologists, and I am one of them, live two lives at the same time. In one they work day to day in the laboratory, or in the field. This is what keeps them in touch with their subjects—the real world that they find so fascinating. The other life is a concern for the big picture: how it all fits together” (cited by Callebaut 2013, p. 416). My suggestion is that, even though experimental work and the elucidation of molecular details are key to the progress of developmental biology, the worry for the ‘big picture’ is as important, and as fruitful, as ever (see also Fraser and Harland 2000; Laubichler and Wagner 2001).

The third reason for putting into question the view that developmental biology does not offer theories is that, presently, *some* very influential developmental biologists do talk about theories in their research. As a first example, Stuart Newman proposes a physico-genetic theory of morphogenesis, according to which some key aspects of morphogenesis have emerged through ‘generic’ physical processes, to which subsequent genetic processes were added (Newman and Comper 1990; Newman, this volume). This framework helps identify developmental mechanisms (both generic and genetic) shared by all animals, or even by all multicellular organisms. It is partly convergent with theories of self-rearrangement in embryogenesis (Brodland 2002), and self-organization theories (e.g., Kauffman 1971, 1993). Secondly, since Wolpert (1968, 1969) has suggested the notion of ‘positional information,’ several theories of positional information have been suggested (Jaeger *et al.* 2008; Jaeger and Martinez-Arias 2009; see also the mechanistic theory based on dynamical systems theory suggested by Jaeger and Sharpe, this volume). The concept of positional information constitutes the basis for a spatial explanation of embryonic regulation. According to Wolpert’s initial views, positional values correspond to a morphogen’s gradient that is measurable by responding cells. Wolpert (1968) famously proposed the “French flag model” to illustrate his concept of positional information. Recently, Jaeger *et al.* (2008) have offered what they call a ‘relativistic’ theory of positional information, to which we shall return at the end of this chapter. Thirdly, Eric Davidson has developed for several decades an explicit theory of the regulation of gene activity in development (Britten and Davidson 1969; Davidson *et al.* 2002; Davidson 2006. See also Garcia-Deister 2011; Morange, this volume). This theory seeks to identify general molecular mechanisms of gene expression, and it leads directly to comparative approaches (Davidson 1991). Fourthly, in a decisive step in the elucidation of homeotic genes, Lewis (1978) proposed what he describes as a ‘model’ of the determination of body segments by the combinatorial action of homeotic genes. Strictly speaking, his suggestion is a set of structured hypotheses, characterized in particular by six ‘rules’ describing how bithorax complex (BX-C) genes are regulated (Lewis 1978, pp. 569-570). In this sense, Lewis’s proposal fits what will be called a ‘theory’ in the next section. Finally, the need for a theory of development has also been expressed by Alessandro Minelli: “What is at stake is the prospect of moving at last toward a *scientific theory of development*”

(2003, p. 2, emphasis in the original). Recently, Minelli (2011b) has suggested a ‘null model’ for development, according to which developmental processes are deviations from a local self-perpetuation of cell-level dynamics, which can be called ‘developmental inertia.’

Many other examples could be mentioned: theories of neurulation (Gordon 1985; Clausi and Brodland 1993); theories of neurogenesis (Simpson *et al.* 2009); morphogen gradients theories (Freeman 2002; Green 2002; Lander 2002); the chondral modeling theory (this theory says that joint congruence is maintained in mammalian limbs throughout postnatal ontogeny because cartilage growth in articular regions is regulated in part by mechanical load) (Frost 1979; Hamrick 1999; Congdon *et al.* 2012); cell lineage theory (Croxdale *et al.* 1992; Bjercknes 1993); cell fate theory (Garcia-Ojalvo and Martinez Arias 2012); cell migration theories (McLennan *et al.* 2012); theories of animal muscle development (Fukushige *et al.* 2006); segmental theories of the formation of the vertebrate head (Kuratani *et al.* 1999); theories of pigmentation pattern (Kondo and Shirota 2009); theories of flower development (Alvarez-Buylla *et al.* 2010); the germ-layer theory and the consequences of the discovery of the neural crest on embryonic theories (Hall 2008); etc.

