

The epistemological resilience of the concept of morphogenetic field

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Dirty boots in metaphysical swamps

The concept of morphogenetic field (hereafter MF) was the central theoretical concept of the *Gestaltungsgesetze* research programme of experimental embryology in the first part of the 20th century. It was introduced by Boveri (1910) and Gurwitsch (1910) in order to account for the phenomenon of coordination of cellular activities across a tissue. Starting from 1922 the latter called them *Embryonalen Felder* (i.e. embryonic fields). Harrison (1918), Weiss (1926), Needham (1931), Huxley and de Beer (1934), and Spemann (1938), among others, defended versions of the concept (Gilbert et al., 1996). The analogy between the concept of morphogenetic field (referring to the putative biological property of groups of cells in developmental contexts) and the concept of electromagnetic field (referring to the epistemically accessible physical properties of groups of electrically charged physical particles) was probably meant to give prima facie respectability to the former. Mangold's and Spemann's (1924) transplantation experiments are a typical example of the kind of research propelled by *Gestaltungsgesetze*. Spemann (1935) labelled the MF *Organisationfeld* (i.e. organizer). The organizer was thought to be analogous to a physical 'force' external to the cells that makes them differentiate and assume the individual characters appropriate within the whole. This determining 'force' is not within the cell but is rather a holistic property of the transplanted tissue. So, despite its acknowledged physical nature, the MF concept challenged the prevailing mechanistic

and preformationist explanations of the phenomena of morphogenesis. The concept of MF was ultimately related to organicist (Haraway, 1976) and even vitalistic metaphysical positions (Hamburger, 1999).

Gilbert et al. (1996) argued that the emergence of developmental genetics is to be considered the main cause of the demise of the MF concept, for the reason that the gene and the MF were perceived as being concepts in competition. The difficult relationships between *Gestaltungsgesetze* and genetics meant, as Lawrence and Levine (2006: R236) recently argued, that 'embryology drifted off into metaphysical swamps, while genetics explored the dry savannahs of statistics'. The central theoretical concept of *Gestaltungsgesetze* remained indefinite. In order to explicate it, not very rigorous metaphorical language was often used (e.g. analogies with Newtonian forces or electromagnetic fields). Furthermore, the concept was used in different ways by different scientists in order to refer to different aspects of complex causal processes. Embryonic fields, organizers and morphogenetic gradients all referred to phenomena of developmental regulation. They were all postulated on empirical grounds in order to conceptualize specific morphogenetic dynamics. They all possessed a physical substrate and a biochemical nature that remained to be investigated and that was largely experimentally inaccessible. They were generally considered as areas of biological information that was not genetic in origin (Gilbert et al., 1996). They were, in brief, concepts referring to material and physical entities (or processes) that contained part of the organizational

information necessary for the regulation of morphogenesis. But, apart from this general definition, it is difficult to extrapolate the commonalities between the varieties of field concepts used. Haraway (1976: 55) notes that developmental biologists disagreed on the issue concerning the 'material status' of the MF. While for Harrison, Needham, and Weiss the substratum was clearly biochemical, Gurwitsch was not so clear, while Spemann considered a purely biochemical definition insufficient (Hamburger, 1999). Such conceptual idiosyncrasy contributed to the general perception that the concept of MF was elusive and mystical and that the *Gestaltungsgesetze* research programme was degenerative (in Lakatos' sense). The MF concept was gradually seen as the embryologists' phlogiston.

Lawrence and Levine (2006) have also argued that developmental biology must supersede, in the light of the available molecular understanding, the historical dichotomies that have plagued its practice. They specifically name four philosophical disputes: preformation vs epigenesis; vitalism vs mechanism; thinking of embryonic cells as preprogrammed vs thinking of them as totipotent; and mosaicism vs regulation. They argue that the conceptual distinctions at the basis of these dichotomies are today indefensible trivializations. We agree with Lawrence and Levine that, for instance, the dispute between preformationism and epigenesis has evolved and that, as a consequence, it is difficult to find a contemporary developmental philosophy that does not share some of the classical features of both positions. No experimental embryologist would today reject the significance of developmental genetics or refuse to characterize developmental processes in molecular terms. Preformationism and epigenesis might be thought of as *metaphysical research programmes* (an expression, intended without derogatory meaning, used by Popper (1992) to characterize Darwinism). They have no essences and change through time like biological species (Hull, 1988). However, accepting the strategy of molecularization does not solve in one stroke all the fundamentally metaphysical issues at the core of developmental biology. For this reason, we believe that the metaphysical swamps in which *Gestaltungsgesetze* supposedly muddled itself are still very squelchy in the molecular age.

Accordingly, in the next two sections the paper will tackle two metaphysical issues. In the second section the focus will be on developmental information. *Gestaltungsgesetze* implicitly defined the MF as an area of non-genetic embryological *information*. However, if the additional information does not physically reside in the nuclear material of the cell, where is it localized? We will consider this issue by analysing the nature of the concept of positional information originally proposed by Wolpert (1969). We will show that the concept of positional information was gradually 'geneticized' by Wolpert, concomitantly with his endorsement of the radical research programme of 'computational embryology'. We will argue that Wolpert's version of the science of morphogenesis (based on informational preformationism and the heuristics of computing the embryo) makes the concept of MF redundant.

In the following section the focus will be on three causal issues that need to be investigated when trying to understand the nature of morphogenesis: (i) How does the formation of a pattern—of a tissue—of an organ—start? (ii) What is the nature of the physical processes governing intercellular information exchange? (iii) What is the nature of the interactions between the components of the developmental system? The various models briefly presented in this contribution provide different answers to these questions because they are based on different metaphysical commitments concerning the nature of developmental causation as well as the nature of the MF. Indeed, we suggest that genuine progress in developmental biology is parasitic on the achievement of more clarity concerning the metaphysical issues we identify. Therefore, we suggest that, contrary to what Lawrence and Levine argue, developmental biologists, like all other scientists, still need to get their boots dirty in metaphysical swamps.

Developmental information

One of the assumptions of *Gestaltungsgesetze* is that the kind of biological information apportioned by the field is not genetic. It would be absurd to think otherwise because undifferentiated cells all have the same genes (what has been called the paradox of cellular differentiation, cf. Sapp, 2003: 181).

