

A POINT OF VIEW

POSITIONAL INFORMATION LIMITS THE SELF-EXPLAINING ENDEAVOUR IN MORPHOGENETIC THEORY (IN THE SENSE OF TURING)

Towards the understanding of the functioning of biological forms (1)

by

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ABSTRACT

The notion of 'positional information' with respect to morphogenetic theories is critically examined. We analyzed the significance of positional information in the original paper by TURING (1952) on morphogenesis through reaction-diffusion mechanisms. It is concluded that positional information is necessary to understand the emergence of biological forms, and hence limits the self-explaining endeavour of these forms. Moreover, it is suggested that positional information is necessary to understand some of the essential functions of biological forms, namely the functions of insulation and transport.

Key words : positional information, morphogenesis, biological functioning, reaction-diffusion models.

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INTRODUCTION

In 1952 TURING presented a paper on « The Chemical Basis of Morphogenesis » having the purpose of « discussing a mechanism by which the genes of a zygote might determine the anatomical structure of the resulting organism ». The paper, which appeared at about the same time that WATSON and CRICK (1953) postulated the double stranded helix model for the DNA molecule, acquired a comparable status in morphogenetic theory as the DNA model did in molecular biology. TURING provided a mechanism for pattern formation based on a model of two morphogens (in later studies expanded to three morphogens) reacting with each other and diffusing through a certain configuration of cells. These models were epithetically called reaction-diffusion models and were further elaborated by many other authors. They became especially famous after PRIGOGINE's (1967) comprehensive theory on color pattern formation in a special class of chemical reactions as discovered by BELOUSOV and ZHABOTINSKY (WINFREE, 1974). Biological applications of reaction-diffusion theory were successfully elaborated in the case of the formation and reorganization of tentacular structures in the coelenterate *Hydra* (GIERER and MEINHARDT, 1972), or in the case of the generation of color patterns resembling the patterns in the coats of various mammals or reptiles (COCHO *et al.*, 1987^{a,b}).

However, from the onset, morphogenetic theory was burdened with the apparently insoluble question of the nature of the so-called 'morphogens'. They are called « presumably chemical » by TURING, although they were « not intended to have any very exact meaning ». The most restrictive interpretation was offered by HARRISON (1987), who formulated the nature of morphogens as « autocatalytic substances producing themselves only by themselves », although these substances might be rather diffusible cells than molecules. In fact, already HÖRSTADIUS (1939, 1950) had pointed towards the involvement of chemical agents in the formation of embryological axes, as was inferred from experimental studies in echinoderm eggs. A full biochemical isolation and characterization of a substance with morphogenetic potential has been achieved very recently (THALLER and EICHELE, 1987, 1990). On the other hand, several authors stressed the need for structural constraints in morphogenesis (cfr. WADDINGTON 1968, 1969, 1970, 1972), which idea was crystallized in WOLPERT's (1969) notion of 'positional information'.

The purpose of this paper is to analyze the disputed notion (cfr. HARRISON, 1987) of 'positional information' and to reveal its significance in morphogenetic theory. We will emphasize its significance in the original paper by TURING (1952), as well as in later studies. We will pay special attention to one remarkable issue of 'positional information', namely the gravitational field of the earth, for the effect of gravity upon dorso-ventral polarization in amphibian eggs has long been a matter of debate for embryologists (reviewed in ALLAERTS, 1991). An ontological description of 'positional information' is inferred from HARRISON's (1987) essentialists definition of the morphogen nature, that results from the denudation of morphogenetic theory into the so-called 'kinetic preconception'.

Further we will show by some examples that the notion of 'positional information' is to be interpreted in its broadest sense not only to account for the com-

plexity observed among biological forms, but also to explain the functioning of these forms. To allow an integration of the concept of functioning of biological forms into morphogenetic theory, an integration that reaches beyond the level of intuitive perception, we will link up with THOM's (1974) ontology of the « logos of living beings », appearing as a « quasi-universality of certain functions and certain morphologies ». The latter position is believed to be helpful towards an understanding of the functioning of biological forms, as well as to a better understanding of the emergence of these forms, which is the final aim of morphogenetic theory.