To all these examples one could be tempted to add the ‘Developmental systems theory’ (DST) (Oyama 2000 [1985]; Oyama *et al.* 2001). This view has offered a fruitful conceptual and experimental framework to conduct research in several fields, from development to evolution and psychological studies. Yet, as acknowledged by its main architects, the DST should not actually be understood as a scientific theory strictly speaking, but rather as a ‘perspective,’ a way of seeing developmental processes (Oyama *et al.* 2001, pp. 1-2; see also Barberousse *et al.* 2011).

Even some textbooks occasionally mention developmental theories. For example, Shostak (1991) discusses the germ-layer theory, the gastrea theory, and sees Spemann’s proposal on induction and the concept of organizer as a theory (Shostak 1991, pp. 577ff). Several textbooks mention ‘hypotheses’ that are in fact highly complex and well-structured sets of hypotheses, e.g., on induction and positional information (Wolpert *et al.* 2011). Finally, even when they adopt quite different perspectives, several textbooks use repeatedly the idea that there are ‘principles of development’ (e.g., Gilbert 2000; Wolpert *et al.* 2011).

Many of the theories mentioned above focus on the most important questions raised by developmental biology (differentiation, morphogenesis, genetic regulation of development, etc.), are testable, and open avenues for original and fruitful predictions. In addition, several of them have been extremely influential in the field. For instance, in a landmark book, Jonathan Slack (1991) devotes a whole chapter, significantly entitled *Theoretical embryology*, to dynamical system theories, gradient models, diffusion of morphogen theories, reaction-diffusion models, clock models, etc. Therefore, though it is true that the majority of developmental biologists do not routinely mention theories in their daily research (Love 2008, this volume), developmental biology does possess several general theories, rooted in broad-ranging concepts (e.g., positional information), which give rise to continuous discussions and experimental assessments by key actors of this domain.

To sum up this section, theories are found in different biological fields other than developmental biology, but also in the past and present of developmental biology. For these reasons, the idea that developmental biology would be an ‘a-theoretical’ domain seems very difficult to defend. Naturally, one possibility here would be to say that these biological theories are not ‘true’ theories because, for example, they do not fit the syntactic or semantic conceptions of theories, or because they are not law-like theories. But why should scientific theories be asked to conform to the utterly unrealistic demands of these conceptions? I suggest that the most fruitful path is to try to construct a notion of a scientific theory that will both be demanding (not anything in science should count as a theory) and fit the present and past uses of the word ‘theory’ by biologists.

## Characterization of theories in biology

The previous section suggests that biology does offer theories, but in a sense quite remote from what mainstream philosophy of science, or more precisely the syntactic and semantic conceptions, have claimed. This should not in fact surprise us, as those conceptions are to be understood as methodological *reconstructions* of scientific theories, and not as descriptions or definitions of what scientific theories are (e.g., Nagel 1961, p. 90; Suppes 1967, pp. 63-64). Our focus here is not the logical reconstruction of theories, but the identification of a meaning of ‘theory’ that will enable us to state if biological sciences formulate theories. What is needed in our case is a conception of a ‘theory’ that will both be consistent with the usage of this notion by the scientific community, and shed light on the roles that theories play in science.

As a reasonably demanding definition of a scientific theory, it is possible to suggest that a theory is *a structured set of testable explanatory and predictive hypotheses* (Pradeu 2009). An isolated hypothesis is one specific statement, not a set of statements, and in addition a hypothesis can be weakly corroborated. A theory, in contrast, is a *hierarchical* organization of several hypotheses (they can be dependent one on the other; one can be the consequence of another; etc.), and these hypotheses are corroborated to a high degree. In other words, a theory is the *articulation* of corroborated explanatory and predictive statements. Most of the time, a theory contains abstract concepts, related to entities that cannot be directly observed as such in the world (e.g., ‘force’ in physics, ‘fitness’ in evolutionary biology, ‘positional information’ in developmental biology).

I agree with Love (2013, this volume) – and with other people who emphasize the importance of scientific practices, in particular Griesemer (2000, 2013, this volume) – that a crucial question is to determine whether the conceptual tools constructed by philosophy of science are useful or not for the scientific community, and correspond to something this community deems to be important. Of course, philosophers of science can develop a reconstruction activity, meaning that they endeavour to reconstruct scientific theories thanks to logical instruments in order to clarify their structure, or perhaps to characterize the ideal that every scientific theory should aim at (this is, at least to some extent, what some proponents of the ‘syntactic’ conception tried to do). But, particularly in philosophy of biology, a domain that has been from its inception very close to biology itself, it seems extremely important to take into account biologists’ discourse, and the effect of our conceptual analyses on biologists themselves. But I disagree with Love on the role played by theories in biology, and in developmental biology in particular. In my view, theories are crucial in science, because they do several key things.