Morphogenesis for *Gestaltungsgesetze* was not a degenerative but an integrative process in informational terms. The task was therefore to account for the nature of the additional information necessary for developmental regulation. Does the additional information physically reside in the cytoplasm, in the internal environment of the developing embryo, or in its external environment? Is it localized somewhere in the first place or is it dispersed? In order to focus on these issues, we will concentrate on the concept of positional information introduced by Lewis Wolpert.

Return to Weismann

The rise of developmental genetics was eventually accompanied by the use of informational language in biology propelled by Crick (1958). The history of information talk in developmental biology is complex. In the book *What is Life?* Schrödinger (1944) famously suggested that development is regulated by a code-script structure. If there is a code, then there must exist, at least metaphorically speaking, 'information'. However, despite this implicit acknowledgment, Schrödinger does not explicitly use the term 'information'. Crick and Watson were probably first to introduce the term in genetics: 'it . . . seems likely that the precise sequence of the bases is the code which carries the genetical information' (Watson & Crick, 1953: 964). Crick (1958) then made this theoretical usage common and philosophically solid. The thesis that DNA contains the instructions to 'code' for proteins and mature phenotypes instead of contributing to 'causing' them is linked to a preformationist view of development, a reductionist view of science, a localized view of causation, and the thesis of the primacy of endogenous factors in biology. Sarkar (2005: Ch. 14) argues that Waddington was the first proponent of a synthesis of developmental biology and genetics based on the idea that genes are the primary source of information. Waddington, according to Sarkar, thought that regulation at the genetic level can explain tissue differentiation and morphogenesis: all these processes are basically a matter of switching genes on and off. Waddington's ideas reflected an informational and genetic *zeitgeist*. In roughly the same period Turing (1952) ventured on the developmental biology scene by making an important contribution

(see 'A clash of causal ideologies'), namely, introducing the concept of morphogen, an atomistic concept that became a competitor of the holistic concept of MF. Around the 1970s two other relevant contributions appeared in the literature on morphogenesis. First, Wolpert (1969) proposed the concept of *positional information* (henceforth PI) in order to conceptualize the process of pattern formation. Second, Crick (1970) suggested that diffusion is the physical process at the basis of intercellular coordination during morphogenesis (see 'A sinking model?').

The idea of PI is that cells have a positional value that is related to a cell's position in a developing system and that cells 'interpret' their positional value and differentiate in specific position-dependent ways. Regulation can be viewed in terms of the process of interpretation of PI. Initially the concept of PI provided an alternative to explanations couched in terms of genes. The phenomenon of spatial organization (i.e. that cells in a developing embryo seem to 'understand' where they are and 'know' how to differentiate in a coordinated and seemingly teleological manner) was generally considered as an insurmountable obstacle for accounts of morphogenesis based on the expression of genetic information. So, given that genes were not considered as carrying spatial information, given that a vitalistic explanation referring to the cognitive capacities of cells was out of the question, and given the popularity of information talk in biology, Wolpert introduced the concept of PI in order to refer to the spatial information required by developing cells. The concept was initially sufficiently vague as to remain interpretable in many physical ways, for instance as the information conveyed by a specific concentration of a diffusing chemical substance or as the information communicated by cells to other cells. Coupled with the French flag model—a representational device that enables to understand how genetically identical cells, by responding to different concentrations of diffusing chemicals in the embryonic context, end up assuming different identities symbolised by the characteristic colours of the flag—the concept of PI provided a theoretical framework to conceptualize the process of spatial regulation. Indeed, Wolpert thought that his framework was general enough to be unifying and supplying a new meaning to traditional embryological

concepts such as gradient, induction, and field. In synthesis, according to Wolpert, the MF of the *Ge-staltungsgesetze* was a variant of positional field.

But the PI concept was problematic from the outset. PI was based on the ability of cells to *estimate* their position within the embryo, that is, on the ability of cells to *interpret* PI. But nothing was known about such interpretive powers. The French flag model just said that cells *estimate* the concentration of a morphogen, *compute* the information provided by the gradient, and then change their fate. The anthropomorphic and information-processing language used by Wolpert should be considered metaphorical. Wolpert's model of morphogenesis constituted a theoretical model of the process of morphogenesis (Wolpert preferred to speak of pattern formation) that not only lacked an explanation of how cells *estimated* their position, but that was additionally naturally coupled to the simplest gradient model based on the diffusion of one morphogen, considered, with few exceptions (see 'A sinking model?'), too simplistic. The idea that the complexity of the variegated processes of pattern formation could be captured with models consisting of the diffusion of just one morphogen was considered a trivialization by Turing himself, who, certainly not a developmental biologist, only considered models with interacting morphogens as biologically realistic. Given these limitations, why did PI become such an important concept in developmental biology? Fox Keller (2002: Ch. 6) reckons that it was because, eventually, the concept of PI was interpreted in terms of genes.

The transformation of the concept happened, according to Fox Keller, between 1971 and 1975, and was an outcome of its original malleability. In 1971 Wolpert rejected the ideas that the genetic material provides the description of the adult and that 'if we understood cytodifferentiation or molecular differentiation then pattern would be explicable' (Wolpert, 1971: 184). This view was in line with the first proposal of 1969, particularly with the idea that it is the egg (and not solely its genetic material) that contains the instructions of a 'programme for development'. This constitutes an embryonic view of preformation, not a genetic one. The egg contains spatial information, and cells are able to estimate this not purely genetic information. But by 1975, in

a paper co-authored with Lewis, Wolpert seems to have changed his mind, embracing the strong research programme of computational embryology: 'A theory of development would effectively enable one to compute the adult organism from the genetic information in the egg. The problem may be approached by viewing the egg as containing a program for development, and considering the logical nature of the program by treating cells as automata and ignoring the details of molecular mechanisms' (Wolpert and Lewis 1975, : 14). Computational embryology is founded on the hypothesis that the egg possesses enough information to make an adult. In fact, Wolpert and Lewis argue, arguments that posit that such information mysteriously increases during development are 'not valid'. What needs to be added is simply that the egg does not contain a complete description of the adult but rather a genetic programme for making it (Wolpert & Lewis, 1975: 14). In fact, genes control cells' behaviour and account for their crucial developmental properties such as memory, competence and interpretation of PI: 'The system of genes controlling a cell provides it with a memory, and governs its behavior according to past as well as present circumstances' (Wolpert & Lewis, 1975: 19). Gene networks with around 100 genes might be complex enough, they argue, to generate complex structures like, for instance, the vertebrate limb. The methodological advantage of considering the programme in terms of gene control networks is that it can be characterized in logical terms. Understanding development in logical terms might have been a very appealing feature in an era in which cybernetics and computer sciences were in full explosion.