A KINETIC THEORY OF MORPHOGENESIS

Recently, JI (1988) proposed a completion of the Watson-Crick model of genetic information, and called this the 'Prigoginian' form of genetic information. The latter concept refers to the so-called 'dissipative structures' of PRIGOGINE (PRIGOGINE, 1967 ; GLANSDORFF and PRIGOGINE, 1971 ; NICOLIS and PRIGOGINE, 1977), which according to JI (1988) would represent the translation of the one-dimensional information encoded in the DNA, into a spatial information field as this genetic information is expressed in the living cell. The idea underlying this concept refers to the kinetic conception of morphogenesis in ontogeny, for the first time explicitly formulated by TURING (1952). The model presented is also designated as a reaction-diffusion model (HARRISON, 1987).

The Turingian concept of morphogenesis

TURING (1952) demonstrated the principle of morphogenesis using the configuration of a ring of similar cells (Fig. 1a). It was shown that a given set of chemical reactions producing the morphogenetic substances X and Y, and the ability of these substances to diffuse from one cell to another, could be sufficient to produce inhomogeneity within the initially homogeneous ring of cells. Small departures from the equilibrium concentration could, after a lapse of time, for the above conditions, result in large concentration differences and the breakdown of homogeneity. If the substances X and Y were endowed with the ability to influence the cell morphology, this would also result in the formation of a certain morphological pattern. Mathematically, these patterns can be described by stationary waves if the dominant terms of the roots of the differential equations, describing the generation of the morphogenetic substances, are real. If the roots concerned are complex, however, the generation of travelling waves is the result. It is noteworthy that according to TURING the wavelengths not only depend on the chemical data, but also depend on the dimension of the ring of cells. Nevertheless, TURING defined some kind of 'chemical wavelength' as being « the limit to which the wavelengths tend when the rings are made successively larger » (TURING, 1952 ; p. 51). The mathematical construction of a 'chemical' wavelength afterwards became popular, for instance in the paper of HARRISON (1987) (see below).

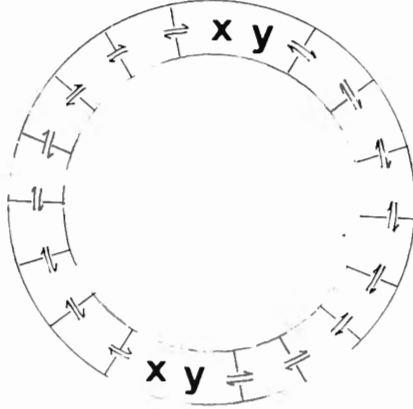
A

Fig. 1A. — Scheme representing the constellation used by Turing (1952) to explain pattern formation by a reaction-diffusion mechanism : a homogeneous ring of cells, containing the morphogenetic substances X and Y, that are able to diffuse from cell to cell.

B

B. — Early stages of gastrulation in the blastula of *Amphioxus* (after BALINSKY, 1981) : polarization in the initially homogeneous hollow sphere indicates the formation of the gastrulation axis.

TURING further demonstrated that other configurations could be also used as a model for morphogenesis, as for instance the hollow sphere of continuous tissue (cfr. the blastula) (Fig.1b). TURING suggested that the events resulting in gastrulation of the blastula could be described by using a similar analysis of reaction-diffusion on the sphere with only two morphogens, where « any small asymmetry of the zygote may be sufficient to provide the 'disturbance' which determines the axis (of the gastrulation) » (TURING, 1952 ; p. 71).

Harrison's Classification of Morphogenetic Theories

HARRISON (1987) envisages three main divisions of physico-chemical theory that are of interest to explain the self-organization of living organisms, namely the 'preconceptions' of structure, equilibrium and kinetics. These preconceptions all represent a 'phylum' of morphogenetic theories. Among the three phyla HARRISON considers the theory related to the 'kinetic preconception' as being most appropriate in explaining living self-organization, although the importance of the other phyla of theories is not clearly circumscribed.