Scientific problems need to be well-defined, well-structured, limited in scope, and, once they are organized into problem agendas (Love 2008, this volume), they constitute a decisive step to do science and to make some progress in a given domain. But, in order to make significant progress, science needs not only problems; it needs *answers* as well. I suggest that what theories do in a given domain is bringing answers; by being novel, daring, testable, and hence often wrong, theories give rise to decisive refinements in science.

It is important to realize that a theory is the best open gate to possible worlds. Possibility is key in science. It is certainly important for scientists to describe what they observe and to organize this knowledge into concepts, categories, and explanations. But it is equally important to project themselves into new answers as to how phenomena *could possibly occur*, and correlatively how their field could *possibly* be deeply re-organized in the near future in the face of newly described phenomena. This kind of projection into possible

worlds occurs especially in the case of major breakthroughs in a given scientific domain. Part of what theories do is to open up new possibilities.

So, what exactly are the roles that are played by scientific theories, and cannot be played by something else? I would like to emphasize here two critical roles of theories. First, theories make possible *explanations* and *predictions* (e.g., Nagel 1961; Hempel 1965). This is in contrast with descriptions, including molecular descriptions, which are often seen by experimental scientists as what their domain should focus on. Nobody doubts that descriptions are indispensable (in particular, nobody doubts that the ‘molecularization’ of several biological fields, notably developmental biology, has led to major progress). Yet the accumulation of descriptions often leaves us without a clear idea of what exactly is being investigated, what should be found if this or that experiment was done, and how all these isolated, local descriptions might fit together into a unified picture. Faced by recent accumulation of flows of data, some biologists have insisted that only well-structured and unified theories can impose an order on this disconcerting diversity: “Biology urgently needs a theoretical basis to unify [what modern technology has to offer us] and it is only theory that will allow us to convert data to knowledge” (Brenner 2010, p. 207). Of course, some order can be brought about by problem agendas; but theories, because they take the form of answers to these problems, offer a stricter order. As a daring set of testable explanatory and predictive statements, a theory articulates a possible order, and the consequences of this order if it is to be vindicated. In rough terms, a scientific theory says: if I am accurate, then this should happen while this cannot happen. Naturally, by making such claims, i.e., by suggesting such an order, a theory runs the risk of being proved wrong. But this is a perfectly normal and fruitful way for science to change. By making predictions, a theory tells us where to look and what to test (Waddington 1968). Therefore, a theory offers explanations and makes predictions in a much more audacious, and hence productive way, than other types of answers. Sometimes, the content of the predictions is unexpected, or even counterintuitive; one of the things theories can do is to compel us to modify our intuitive ontology and/or what we have up to now taken for scientifically granted. As evolutionary biologist George C. Williams said:

[The] most obviously fruitful role [of theory] is in providing explicit direction for research. From theory we can deduce conclusions not previously reached and that are occasionally counterintuitive.... (Williams 1988, p. 297, cited in Gorelick 2011)

Interestingly, examples of counterintuitive conclusions coming from theoretical insights can be found in the developmental biology literature (e.g., Freeman 2002 about gradient diffusion). A related role of theories is that, by offering highly general and daring answers to identified problems, they immediately stimulate *challenges*. As soon as a theory is formulated, scientists will be tempted to assess it, to find exceptions or inadequacies, to ask for more precise definitions of the key terms of the theory, etc. Testability is a prominent feature of science, and theories help favouring testability (to say this is not to deny the difficulties associated with scientific testability; see, e.g., Duhem 1954 [1906]; Kuhn 1970 [1962]; Quine 1980 [1951]). That one of the main roles of scientific theories is to formulate specific and testable explanations and predictions is an idea shared by philosophers and historians of science as different as Ernest Nagel (1961, p. 93), Thomas Kuhn (1970 [1962]), David Hull (1988, p. 466), and James Griesemer (2013).