The crucial assumptions at the heart of computational embryology are, first, that the egg contains internally all the developmental resources it needs to build an organism; second, that these resources are genetic; and third, that they control cells' behaviour. While the first and second theses were part of Wolpert's theoretical framework from the start (i.e. 1969), the third was added later. Fox Keller's interpretation of Wolpert's developmental philosophy stresses the rupture between the original concept of PI and the programme of computational embryology, whereas, as a matter of fact, there are many continuities between the two. Despite acknowledging

such continuities, we argue that the genuine rupture is in assuming that genes control cells' behaviour, making cells causally redundant. Since 1975, Wolpert's model of morphogenesis effectively reduced the process of spatial regulation to the process of differential gene expression. The concept of developmental programme was subsumed under the category of genetic programme, and the concept of PI was subsumed under the category of genetic information. In the end, the problem of spatial regulation was subsumed under the problem of cellular differentiation, a view originally proposed by Weismann (1893).

Computing the embryo

In computational embryology all the major features that characterize classic preformationism can be identified: the egg contains a genetic programme (i.e. the latent preformed structure) for development that is complete and operates deterministically (i.e. it is an algorithm potentially allowing the computation of the adult organism, discarding the informational contribution of all non-genetic factors). The 1970s were possibly an over-optimistic period dominated by the misuse of information language (Kay 2000) and the assumed impending vindication of genetic reductionism. Wolpert's developmental philosophy is seasoned with such over-optimism. But this attitude was unjustified in the face of the conceptual void left by Wolpert's model of morphogenesis. In fact, the nature of the process by means of which cells interpret PI was totally unknown. Of course, Wolpert realized that this was the most problematic aspect of the conceptual framework he proposed: 'the least attractive feature of positional information . . . is that it places a great burden on the process of interpretation' (Wolpert, 1989: 3). If one considers cells as automata, as Wolpert and Lewis (1975) did, a clear problem emerges: for cells to be automata, a plan—a software—is required. Wolpert's (1989: 8) solution to the problem of how cells manage to build a pattern given specific positional values was to postulate such a master plan: 'A formal solution is that each cell contains a complete specification of the behaviour of every cell in every position. There must be a complete list of the cells that will differentiate as type A, and another list of those that

form type B and so on.' This radical and 'formal' solution is consistent with a form of extreme preformationism: all 'lists' postulated by Wolpert are presumably localized in DNA: 'there is some evidence that there may be a listing of the type postulated for the sensory bristles in *Drosophila*. There are 11 sensory bristles on the thorax of the fly which can be removed, often in pairs, by a series of mutations in the *achaete-scute* complex' (Wolpert, 1989: 8). It is also deterministic given that cells just follow automatically the rules set by the master plan. In effect, the concept of interpretation seems to be eliminated in favour of an automatism.

Wolpert's original aim was to supply a unifying framework in which it could be possible to translate in a 'rigorous' and 'precise' language idiosyncratic concepts such as fields and gradients. However, the concept of MF received a blow with Wolpert's proposal. The interpretation of the concept of MF as a kind of *positional field* lacks many of the characteristics of the original concept, particularly its holistic and non-genetic character. We argue that the 'geneticization' of the concept of PI, coupled with the over-optimistic expectations of the programme of computational embryology, effectively makes the concept of MF redundant for the reason that all the relevant embryological information necessary for all kinds of regulative developmental processes is thought to be specified in the genes. In its strongest form, the research programme of computing the embryo is based on the methodological simplification of considering position to be totally specified by DNA, because each cell contains a list of rules determining its behaviour. The original concept of PI contained two variables: the informational one and the interpretive one. However, by making interpretation equivalent to the processing of the genetic information encoded in the series of preformed lists with which every cell is supposedly endowed from the start, the interpretation variable is reduced to the information one. Thus, it could also be argued that, instead of providing a way to translate the concept of MF in biochemical terms, Wolpert's geneticized version of PI makes the concept of MF redundant. Thus, in their geneticized versions, the concepts of PI and positional field are rather the ultimate realization of informational preformationism in developmental biology (Mahner & Bunge, 1997:

Section 8.2.3.1). The nuclear DNA contains all the necessary information—the ‘programme’ that will underwrite a successful and normal developmental process. The cytoplasmic and embryonic environments are just negligible variables from this preformationist perspective. As Wolpert (1991) surmised, paraphrasing William Harvey: *ex DNA omnia*.

An important corollary of the view Wolpert endorses from 1975—with its emphasis on the programme of computational embryology and the geneticized version of the concept of PI—is that cells’ responses become causally irrelevant, that is, redundant causal intermediaries between the fundamental generative process (i.e. input) of gene expression and the fundamental effect (i.e. output) of morphogenesis. This point has also been highlighted by Rosenberg (1997), who argues that the aim of computational embryology is to understand how development can be fully explained through the identification of the relevant molecules and their rules of interactions. The basic idea of computational embryology is therefore to compute embryological output given only the macromolecular input relative to the components (i.e. nucleic acids and proteins) of the embryo, abstracting from the cell’s behavioural responses. As Wolpert (1994: 572) explained, computing the embryo ‘is a formidable task, for it implies that . . . it may be necessary to compute the behavior of all the constituent cells. It may, however, be feasible if a level of complexity of description of cell behavior can be chosen that is adequate to account for development but that does not require each cell’s detailed behavior to be taken into account.’ The level of description chosen by geneticizing the concept of PI is to ignore the interpretive variable and the nature of cellular responses. In Rosenberg’s (1997: 450) clear words: ‘Wolpert’s thesis must be understood as claiming that the function which renders the embryo computable will take us from macromolecules to organisms without having to pass through the way-station of a complete description of all the constituent cells.’