The **structural theory** (cfr. LEHNINGER, 1970a) relates the generation of a certain morphology to the assembly of smaller parts into a larger entity (**self-assembly theory**). HARRISON considers the latter theory, designated as the preconception of molecular biology, to be only successful to explain pattern and form on the « spatial scale of viruses ». To the same phylum of morphogenetic theories HARRISON counts also the theories that provide explanations of cellular and multicellular organization through the cytoskeleton (HARRISON, 1987 ; p. 370).

On the other hand, **equilibrium theory**, which attributes form to the minimization of free energy, a preconception dating back to THOMPSON (THOMPSON, 1917), is considered to be definitely incomplete for living organisms are « intrinsically out of equilibrium in thousands of ways » (HARRISON, 1987 ; p. 371). Nevertheless, the latter phylum of morphogenetic theories is not totally neglected for some theories, such as that of STEINBERG (1970) on the assembly of cells by differential adhesion, are possibly of interest. Within this context, attention should also be paid to the contribution by THOM (1974), not mentioned by HARRISON, who integrated THOMPSON's preconception of minimization of free energy, into a more general topological theory of morphogenesis, taking advantage of the theory of catastrophes in mathematics.

HARRISON is most interested in **kinetic theory**, envisaging the generation of pattern and form by movement away from equilibrium, for the other theories apparently do not satisfy. He concludes that « most physical scientists adopt the kinetic preconception, because they see nothing else in all our philosophies » (p. 370) to « envisage living organisms non-vitalistically » (p. 370). « What else could do it? », he exclaims (p. 370). With regard to the biologists, HARRISON correlates their « distaste for mathematical explanations » to a deep, philosophically inspired, « reluctance to adopt the kinetic preconception » (p. 369). It would be far beyond the scope of this paper to treat POPPER's (POPPER and ECCLES, 1977) elaborate argument on the emergence of living self-organization, as an answer to HARRISON's query for a non-vitalistical explanation. In our opinion however, there is no philosophical reason for not considering the constructiveness of each of the three phyla of physico-chemical theory mentioned by HARRISON. A well known example of theories that account for integration of structural and kinetic preconceptions is found in BISSELL *et al.* (1982). BISSELL *et al.* (1982) and also GOODWIN and TRAINOR (1985) attribute an important role to the cytoskeleton and extracellular matrix on the one hand, and to diffusible and/or ionic components inside and outside the cells on the other hand, in directing gene expression.

THE SIGNIFICANCE OF 'POSITIONAL INFORMATION' IN MORPHOGENETIC THEORY

The concept of 'positional information' related to morphogenetic theory was first proposed by WOLPERT (1969). According to WOLPERT (1969), positional information is to be specified as the information represented by the position of cells with respect to one or more points in a system (constituting a co-ordinate system) (see below). The specification of positional information in general precedes and is independent of molecular differentiation. We will further expand this concept to account for all types of information from outside the cell, that precede and are independent of molecular differentiation. These may include other cells, a geometrical configuration, a certain field of forces, a certain temperature distribution, and so on. The significance of an expansion of WOLPERT's concept will be clarified by the subsequent analysis of HARRISON's (1987) criticism of 'Wolpertization'. In the late papers of WOLPERT (e.g. WOLPERT, 1992) positional information is defined as the coordinate position within the biological structure, which can be read off from the chemical or molecular concentration gradients within the structure. These gradients of molecular substances would in turn be encoded by the genes of the individual cells of the structure. To our opinion it may be instructive to distinguish between secondary mediators, i.e. molecules that affect gene transcription in a concentration-dependent manner, and so-called pre-existing vector fields, such as the gravitational field or the intra-uterine environment (ALLAERTS, 1991). The latter distinction is related to the distinction between pattern formation and axis formation, as previously mentioned (ALLAERTS, 1991).