A second role of scientific theories is *unification*. A theory unifies into a simple and coherent picture a diversity of heterogeneous phenomena (Nagel 1961, p. 89). By suggesting a common structure and common principles, a theory makes some connections between phenomena that, before the formulation of the theory, had seemed distinct, with no obvious link one to the other. The canonical example of such a theoretical unification is, naturally,

Newton's theory of mechanics, which succeeded in accounting for phenomena that had been hitherto considered as very distinct (planetary motion, freely falling bodies, tidal action, etc.). But the same thing occurs in all scientific domains, including developmental biology – as, for example, when Eric Davidson and colleagues construct a theory of gene regulation that aims at exhibiting the common principles of this regulation across phyla (e.g., Britten and Davidson 1969; Davidson 2006) – and other 'mechanistic' domains of the life sciences (for a recent attempt in immunology, see Pradeu *et al.* 2013). It is important to emphasize the difference between unification and universality. Contrary to what is often believed, a scientific theory is not necessarily universal, in the sense that it would hold in the entire universe without spatiotemporal restrictions. In fact, most scientific theories are *not* universal, and one could even argue that *no* theory is universal. Even highly general theories of physics have exceptions, and hold only within certain conditions (this has been one of the main reasons for criticizing the notion of scientific 'laws' understood as universal statements: Cartwright 1980; Giere 1999). A theory holds for a given *domain*, and what is important is to delineate clearly this domain (the clonal selection theory in immunology has been shown above to be an example of a scientific theory with a quite narrow domain). Most theories do not seek universality, but rather they seek unification, that is, they aim at gathering seemingly heterogeneous phenomena under a unique framework of common principles and explanations. A related role of scientific theories is *comparison*. Because of their condensed formulations and the need to always better define their domain, theories call for comparisons, articulations and confrontations. These comparisons can occur within a given field (for instance within developmental biology), but also among different biological fields (a key example is, of course, the articulation between evolution and development, or 'evo-devo'), or even among different scientific fields (e.g., Newman, this volume, shows how physics of soft matter can shed light on the past and present of the process of development). These comparisons can be tremendously helpful, since they can suggest new ideas or analogies, but in addition they often play a key role in the unification process just described, as when, for instance, two competing theories are reconciled under a common framework (for example corpuscular and wave theories of light), or a theory of a given domain inspires and deeply modifies another domain (for example when microbiology resorts to ecological theory to better understand the inner ecological system constituted by commensal gut bacteria: Costello *et al.* 2012).

These two key roles – the formulation of explanations and predictions, and the unification process – demonstrate the indispensability of theories in science, and in particular in biology, provided that a simple, not excessively demanding, definition of "theory" is adopted. Thus, the convergence between the perspective defended here and that presented by Love (this volume) is clear: I agree with Love that theories as they have traditionally been defined in philosophy of science are not necessary to produce explanations, predictions, unifications, etc. What I suggest, though, is that Love's view is still too dependent on the traditional definition of a theory and that, if one is ready to adopt a more 'relaxed' conception, then theories are found in many biological sciences.

According to the view defended here, therefore, constructing explanatory, predictive, unifying, and comparative theories should be seen as a legitimate goal in the biological sciences, and one that is in fact much more often realized than sceptics would think. As a recent report of the National Research Council said:

Theory is already an inextricable thread running throughout the practice of biology, as it is in all science. Biologists choose where to observe, what tool to use, which experiment to do, and how to interpret their results on the basis of a rich theoretical and conceptual framework. Biologists strive to discern patterns, processes, and relationships in order to make sense of the seemingly endless diversity of form and function. Explanatory theories are critical to making sense of what is observed—to order biological phenomena, to explain what is seen and to

make predictions, and to guide observation and suggest experimental strategies. (National Research Council 2008, pp. 13-14; see also Gorelick 2011)

To sum up, theories are here viewed as structured sets of testable explanatory and predictive hypotheses. This definition is demanding (not just anything can be called a scientific theory), but not too demanding (it does not make the formulation of theories an unreachable horizon in scientific research). In particular, this definition makes possible the identification of key theories in biology, including developmental biology. According to the view defended here, the formulation of theories is immensely useful for the advancement of a given scientific field, as theories, because they are well-articulated answers to specific problems, make possible explanations, (testable) predictions and unifications, to a degree that cannot be reached without theories. The next section examines developmental theories and the way different theories can be articulated in order to build a more unified picture of development.