It must be acknowledged that, in its strongest form, Wolpert’s conceptual framework is capable of yielding a set of coherent answers to some of the questions concerning the nature of information and causation set in the introduction: PI is ultimately

assumed to be genetic information, actualized in the putative genetically determined lists all cells possess; cells are automata that compute rather than interpret PI; genetic switching is the triggering event that could be considered the proximate cause of the process of pattern formation; and genes are the prime movers of all developmental processes. At the same time, it must be highlighted that Wolpert’s framework is just a *formal conceptualization* of the morphogenetic process; that is, an idealized, over-optimistic simplification. Note that Wolpert and Lewis wanted to emphasize ‘the logical nature of the [developmental] program by treating cells as automata and ignoring the details of molecular mechanisms’. As Wolpert acknowledges today (Kerszberg & Wolpert, 2007), his conceptual framework does not provide a satisfactory model for understanding morphogenesis for at least two reasons: diffusion of morphogens is not the only physical process of information transmission between cells, and cells are not programmed automata. Computational embryology is based on the methodological assumption that the molecular interactions between cells are ‘logically’ secondary, even though they are, without doubt, biologically primary for most experimentally prone developmental biologists; and, second, in Wolpert’s model cells remained ‘black boxed’, with no attempt to answer the crucial question of how they were actually interpreting PI. In both cases, we suspect that the rationale substantiating such a position was that cellular processing and communication were until very recently beyond the reach of molecular methods. Wolpert (1994) in fact considered cellular complexity to be much greater than the embryo’s. Accordingly, genes assume the fundamental causal role in computational embryology, while cells simply act as causal proxies, dispensable because they represent an irrelevant intermediate hierarchical level between molecular input and organismal output. In its most extreme, geneticized formulation, the metaphor of PI masquerades as a preformationist and genetic reductionist bias that privileges the causal importance of the endogenous and rejects the role of context-dependence in developmental processes (Laubichler & Wagner, 2001). Informational preformationism commits what could be called the

endogenous fallacy, that is, the fallacy of considering gene sequences as determinants rather than as co-determinants of developmental processes (Gilbert & Sarkar, 2000).

We conclude our analysis in this section by suggesting that the basic limit of Wolpert's theory of morphogenesis might reside in its theoretical nature. The tension between proposing theoretical models and engaging in experimental work is well known. Meinhardt (Gordon & Beloussov, 2006: 110) states that the usual reception of his models was the following: 'First they were regarded as unrealistic or misleading: "cannot be". More or less abruptly this changed later into: "that is trivial, how else should it be?"' Analogously, the two major assumptions at the core of computational embryology (i.e. the 'geneticization' of the concept of PI, and the heuristic strategy of ignoring the causal role of extremely complex cellular responses) can be perceived as unrealistic as well as misleading. We also argued that they effectively made the concept of MF redundant.

Another way to spell out our suggestion is the following. Wolpert's theory of morphogenesis is partly couched in informational terms. Exploiting metaphorical informational terminology might be perceived as a way to avoid dealing with crucial causal issues. Accordingly, it could be argued that the model of computing the embryo was not accompanied by a serious attempt to delve into the causal issues we have identified in the introduction. The reason is straightforward in Wolpert's case: DNA is the prime mover of development. If DNA is the only causal agent, all the other causal questions we identified become uninteresting. In the following section we will show that the recent interpretations of the concept of MF we illustrate not only eschew information language but primarily deal with issues of causation.

Developmental causation

In the introduction we proposed three causal questions:

- (i) How does the formation of a pattern, a tissue, or an organ start? More specifically, what is the triggering event of specific morphogenetic processes?
- (ii) What is the nature of the physical processes governing intercellular information exchange during morphogenesis?
- (iii) What is the nature of the interactions between the components of the developmental system?

In this section we will try to give answers to these questions by partially analysing some historically relevant and contemporary interpretations of the process of morphogenesis. We will first analyse the causation involved in the source-sink model, using it as a kind of conceptual scapegoat and default model. We will then start to introduce, not in chronological order, conceptual complexity to this default model by considering contributions that led to the postulation of more complex causal interactions.

A sinking model?

Crick (1970: 420) proposed that diffusion might be the causal mechanism that could explain the nature of the 'embryonic fields' of the developmental literature. His source-sink model was theoretically simple: 'At one end of a line of cells one postulates a source—a cell that produces a chemical (which I shall call a morphogen) and maintains it at a constant level. At the other end the extreme cell acts as a sink: that is, it destroys the molecule, holding the concentration at that point to a fixed low level. The morphogen can diffuse from one cell to another along the line of cells.' The great advantage of the source-sink model is that the postulated causal process is familiar: the diffusion of a substance is an example of mechanistic causation via contact. The alternative proposed by some *Gestaltungsgesetze* theorists never seemed to be so easy to grasp (i.e. as it involved the downward causation exerted on the differentiating cells by a physically unlocalizable entity such as the MF). Crick substituted a holistic concept whose causal influence is difficult to conceptualize mechanically (i.e. the MF) but with clear reference (the organizational effect of the MF was experimentally observable) with an easily conceptualizable mechanistic concept with indefinite reference (i.e. diffusion of hypothetical chemical substances). After estimating the value of the diffusion constant, of the permeability of cellular membranes and of the time needed to set up a gradient,

Crick concluded that diffusion could work if the tissue width is around 30–70 cells, depending on the size of the cell. Embryonic fields of a millimetre or less are possible, but larger ones are not. The results are ‘striking’: ‘Even allowing for the very approximate nature of the calculations, the agreement with the figures given in the quotation at the start of the article is striking’ (Crick, 1970: 421). The figures referred to come from Wolpert’s first paper on PI (Wolpert, 1969), in which the latter suggests that most embryonic fields seem to involve distances of less than 100 cells. It is interesting to note that, at the time, Crick was one of the few supporters of Wolpert’s French flag model (Richardson, 2009: 661).

After illustrating the basics of the model, let us now analyse the nature of the answers it provides to the causal questions we posed above. Crick’s answer to our first causal question was that the triggering event should be identified with the time when the source (i.e. the founder cell of the field) starts secreting the morphogen. But Crick did not try to answer the question of why that specific cell starts secreting the morphogen at that specific time. Crick gave a clear answer to the second causal question: diffusion is the central physical process of intercellular communication. The third causal question was implicitly answered by assuming that all the causal interactions are molecular and mechanical, determined by the source-produced morphogens diffusing through the extracellular matrix and affecting cells’ behaviour.

Crick’s model can be criticized for three reasons: the first concerns the explanatory power of diffusion theory in biology; the second concerns the nature of the cellular response to morphogenetic inputs; and the third regards the universality of the process proposed.