Harrison's crusade against 'Wolpertization'

As we mentioned before, HARRISON's (1987) preoccupation with the 'kinetic preconception' is inspired by a dissatisfaction concerning other physico-chemical explanations. This preoccupation incites the author to elaborate an essentialist view of reaction-diffusion theory. Therefore, the « essential nature of a morphogen » (HARRISON, 1987; p. 372) has to be carved out of the semantics of the word morphogen, and in the first place, has to be discarded from connotations like 'diffusibility' or 'diffusion-driven instability' (MURRAY, 1982). HARRISON imputes the latter connotations to WOLPERT's (1969) concept of morphogenesis, where « an essentially passive signaller of information » is grafted « on a pre-existing pattern ». And HARRISON specifies: « Reaction-diffusion theory treats a different problem [than WOLPERT does]: it treats the origin of the distinction between source and surroundings » (HARRISON, 1987 p. 372). By putting forward the latter proposition, HARRISON has recourse to a distinctly metaphysical position. His reluctance to adopt the possibility of a « pre-existing pattern » ensues a reluctance towards any kind of 'positional information', giving rise to the metaphysical position mentioned. The key to the understanding of this « deep, philosophically inspired reluctance » (cfr. HARRISON's criticism against the biologists), is provided by the original paper of TURING (1952) itself, as we will demonstrate below.

The deep, irreconcilable contrasts between HARRISON's and WOLPERT's notions of morphogenesis, lead to the former's crusade against 'Wolpertization'. WOLPERT indeed has significantly contributed to the development of morphogenetic theory, and also has contributed to the discovery of some of the molecular cornerstones for morphogenesis, which are needed in modern molecular biology. One of these candidates for a molecular morphogen is *retinoic acid*, which has been shown to be able to induce a second polarization region in the developing wing of the chicken embryo, resulting in a doubled wing structure (THALLER and EICHELE, 1987, 1990). We borrowed the martial phraseology from HARRISON himself : « closely allied forces fighting on the same side, which is that of the kinetic preconception » (HARRISON, 1987 ; p. 371), and « of the two British tribes, I consider 'morphogen' to belong to the language of the Turingians, not the Wolpertians » (p. 375). However, « the warriors in the cause of kinetic theory » (p. 383), i.e. those who are of a like-mind to HARRISON, are not averse to the « popularity of positional information theory » (p. 375), which makes an alliance with the « Wolpertization of British developmental biology » as a first step « towards acceptance of the kinetic preconception » (p. 375). These statements indicate a certain pragmatism that would mitigate the seclusion resulting from HARRISON's metaphysical position, but this pragmatism is probably necessary to make the concept of 'chemical wavelength' work (see below).

Living Self-Organization, 'Chemical Wavelength' and Teratogenesis

To account for the self-organizing ability of living organisms, HARRISON (1987) inclines towards the definition of a morphogen as an auto-catalyzing substance. This latter substance needs not necessarily to be a chemical substance, for the cells themselves might be regarded as « a diffusible species, such as mesenchyme cells » (HARRISON, 1987 ; p. 374). To make the self-organizing system work, one also needs to extrapolate TURING's (1952) notion of 'chemical wavelength', to let this « chemical wavelength grow in proportion to the size of the system » (HARRISON ; 1987 ; p. 375), to make it independent from the system size. It is important to note that HARRISON's concept of 'chemical wavelength' is no longer a mathematical construction as it was in TURING's (1952) paper, but now became a true physico-chemical concept : therefore reacting chemicals ('reactants') in the reaction-diffusion processes are assumed to have constant concentrations, but it is accepted that these concentrations might vary between different positions within the morphogenetic region (HARRISON, 1987 ; p. 375). It is not clear whether HARRISON here admits the existence of a pattern preceding morphological differentiation.

An interesting implication of HARRISON's use of the notion of 'chemical wavelength' results from experimental studies on teratogenesis in response to the disturbance of normal development. Reaction-diffusion theory is hence able to account for malformations, such as, for instance, those observed in insect embryos that develop two abdomens after being damaged at what should have been the anterior end. However, these experiments either answer a question that differs from the question as to what are the determinant causes of a normal development, or

they would lead, among others, to the trivial explanation that the absence of damage is a determinant cause of normal development.

It is also noteworthy that HARRISON thinks of mesenchyme cells and not of neoplastic cells as examples of a 'diffusible species'. It is a tempting idea that reaction-diffusion theory might provide new insights into the problem of metastasis in tumorigenesis, but so far this idea has only a speculative value.

A View on the Origin of Positional Information in Morphogenetic Theory : the Egg of Columbus ?