### **Towards developmental theories**

The word ‘mystery’ is used again and again in the scientific literature to describe development (e.g., Barinaga 1994; Wolpert 2008 [1991]; Travis 2013). This sense of mystery unfortunately suggests that today’s developmental biology would not be very different from embryology as described by Spiegelman in 1958:

I have found it difficult to avoid the conclusion that many of the investigators concerned with morphogenesis are secretly convinced that the problem is insoluble. I get the feeling that many of the intricate phenomena described are greeted with a sort of glee as if to say, “My God, this is wonderful, it is so complicated we will never understand it.” (Spiegelman 1958, p. 491)

Though the feeling that development is mysterious is understandable, as development has obviously fascinated humans at least since Aristotle, we should resist it. In Spiegelman’s (1958) footsteps, we could say that “the phenomena of morphogenesis can hardly be as complicated as implied by the welter of apparently unrelated observations constituting the literature of embryology.”

A first way to dissolve the apparent mysteries of development is to transform them into scientific *problems*. But I suggest that the second, equally important, step is to suggest *answers* to these problems. Here is how, in 1998, Scott Gilbert described the embryology of the beginning of the 1980s: “Fifteen years ago, embryology was what could be characterized as the only field of science that celebrated its questions more than its answers. We had the greatest problems one could imagine ... But we had very few answers” (Gilbert 1998, p. 169). The construction of present-day developmental biology needs to focus on answers, and not on problems or problem agendas only. As suggested above, theories are the best articulated answers to scientific problems, and as such they can greatly improve our current understanding of development. In this section, we examine how theories of development can be constructed, how they can play a decisive role in the field of developmental biology, and how they can be progressively articulated together in order to build a unifying picture of development. Hence, the attitude on which this section rests is in fact quite similar to that of Bonner forty years ago:

By this rocking back and forth between the reality of experimental facts and the dream world of hypotheses, we can slowly move toward a satisfactory solution of the major problems of developmental biology. So our watchword in this last chapter, which considers the grand themes of development, is never to admit mystery, defeat, or chaotic complexity, but with Calvinistic zeal put such easy, backwards thoughts to one side and bravely make a hypothesis at each breach. (Bonner 1974, p. 219).

The previous sections have shown that biological fields in general can, and do, offer theories. They have also emphasized that developmental biology has offered theories in the past, and still offers theories today. We can now show, through the analysis of some examples, that these developmental theories fit the general definition of theories as structured sets of testable explanatory and predictive hypotheses. But a preliminary remark is that we should not be too surprised by the capacity of developmental biology to offer theories. In fact, developmental biology is in a particularly favourable situation to offer theories, for several reasons: it has a long experimental and mechanistic history (in particular *Entwicklungsmechanik*); it has gathered a huge quantity of data, at many different levels (molecules, cells, tissues, organs, as well as the whole organism); and development is characterized by at least some highly general mechanisms (Nüsslein-Volhard 1994; Wolpert 1994), sometimes subject to mathematical analysis and modelisation.

A remarkable example of a theory in developmental biology has recently been offered by Jaeger *et al.* (2008). They call their theory the "relativistic theory of positional information." As stated explicitly by the authors, this theory must be understood in contrast with the 'classic' theory of positional information that originated in Wolpert's (1968, 1969) conception of positional information. According to the classic theory, the establishment and interpretation of positional values are independent of each other: the cells are 'passive' in that they simply measure the morphogen gradient but do not themselves influence the developmental field. The classic theory, however, fails to account satisfactorily for important phenomena, including size regulation and developmental robustness. Using diverse experimental data, established in particular in *Drosophila* (Jaeger *et al.* 2004) and in neural tube patterning in vertebrates, Jaeger *et al.* (2008) show that positional specification actually depends on *regulative feedback* from responding cells. Most fundamentally, the relativistic theory of positional information suggests the existence of a dynamic metric that allows cells to measure their relative position within a developing field that itself changes in response to the activity of those cells. The authors then describe in more details this metric using the tools of dynamical systems theory. The take home message is that it is possible to explain and predict how cells during early development, far from being simple passive 'receivers' of a positional information coming from the morphogen gradient, participate actively in the process through feedback mechanisms that affect the developmental field.