Starting with the first, it should be noted that diffusion theory had been strongly criticized in biology since the 1930s. Agutter et al. (2000: 103) contend that the long-term success of diffusion theory in biology was due to the simplified and idealized nature of the causal framework it provided. However, it must be highlighted that Agutter et al.’s analysis mainly refers to intracellular rather than intercellular diffusion. This implies that the putative epistemological limits of diffusion theory can be considered deficiencies of Crick’s model only to a partial extent.

Passing to the second and third criticisms, it must be remembered that Crick proposed his model emphasizing that it was important ‘to make two reservations’. The first caveat concerned an already known problem: ‘Even when the gradient has been set up the cell has to recognize it’ (Crick, 1970: 421). This is the problem concerning the way cells process and interpret the morphogenetic input. Crick did not provide many clues on how to solve this conceptual and empirical problem, even though one could argue the following. His model is heavily based on Wolpert’s insights on PI. In ‘Developmental information’ we saw that eventually Wolpert’s conception of PI relied on the strategy of ignoring cellular complexity. This strategy is compatible with one important simplification Agutter et al. (2000) see in diffusion theory as applied to biology: cells are considered passive entities, but passive entities cannot be the actors of regulative processes like those observed in physiology and development for the reason that they require ‘sensors, effectors, information processing and feedback mechanisms’ (Agutter et al., 2000: 85). The way in which the information conveyed by morphogens is processed and communicated by cells could not be answered in 1970. It would therefore be preposterous to criticize Crick for this reason. However, neglecting the complexity of cellular responses was arguably a common strategy in developmental biology in the period in which Crick’s model was proposed.

The third criticism is related to the other reservation introduced by Crick: ‘There may be special cases, involving setting up gradients quickly over large distances (of the order of several centimetres) which may require other mechanisms’ (Crick, 1970: 421). This reservation concerned the limitations, but just in ‘special’ cases, of the process of morphogen diffusion in reaching the sink when the sink is very distant. In such cases Crick thought that additional processes of cellular signalling might be involved. The issue at this level was partly empirical (i.e. was the evidence in favour of Wolpert’s hypothesis that most fields consist of maximum 100 cells reliable enough?) and partly methodological (i.e. what was the theoretical rationale for deeming that a model so simple could be universal and causally primary?).

In retrospect, it should be stressed that Crick’s model has been recently confirmed experimentally

(Yu et al., 2009): it is henceforth not a sinking model. However, such experimental vindication must not overshadow the fact that the model is based both on a simplified account of cellular processing and intercellular signalling, and that these limitations might have implications concerning its putative universality and primacy. Furthermore, it could be argued that the idea of process universality and primacy itself is anachronistic in the light of current experimental evidence. First, Crick's model was proposed in order to account particularly for the dynamics of early embryogenesis, when the number of cells is low and the fields to be organized relatively small: in this context diffusion might work, but in the context of later stages of development it might not. Furthermore, and more importantly philosophically speaking, today a variety of ways are known by means of which groups of cells can differentiate and form specific tissues. Minelli (2009: 118–119), for instance, identifies four such ways: apart from inheriting the epigenetic state of their mother cells, cells could process the morphogenetic information from neighbours, engage in self-sorting, and participate in what Minelli calls the 'chorus effect', that is, 'the sustained, two-way exchange of chemical or electrical inputs between neighbouring cells'. Note that in Crick's model only the first two processes are taken into account. And also note that it is the latter in particular that evokes the traditional concept of MF (see 'The renaissance of a concept in two forms').

A clash of causal ideologies

Turing (1952) not only introduced the concept of morphogen in the literature, but he arguably proposed the first physically plausible model of morphogenesis (Fox Keller, 2002: 100). And he achieved this result by means of an extremely idealized mathematical model based on a number of biologically powerful simplifications. One of these simplifications concerned cells. In Crick's and Wolpert's models, morphogens diffuse and cells interpret their information. But in Turing's the details of the interpretive process remain irrelevant because cells are treated as 'idealized geometrical points', analogous to Leibniz's monads. The outcome is that the diffusion of morphogens is assumed to happen in

an embryonic context that is continuous and totally homogeneous. This is an unrealistic simplification, but it bore an unexpected fruit.

It must be emphasized that, even if this simplification had been part of Turing's original proposal, it is certainly not part of the most popular biological version of his reaction–diffusion model (Meinhardt & Gierer, 2000). Naturally, in the local activation–lateral inhibition model proposed by Meinhardt and Gierer, the reactors are cells. There is therefore a huge biological difference between the nature of the physical interactions that can be imagined between self-synthesizing chemical substances (i.e. Turing's actual model) and the nature of the physical interactions between chemical substances mediated by complex information-processing organisms like cells (i.e. all contemporary models based on Turing's mathematical insights). Also note that Wolpert and Lewis (1975:16) observed that Turing totally ignored the crucial process by means of which cells interpret new morphogenetic signals in the light of their developmental history. This is certainly true given that in Turing cells are totally black boxed. It is also true that computational embryology makes cellular activity totally dependent on genes, making cells cybernetic automatons (see 'Computing the embryo').

Nonetheless, the simplification bore an unexpected fruit in the sense that Turing's model offered a creative solution to our first causal question. When it is asked 'What is the triggering event of X, where X is a specific morphogenetic process (i.e. the formation of a pattern, of a body segment, of a leg)?', a variety of answers are possible. Within such variety a first rough dichotomy can be recognized: either a causal agent or initiating event is identified, or it is not. In the first case the answer to the question is 'classical': the attribution of causal responsibility to localizable entities or precipitating events is conceptually necessary in order to explain the emergence of the effect. In the second case the attribution of causal responsibility is not to some specific causal agent or event, but rather to the instability of the initially stable interaction dynamics; in this case 'causes' are distributed and unlocalizable. These two conceptualizations of causation represent a clash of causal ideologies (Fox Keller, 2002). Which one is preferable in the case of morphogenesis?

The great disadvantage of the first conceptualization is that it leads to infinite regress, apart from being compatible with incompatible biophilosophies. In the first respect, assuming there exists a triggering event implies the existence of an agent causing that event. We end up with the Aristotelian concept of the prime mover, where the prime mover has been traditionally associated either with an intelligent founder cell or with DNA. Delbrück (1971: 55), for example, argues that: “‘unmoved mover’ perfectly describes DNA: it acts, creates form and development, and is not changed in the process’.” In the second respect, assuming the existence of a prime mover does not tell us anything about its nature. A variety of answers are available: it could be the MF, or DNA, or the cell. These three answers could not be more different, as they have been respectively historically linked to three different biophilosophies: the MF to organicism, DNA to genetic reductionism, and the intelligent founder cell to vitalism.