According to TURING (1952) or WOLPERT (1969), an essential feature of the departure from homogeneity is the loss of symmetry, or the reduction of symmetry to a 'lower degree'. This means polarization. Examples are easily found in which the breakdown of homogeneity depends in some manner on 'positional information'. An experimental example of the influence of positional information on the development of cell polarity is given by ZIOMEK and JOHNSON (1980). In the latter study it was demonstrated that the development of surface polarity of the 8-cell blastomere depends upon intercellular contact. After polarization, intercellular features follow such as the flattening of the cells (compaction) and the formation of specialized junctions. 'Positional information' received by the developing cell considered in this case is to be interpreted as the close presence of the other cells.

Also, in TURING's most simple model, positional information is offered by the geometrical constraint of a ring-like configuration of cells and, in the advanced model, by the hollow sphere or blastula. The question is therefore shifted to an earlier situation, as to what causes the emergence of polarization in the 'most primitive cell', not to be confused with the zygote. This represents a variant of the well-known question expressed by the riddle of the hen and the egg : which of them was first ?

According to TURING, the question has even to be shifted to an earlier event in the evolution of living organization, namely to the emergence of left-handedness or right-handedness, i.e. to the origin of asymmetry in biomolecules. It is commonly accepted that once a choice was made between left-handed and right-handed stereoisomers, this preference was maintained throughout evolution, because of the template relationship between polynucleotide and polypeptide molecules (the template theory, cfr. LEHNINGER (1970b)). The choice of one of the two possible stereoisomers would be purely determined by chance.

Similarly, TURING provides an effort to assign the emergence of polarization in living organisms to 'random disturbances'. In a paragraph « definitely devoted to trained mathematicians », TURING (1952 ; p. 40) states that the laws of physics and the distribution of (mature) living organisms have apparently not the same symmetry. Leaving the technical aspect concerning the type of symmetry out of consideration, one can easily follow TURING, when he says that « men are more often found standing on their feet than on their hands » and « this may be corrected by taking gravity into account in the laws » (TURING, 1952 ; p. 45). This sentence is immediately followed by the extraordinary idea, that « it will be more convenient,

if, for the sake of argument, it is imagined that some species has been reared in the absence of gravity ». Indeed, gravitational force is one type of 'positional information' which is no longer mentioned in TURING's paper, but, on the contrary, 'random disturbances' are considered as the source of breakdown of homogeneity, as TURING concluded in the abstract of his paper.

One can summarize TURING's solution to the riddle of the hen and the egg by the following phrase : *The egg was laid without a hen, but there had to be no gravitational force !* However, we are now able to leave the meaning of this phrase behind, for it recently became clear that TURING indeed might have forgotten an important issue. Recent experiments have revealed the important role played by gravity upon the development of the dorso-ventral axis in the embryo of *Xenopus* (GERHART *et al.*, 1981 ; UBBELS and BROM, 1984). Experimental support for the role of gravity upon dorso-ventral polarization was achieved using rotation and centrifugation experiments in monospermic *Xenopus* eggs (GERHART *et al.*, 1981) as well as in fertilization experiments of these eggs during spaceflight (UBBELS and BROM, 1984). However, various experimental studies in mammals (ALDEN, 1945 ; SMITH, 1980) have indicated that gravity in itself was not the responsible agent for directing axis formation in the mammalian embryo, but that an assumed gravitational axis could be perceived by the developing embryo within the uterus (reviewed in ALLAERTS, 1991). Recently, it was also suggested that an enhanced cell proliferation and diminished cell differentiation might result from the absence of a 'normal' gravitational field, as the latter effects were invoked to explain a diminished maturation of lymphocytes (COGOLI *et al.*, 1984) and a weaker immune response in astronauts after a prolonged stay outside the earth's atmosphere (BATKAI *et al.*, 1988). Though speculative, these ideas might emphasize the importance of a 'normal' gravitational field upon different aspects of the ontogenesis of living organisms (ALLAERTS, 1991).