What can be deduced from this specific example and other examples of developmental theories analysed in the course of this chapter? It seems now clear that establishing structured sets of testable explanatory and predictive hypotheses is a major goal of today's developmental biology. Indeed, we find in current developmental biology all the characteristic features of scientific theories identified above. First, developmental biologists try to *explain* and *predict*. Explanations usually take the form of the elucidation of *mechanisms*, often of a high level of generality. For instance, Jaeger *et al.* (2008, p. 3176) assert that their aim is to find a "precise, mechanistic understanding of regulative phenomena and developmental robustness" (see also Jaeger and Sharpe, this volume). They also draw consequences and predictions from their theory, in particular about how taking into account feedback mechanisms will impact our understanding of specific developmental processes. More generally, developmental biologists regularly make bold testable predictions (e.g., Maini *et al.* 2006; Sick *et al.* 2006; Bansagi *et al.* 2011). Second, developmental biologists give an important role to *testability*, meaning that they regularly try to test hypotheses and theories (e.g., Kuratani *et al.* 1999; Jaeger *et al.* 2004; Yu *et al.* 2009). In a recent and fascinating work, Collart *et al.* (2013) measured the abundance of replication initiation factors in *Xenopus laevis* embryos, with the explicit aim to test a hypothesis put forward in 1982 (Newport and Kirschner 1982). In their original paper, Newport and Kirschner (1982) sought to better understand the precise timing of biochemical events in early morphogenesis. Using

*Xenopus* as their system, they showed through precise experimental arguments that the timing of the midblastula transition (MBT) depended not on cell division, on time since fertilization or on a counting mechanism involving the sequential modification of DNA, but on reaching a critical nuclear to cytoplasmic (N/C) ratio. They concluded: “We can speculate that the nucleus may act only passively to titrate some component of the cytoplasm, the removal of which in turn could initiate several cytoplasmic events that collectively make up the MBT” (Newport and Kirschner 1982, p. 684). Thirty years later, Collart *et al.* (2013) tried to assess this hypothesis; they showed that four DNA replication factors (Cut5, RecQ4, Treslin and Drf1) function as key regulators of cell cycle duration during development, and thus are key for the MBT and more generally for the normal development of the *Xenopus*, confirming the hypothesis of Newport and Kirschner (1982). Third, *unification* is often an explicit goal of theoretical work in developmental biology. For instance, Wolpert (1994), reflecting on what the future of developmental biology would be, called for integration and for the identification of an ‘underlying logic’ of developmental processes (see also Jaeger *et al.* (2008) and Jaeger and Sharpe, this volume):

Almost certainly there will be new ways of integrating particular aspects of development, and so we will learn, for example, the logic underlying the apparently varied mechanisms for generating periodic structures and the reasons for the variety of mechanisms for setting up the axes in early development.

Along the same lines, McMahon (1974) emphasizes the importance of expressing many things about various developmental processes thanks to a very limited number of structuring statements, an idea expressed by many others in the field (e.g., Garcia-Ojalvo and Martinez Arias 2012).

We can conclude that current developmental biology offers theories in the sense suggested in this chapter, and that these theories express all the characteristic features of a scientific theory detailed above. But can developmental biology offer *a unique, general, theory for development as a whole*? I suggest that what is presently at stake in the field of developmental biology is not to find a single general theory of development (interestingly, in this volume, while Bard and Gilbert reject this idea, Jaeger and Sharpe make a stimulating attempt to construct a general theory of development, one rooted in dynamical systems theory). According to the perspective defended here, the aim is, rather, to construct several theories, in the demanding, but not too demanding, sense proposed above: theories should be structured sets of testable explanatory and predictive hypotheses. The identification or construction of several such theories will subsequently be the basis for *intertheoretic comparisons*. Let’s get back to our example of the relativistic theory of positional information to better understand how this process works. First of all, this theory is intrinsically in opposition to another theory, namely the ‘classic’ theory of positional information, thus expressing the kind of theoretical tension the importance of which is emphasized by Wallace Arthur (this volume). Second, the authors of this theory try to situate it with regard to other theoretical frameworks, including Turing’s morphogen gradient theory (Turing 1952; Gurdon and Burillot 2001) (this is ‘intrafield’ theoretical comparison, that is, comparison of theories within developmental biology). Third, the authors relate their theory with other biological theories, in particular instantiations of developmental systems theory in other biological fields (this is ‘intradomain’ theoretical comparison, that is, comparison of theories within biology). Fourth, they draw an interesting comparison between the move from classic theory of positional information to relativistic theory of positional information on the one hand, and the move from classical mechanics to Einstein’s theory of relativity on the other hand (this is ‘interdomain’ theoretical comparison, that is, comparison of theories between distinct scientific domains, here biology and physics). Two other important examples of intertheoretic comparisons are ‘evo-devo’ (a fruitful way to make progress in this domain will be through