The great disadvantage of the second conceptualization of causation is that it looks just like a partial explanation. Turing claims that it is a random disturbance that causes the instability of the homogeneous equilibrium in the embryonic environment which, as a consequence, causes the emergence of the pattern or morphological structure. This process is spontaneous and lacks the central control through agency. Or does it? At least, it remains always compatible with the postulation of an agent as the creator of the random disturbance. Furthermore, given that the order, form, and organization Turing tries to explain arise *de novo* in each generation spontaneously thanks to the amplification of random fluctuations and positive feedback processes, one might still wonder what is the evolutionary origin of this precise and robust sequence of events in the first place. But in Turing’s model the random disturbance that unsettles the homogeneity of the embryonic system is not temporally and spatially programmed. The localization of the random disturbance is not predictable: many cells could happen to be the source. It could be thus said that in Turing’s model causation is distributed and organization decentralized over the components of the system. The robustness of the morphogenetic process and its capability to resist perturbations is

based on this distributed logic. Nonetheless, the random disturbance has causal efficacy as it precipitates a self-organizing process: Turing’s analysis is appealing precisely because ‘it offered a way out of the infinite regress into which thinking about the development of biological structures often falls. That is, it did not presuppose the existence of a prior pattern, or difference, out of which the observed structure could form. Instead, it offered a mechanism of self-organization in which structure could emerge spontaneously from homogeneity.’ (Fox Keller, 1983: 515–516). In brief, Turing provided a powerful conceptualization of how structure can arise from undifferentiated material due to self-organization and without central planning and preformationist input. Thanks to Turing, self-organization became a respectable alternative biophilosophy.

We suggest that it is this ontological property of Turing’s model that makes it epistemically persistent and theoretically suggestive. Turing’s greatest achievement in biology might be considered the fact that he proposed a viable new conceptualization of one important aspect of the process of morphogenesis (i.e. the nature of the event triggering morphogen formation) by abstracting away from the details relative to the nature of genes and cells. Following Turing’s line of reasoning, there might be no need to conceptualize DNA as the prime mover of developmental processes, nor any need to think in terms of programmed or intelligent founder cells. Thus, Turing’s model provides a serious alternative to the preformationist, genetic reductionist, and vitalist biophilosophies that have traditionally dominated developmental research.

At the same time, it might also be added that Turing’s model remains naturally compatible with all these philosophical positions. For instance, in Meinhardt’s and Gierer’s model, genes are particularly important as the producers of the signalling molecules (i.e. morphogens), and this might be interpreted as compatible with the attribution of a primary causal role to genes in development. But it would be stretching the point too far, since, as Meinhardt reminds us, ‘Equally important is the interpretation of these signals’ (Gordon & Belousov, 2006: 7), and henceforth cellular behaviour. Turing’s model is therefore philosophically neutral despite being causally loaded.

The renaissance of a concept in two forms

All the conceptual models we have brought so far to the attention of the reader try to capture the *essence* of morphogenesis. Turing's reaction–diffusion model, Crick's source-sink model, and Wolpert's computational embryology are all instances of theoretical contributions that adopt powerful and inevitably partially misleading simplified auxiliary hypotheses in order to describe the 'logic' of morphogenesis. It is well known that mathematical and theoretical biologists have a penchant for simplicity, symmetry, and other aesthetical virtues. For instance, Meinhardt argues: 'signalling between cells requires the production and secretion of ligands, their reception by another cell and a signalling cascade to the nucleus. The assumption of a simple diffusion, however, is in most cases a sufficiently good approximation' (Gordon & Belousov, 2006: 8). In a recent review of Turing's model, Kondo et al. (2010: 1616) claim that 'the logic of pattern formation can be understood with simple models, and by adapting this logic to complex biological phenomena, it becomes easier to extract the essence of the underlying mechanisms'. One of the basic features of Turing's model, at least in the form generating the so-called 'Turing pattern' (Kondo et al., 2010: 1618) is that the morphogens interact. It is because of such interaction that the system becomes self-regulating and the embryo organizes itself. Crick's source-sink model (the causal model at the basis of Wolpert's account of morphogenesis) can be considered as the simplest form of a reaction–diffusion model in which the reaction term is removed (Kondo et al., 2010: 1617). This interpretation provides a straightforward way to capture one basic difference between Crick's classic source-sink model and Turing's. While in the source-sink model a morphogen diffusing from the specific location known as the source forms a gradient that provides PI to the cells in the embryo, thus producing a pattern/form programmed and determined from the outset, in Turing's model the gradient is rather the result of the interactions between morphogens which produce a pattern/form that is dependent on the feedback relationships between the reacting elements. In the actual model proposed by Turing, the reacting elements were two self-synthesizing morphogens diffusing across a continuous embryonic context. As

already pointed out, the model is therefore very idealized. But the 'logic' of the model remains intact whenever a non-linear wave is maintained by the dynamic equilibrium of the interactions between its constitutive elements. The real biological system could consist of more morphogens interacting, its constituents elements could be molecules, cells, circuits of cellular signals, or even other organisms (see Nyholm and McFall-Ngai, this volume), and the physical processes of biochemical information transmission could be diffusion, chemotaxis, 'chorus effect', or other mechanisms of cell signalling. Again, the 'logic' of the Turing model remains intact despite these biological refinements. After Turing, what was needed was more knowledge concerning the physical realization (i.e. molecular components and physico-chemical processes of interaction between them) of the developmental system he hypothesised. In the last 60 years developmental biology has advanced tremendously in this sense.