POSITIONAL INFORMATION AND THE FUNCTIONING OF BIOLOGICAL FORMS

In the previous paragraph, we treated various examples of 'positional information' considered as structural constraints in morphogenesis through reaction-diffusion models. The above idea allows environmental factors to play a role in developmental processes, a phenomenon well known to result in the interaction between phenotype and genotype. The notion of positional information is also related to GOODWIN's (1987) concept of 'morphogenetic fields', which are defined as « fields in which electrical, mechanical and chemical properties are combined in a particular manner, resulting in a spatio-temporal system (...) with the capacity to perform the mechanical work that underlies morphogenesis » (GOODWIN, 1987 ; p. 337). GOODWIN states that « these fields can generate ordered spatial heterogeneities that can influence gene activities, resulting in so-called harmonic patterns, but, in turn, gene products can also influence the morphogenetic fields » (GOODWIN, 1987 ; p. 337). However, WOLPERT's (1969) remark concerning the notion of 'positional information', as « preceding and being independent of molecular differentiation »,

is not devoid of importance, as we just stressed the fact that certain fields of physical forces (e.g. gravity) entirely independent from and preceding living organization, are able to influence morphogenesis.

To answer the question whether an ontological definition of 'positional information' in terms of a physico-chemical reality can be provided, we first have to offer a general specification of the notion of 'information' as provided by THOM (1974). It will thereafter be shown that THOM's conceptualization of 'information', applied to the notion of 'positional information', offers interesting perspectives to account for the 'functioning' of biological forms. The possibility of an ontological definition of the functioning of biological forms is discussed in the light of THOM's (1974) definition of «logos of living beings». An example is provided in which reaction-diffusion theory not only accounts for pattern formation in biological forms, but also explains some typical biological functions. Moreover, the idea presented here will shed some light on the paradox mentioned by GOODWIN (1987) concerning the «stability of nature» and «natural forms».

The 'nature' of positional information

Essentially 'positional information' has to be regarded as 'information'. With regard to living organization, according to JI (1988), it is an essential feature «for the living cell to possess the ability to transmit (genetic) information in time (e.g. from parents to progeny) as well as in space (from nucleus to extracellular space)» (JI, 1988 ; p. 239). The concept of 'transmission of information' is also the subject of communication theory (cfr. the Shannon-Weaver concept of information) (PIERCE, 1980) of which, according to JI (1988), one of the most fundamental aspects is that «the amount of information carried by a given message is determined not by the intrinsic properties of the message itself but by the property of the message source called the 'entropy of the source'» (p. 239). However, THOM (1974) cautions against the equation of the concept of information with its homologue in communication theory (in the sense of Shannon-Weaver), for this might result in the omission of information source and destination, and retain only an interest in the properties of the communication channel. Moreover, THOM objects to the probabilistic definition of information (in the case of biological forms), identifying information and 'néguentropie', for «the thermodynamic equivalent of spatial forms generally is not known or even not defined...» (THOM, 1974 ; p. 187). However, the probabilistic notion of information does have some value, according to THOM, for it conceals a relationship «connecting the rarity of the initial conditions of an instable process with the topological complexity of the resulting situation» (THOM, 1974 ; p. 188).

Concerning the information conveyed by living organisms, THOM states that the living organism itself is the 'locutor' of the information, or, «the natural morphology has to be considered as a message emitted by a fictive source toward the observer, e.g. the scientist» (THOM, 1974 ; p. 184). Quite differently formulated but essentially the same idea is expressed by GOODWIN (1987), stating that organisms should be understood as «instances of a particular state of organization of matter

that is inevitable because it is possible, and the conditions for its appearance exist on Earth » (GOODWIN, 1987 ; p. 331).

From the latter statements we can infer an 'ontological' definition of 'positional information to living organization' as the spatio-temporal system consisting of physico-chemical properties of either inanimate or animate (other living organizations) nature, that provide the conditions for the appearance of the living organization. The content of such a general definition of course suffers from vagueness, but the definition does not exclude the possibility of a minimal number of conditions for the appearance of a certain morphology. As a consequence, since the complete set of possible physico-chemical properties is in itself no longer a physico-chemical property strictu sensu, the above definition of 'positional information' limits the self-explaining endeavour of living organisms regarded purely as physico-chemical systems (cfr. HARRISON, 1987). To explain living self-organization, it therefore seems necessary to consider a physico-chemical system plus information which does not depend on the physico-chemical system. The latter statement recalls an analogy to Gödel's argument on the consistency of (mathematical) formal systems (as a reaction to the Hilbert program) (HOFSTADTER, 1979), and therefore can be considered as a kind of Gödelian argument applied to the biological sciences.