the confrontation of *specific* developmental theories with *specific* evolutionary theories) and the elucidation of generic morphogenetic mechanisms understood thanks to physical theories (Newman, this volume). Ultimately, it is probably these kinds of articulations and confrontations that will lead to the emergence of general theoretical frameworks in developmental biology and beyond, and to an elucidation of what the evasive notion of ‘development’ means.

## Conclusion

Scientific theories should not be seen as the logical apparatuses depicted by many 20<sup>th</sup>-century philosophers of science, in particular through the syntactic and semantic conceptions. This chapter has suggested a more modest and practice-oriented conception of scientific theories, defined as structured sets of testable explanatory and predictive hypotheses. With such a definition in mind, it becomes clear that biology does offer theories, and can benefit from the important advantages associated with the formulation of theories (in particular, explanations, predictions, testability and unification).

As a matter of fact, even if current literature rarely mentions theories, developmental biology has always offered, and still offers, theories. In my view, one can say of developmental biology, word for word, what Scheiner and Willig (2008, p. 21) say about ecology: “pessimism about the theoretical foundations of ecology is ill founded: ecology has had a robust theoretical framework for many years. We ecologists simply have not recognized that fact, in part because we have misunderstood the nature and form of a comprehensive theory.” The taste for constructing theories in developmental biology should be regenerated, and in turn those theories will undoubtedly regenerate our understanding of development.

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	“Theory” in article title	“Theory” in article abstract
<i>Annual Review of Cell and Developmental Biology</i> (1985-2012)	0	2
<i>Current Opinion in Genetics and Development</i> (1995-July 2013)	3 (including two about the neutral theory of evolution)	27
<i>Current Topics in Development Biology</i> (1966-July 2013)	4	35
<i>Development</i> (1987-2012)	6	92
<i>Development Genes and Evolution</i> <sup>1</sup> (1894-July 2013)	6 (mainly in 19 <sup>th</sup> century papers)	NA
<i>Developmental Biology</i> (1959-July 2013)	2	32
<i>Developmental Cell</i> (2001-July 2013)	1	7
<i>Genes and Development</i> (1987-July 2013)	2	11
<i>Seminars in Cell and Developmental Biology</i> (1996-July 2013)	3	10

Table 2.1. Number of occurrences of the word ‘theory’ in the titles and abstracts of papers published in the main developmental biology journals. The first column indicates the name of the journal, as well as the period examined.

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<sup>1</sup> This journal has been published since 1894. From 1894 to 1923, it was published as *Archiv für Entwicklungsmechanik der Organismen*. Then, its name was changed five times. Since 1996, the journal is published under the title *Development Genes and Evolution*.

<b>Domain</b>	<b>Papers with ‘theory’ in title or abstract</b>	<b>Total number of papers in the domain</b>	<b>Percentage</b>
Applied Biological Sciences	6	791	0.76
Biochemistry	49	8513	0.58
Biophysics and Computational Biology	234	4046	5.78
Cell Biology	21	4172	0.50
Developmental Biology	5	1648	0.30
Ecology	106	1116	9.50
Evolution	180	2391	7.53
Genetics	32	4175	0.77
Immunology	10	3404	0.30
Microbiology	4	3039	0.13
Neuroscience	107	5839	1.83
Physiology	23	1509	1.52
Psychological and Cognitive Sciences	75	954	7.86
Systems Biology	9	146	6.16

Table 2.2. Number of occurrences of the word ‘theory’ in the titles and/or abstracts of papers published in the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* in each field of the biological sciences, between 1915 (first issue of the journal) and July 2013. The second column indicates the total number of papers published in each field, and the third column shows the percentage of papers having the word ‘theory’ in their titles and/or abstracts (Please note that papers in *PNAS* can sometimes be attributed to several categories).