It has been suggested that a developmental system instantiates a Turing model if it includes a network with two self-regulating feedbacks (one enhancing and one inhibitory). De Robertis (2009) thinks that exactly a biochemical system of this kind regulates the development of dorsal–ventral tissue differentiation in the embryos of all bilateral animals. The developmental system De Robertis postulates obeys the logic of the Turing model; but what is most interesting is that such a system supplies a biochemical and molecular description of the classic MF concept, specifically a vindication of Spemann's organizer. De Robertis started to unravel the molecular nature of the organizer in 1991, and in the last 20 years he has advanced considerably in this task. The revived concept of organizer is defined as the reciprocal transcriptional control between two signalling centres localized in the ventral and dorsal sides of the developing embryo where, for each action on the dorsal side, there is a reaction on the ventral one: 'Self-regulation occurs because transcription of ventral genes is induced by BMP [bone morphogenetic protein] while transcription of dorsal genes is repressed by BMP signals.' (De Robertis, 2009: 925)

De Robertis's model is interesting because it provides an alternative answer to our second causal question. Turing considered only diffusion as the

process of transmission of biochemical information. This is because, in Turing's model, cells are black boxes, as they effectively were, so we argued, in Wolpert's computational embryology. But the formation of morphogen gradients over long distances (apparently an existing phenomenon) is a process that cannot be explained through diffusion dynamics alone. De Robertis and colleagues have established that field formation requires intercellular information signalling and cell-cell interactions. The basic point is that the simplified source-sink model with diffusion of biochemical information is abandoned in favour of a much more complex model in which a variety of proteins and molecules are involved in the process of intercellular signalling (see also Newman, this volume).

In the molecular era conceptualizing cellular communication becomes necessary in order to solve the puzzle of morphogenesis. Informational interactions between cells can be conceptualized in different ways. One traditional way is, of course, to avoid the problem by treating cells as black boxes (Turing). Another is to consider molecule-mediated interactions. In this latter case causation is reducible to interaction by contact (for instance mediated by signalling molecules). This is a standard view of causation that relies on mechanically understood physical processes and molecular interactions. This causal view is at the basis of the MF envisaged by De Robertis's model. But, are there any other conceptually viable alternatives to this model? As a matter of fact, Newman and Bhat (2009) propose that cells in an embryonic context act in certain circumstances as biochemical oscillators. This is relevant because, as they (Newman & Bhat 2009: 699) remind us, a 'key property of oscillators is their ability to become synchronized'. They then propose that the synchrony of biochemical oscillators is a possible physical process explaining the 'coordination of cell state . . . over a broad tissue domain, a phenomenon described in the older embryological literature as a "morphogenetic field"'. Minelli (2009: 119) labels this phenomenon a 'chorus effect' (see 'A sinking model?') stating that 'a developmental system that is suggestive of this mechanism is the insect wing disc, within which small clusters of cells within the disc progress through the cell cycle together, tightly coupled to

their neighbours, irrespective of their clonal origin', with reference to Johnston and Gallant (2002).

Returning to Newman and Bhat, what is interesting about this alternative interpretation of the concept of MF is the fact that it relies on a physical process (i.e. synchrony) whereby the physical interactions between the components of the system are seemingly not by contact but at a distance. Given the bad reputation action at a distance has in some physical quarters, a similar reaction to such claims might be expected in the biological community. However, the phenomenon of synchronized oscillation is well established in biology (e.g. Garcia-Ojalvo et al., 2004) and was not suggested in the first place by Newman and Bhat in its biological form. Nonetheless, they were the first, to our knowledge, to associate this process with the MF of the literature. Newman and Bhat believe that the explanation they provide is mechanistic. We would contend that it could be considered mechanistic if it were possible to identify the way in which the coordination effect they describe (i.e. between the oscillatory behaviour of the cells belonging to the field) were to be explained as instantiations of causation via contact through the transmission of some physical entities (e.g. molecules, chemical stimuli, electrical stimuli). But in this latter case cellular synchrony would not be genuine causation at a distance. In any case, the novelty of this approach, independently of whether cellular synchrony is a mechanical process or not, is its reliance on a clear alternative to diffusion dynamics. If it is indeed true, as it seems, that embryonic developmental processes sometimes require longer cellular distances than the maximum 70 cells calculated by Crick (1970), then cellular synchrony provides a suitable alternative to the various processes at the basis of De Robertis' model.

Ontologically speaking, the MF in this latter model is the effect of the synchronic oscillatory behaviour of the cells involved. Newman and Bhat (2009) ascribe this effect to a specific cause, what they call a developmental patterning module or DPM. DPMs are defined as a category of the toolkit genes supposedly constituting the pre-metazoan genome and that specify for characteristic molecules which, in turn, mobilize certain specific physical processes and, finally, produce specific effects (e.g. field formation) when applied on specific biological substrates

(e.g. the cells of a vertebrate embryo). They label as OSC (reference to oscillation) the DPM that causes the MF. OSC chemically consists of the interaction of characteristic molecules (e.g. Wnt, Notch and Hes); is physically realized by means of synchronous biochemical oscillation; and produces a MF when applied to the cells of a vertebrate embryo. Newman's and Bhat's model apparently mixes the self-organizing and systemic properties already found in Turing's and De Robertis's models with the allure of the action at a distance that preserves the holistic character of the original MF concept. Its novelty resides in giving an alternative answer to the second causal question we posed, an answer that is different from that provided by De Robertis but compatible with it.

Conclusion

In 'Developmental causation' the focus was on three causal questions. The aim was to show that understanding proximate causation in developmental biology requires exploring the metaphysical swamps Lawrence and Levine urge developmental biologists to avoid. In the conclusion of this contribution, our only constructive task will be to identify many of these open metaphysical questions while summing up our preceding analysis.

In the case of the first causal question, we identified a clash of causal ideologies: one could either assume a causative agent or accept that what causes the precipitating event is a random instability. In the latter case we appeal to self-organization: one cell just happens to start secreting a morphogen, or starts oscillating, etc. On the other hand, if we choose the first causal ideology, we need to postulate a specific agency. But what kind of agency? At this point, other metaphysical disputes emerge: the agent could be DNA as the creator of form, the MF considered as a holistic entity, or even the intelligent founder cell. The last response might be considered ludicrous unless we accept that cells are agents. The histories of embryology and developmental biology show that many attempts to understand regulation were based on the strategy of black-boxing cells, effectively nullifying their behaviour. To take an extreme case, Wolpert's solution to the puzzle of how cells interpret morphogenetic

information was to assume they are programmed. At the same time Wolpert constantly uses terms like 'record', 'compare', 'compute', and 'estimate' in order to describe the cells' abilities to interpret PI. The use of this teleological language is assumed to be largely metaphorical. But what happens if cells turn out to be processing and sensing organisms? First, cells would be considered cognitive, rational, possibly intentional agents (Shapiro, 2011). Secondly, the appeal to teleological behaviour on the part of cells, whose elimination presumably represents one of the central achievements of molecular biology, would be considered suspicious. *Pace* Lawrence and Levine, there remains a world of difference between treating cells as programmed machines and treating cells as interpreting agents. One could consider this contrast as identical to the classic debate between mechanicism and vitalism, but it would be partly missing the point as these philosophical positions have evolved. After all, some biologists have coined the oxymoron *molecular vitalism* (Kirschner *et al.* 2000).

The second causal question was traditionally answered by considering diffusion as the central physical process in morphogenesis. Molecular biology has enabled the study of cellular information processing and signalling. The answer to the second causal question therefore is also inextricably linked to issues concerning the nature of the cell. One outstanding issue concerns the nature of the physical processes necessary in order to comprehend cellular signalling, and whether such processes can be understood molecularly and mechanically. At the end of 'A sinking model?' we indicated that a variety of ways are recognized through which cells can process environmental information in order to co-ordinate phenogenesis (cf. Minelli, 2009: 118–119). It seems to us that the process of synchronized oscillation on the part of cells is, causally speaking, particularly interesting as it seemingly contravenes some of the most coveted intuitions concerning the mechanistic view of physical causation.

The third causal question concerned the kinds of interactions involved in the process of developmental regulation. It seems to us that De Robertis as well as Newman and Bhat eschew appeal to causal interactions such as holistic, top-down, or downward causation. In both models all the interactions

between the components of the system constituting the MF are molecular (e.g. protein–protein and protein–cell), ultimately mechanistic, and therefore reducible to the components’ level.

We suggest that a reductionist position labelled *molecular reductionism* is compatible with the two contemporary models we illustrated. Molecular reductionism includes as a special case genetic reductionism because it allows all molecular interactions, and not only those that pertain to the replication and transfer of genetic information. A similar view to ours, ontologically speaking, has been endorsed by Rosenberg (1997), who defended the reductionism inherent in computational embryology. However, we disagree with Rosenberg in a variety of respects. Rosenberg makes two additional claims with which we deeply disagree. The first is that understanding cellular behaviour is epistemologically irrelevant for a comprehensive theory of development (see ‘Computing the embryo’), and the second is that all the genuine generalizations of developmental biology will eventually make use solely of molecular concepts. Contrary to what argued by Rosenberg, we would only like to note that progress in developmental biology has been parasitic on increased knowledge concerning the mediators of molecular interactions, namely cells. It is simply not true that cells can be black boxed and treated as an irrelevant intermediate hierarchical level between the molecular and the organismal. Indeed, this whole contribution was founded on the realization—we believe historically grounded—that ignoring cells’ behaviour has been increasingly seen as a fundamentally misleading simplification in developmental biology. Furthermore, there are many good philosophical reasons to reject the epistemological legitimacy of purely molecular generalizations in developmental biology. The most general is that to assume that the molecular is the most fundamental ontological level in biology, and therefore the most fundamental level of biological analysis, are two controversial theses probably without sound metaphysical grounding. The second reason stems from empirical considerations: the same morphogenetic function can be molecularly realized in different ways, suggesting that morphogenetic function is developmentally more stable than its molecular basis (Laubichler & Wagner, 2001).

At the same time, the epistemological deficiencies of Rosenberg’s reductionism have no straightforward ontological repercussions in our opinion. In particular, we do not think that the obvious fact that developmental biology needs non-molecular concepts implies the causal primacy of function vis-à-vis its molecular realization or that it vindicates the attribution of causal powers to non-molecular properties and entities. Laubichler and Wagner (2001: 58) disagree, criticizing Rosenberg’s molecular reductionism, and denying that the fact that all developmental entities (e.g. morphological phenotypes, etc.) can be characterized in molecular terms ‘is opposed to the possibility that functionally characterized biological objects can have an autonomous reality’. Among such objects Laubichler and Wagner would include MFs. The nearest to an argument for this claim is the suggestion that the same molecular basis can produce different developmental outcomes in different developmental contexts. If this is the case, then, the argument seems to imply, the difference maker in causal terms is the developmental context (cellular and organismal) itself. But, we ask, are the developmental contexts identical at the molecular level?

The supposed centrality of the concept of MF for a theory of development depends on providing a satisfactory answer to two questions concerning their ontological nature. The first is: what kind of things are fields? Are they entities or processes? Causes or effects? Gilbert et al. (1996) define MFs as heritable developmental causal processes (i.e. homologous developmental pathways). De Robertis defines the MF interchangeably as a self-regulating system, a biochemical pathway, a positional information network and an extracellular biochemical network of interacting proteins. Laubichler and Wagner (2001: 63) seem to consider the MF as the holistic developmental context in which macromolecules interact in order to produce specific morphogenetic outcomes. Newman and Bhat (2009) describe the MF as the effect of the action of physical processes of synchronous biochemical oscillation on cells. It might be argued that the same kind of conceptual idiosyncrasy characterizing the historical interpretations of the field concept is represented in its contemporary interpretations. All these definitions have a sound molecular basis, but they

seemingly radically diverge ontologically, either considering the MF as a cause (Gilbert et al., Laubichler and Wagner) or reducing it to a mere effect (Newman and Bhat, De Robertis).

The second question concerns the evolutionary origin of the MF, an issue we did not even try to touch. At this level questions of proximate and ultimate causation (Mayr, 1996) mingle. Gilbert et al. (1996), De Robertis (2009), and Newman and Bhat (2009) all agree that fields are evolutionarily central, even though they might disagree about the way the MF is inherited: how is the robustness of the morphogenetic process achieved de novo at each generation unless it is genetically inherited? And do the 'teleonomic' features of the morphogenetic process cry for an explanation in terms of genes, programmes and agency? We would only like to report a lurking confusion concerning these partly metaphysical issues.

The concept of MF clearly shows some kind of epistemological resilience. Its renaissance provides a test case for evaluating epistemological issues concerning the nature of scientific change. Is the path of developmental biology progressive, at least in the sense of overcoming traditional dichotomies and metaphysical traps? Pace Lawrence and Levine, in this essay we have tried to show that, despite the undeniable advances of molecular biology, deep-rooted metaphysical questions remain without a clear answer. But this would not be particularly surprising if, as Feyerabend (1975) argued, the only way in which science can progress is by guaranteeing conceptual pluralism. It might be that the 'epistemological persistence' (Chang, 2011) of the concept of MF vindicates the function of conceptual pluralism in developmental biology. Its renaissance should therefore be welcomed.

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