Interaction between form and function in morphogenesis : some examples

Before we proceed onto the nature of biological functions, we will first cite some examples of reaction-diffusion models applied to the genesis and functioning of biological forms. The first example is a well known application of morphogenetic theory, namely the generation of color patterns as in the coat of mammals or reptiles (COCHO *et al.*, 1987^{a,b}) ; the second example is related to molecular diffusion phenomena in biological materials (WEINBAUM *et al.*, 1988 ; WEN *et al.*, 1988 ; ALLAERTS *et al.*, 1990).

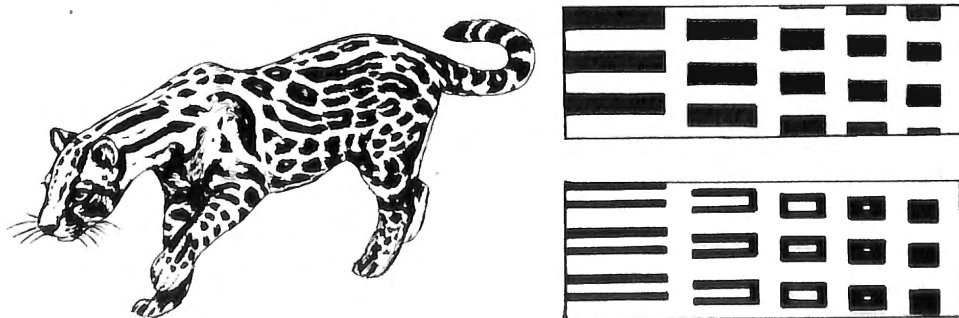


Fig. 2. — This figure should be seen as an exercise : the aim of the exercise is to produce a pattern of spots and stripes resembling the coat pattern of the ocelot (left), by increasing the number of geometrical gradients in a field of black and white rectangles. The right panels give some examples of these gradients (Idea borrowed from COCHO *et al.* 1987^b).

Concerning the first example, it was demonstrated that a minimal number of 'structural and dynamical constraints' (cfr. WADDINGTON, 1968, 1969, 1970, 1972) were indeed sufficient to produce patterns such as the stripes and patches in the fur of mammals and in the integuments of reptiles and fishes (COCHO *et al.*, 1987^{a,b}). The structural and dynamical constraints concerned were differential cell adhesion on the one hand (i.e. short range interactions between cells, due to the macromolecules present at the cell surface) and, on the other hand, the diffusion of chemicals (representing the long range interactions). With regard to the coat patterns of mammals, however, the following remarks can be made. If reaction-diffusion models are able to reproduce some handsome patterns, these patterns still are not identical to the real patterns present in the furs of living ocelots, jaguars, ... mentioned by COCHO *et al.* (1987^b) (Fig. 2). Moreover, these reproductions of patterns apparently lack the dimensions necessary for the understanding of their functioning as well as their genesis and stability. It is not anymore mentioned that these color patterns are formed by many millions of hairs, and that the specific regions of these hairs producing the coloured pattern, vary from one species to another from somewhere at the hair root to somewhere at the hair tip. This feature is nevertheless important with respect to the stability of the pattern, for wearing of the hairs would damage them and destroy the pattern. (Therefore, the fur also consists of coarse protective hairs, as well as the thin hairs that produce the basic color tints). To account for the generation of the above patterns, information is needed concerning the regulation of the successive time periods of the hair growth cycle, for moulting of the fur results in a periodical renewal of all coat patterns, as well as of the successive periods of pigment deposit that cause the banded patterns of the individual hairs and finally the color patterns of the coat. An example of the interaction between diffusion processes and anatomical constraints in the renewal of coat patterns at moulting is illustrated in ALLAERTS and VANDEVELDE (1984).

We previously stressed the need for 'positional information' to understand the genesis of biological forms (ALLAERTS, 1991), and, the present example also illustrates the need for 'positional information' to understand the functioning of these forms. The color patterns reproduced by COCHO *et al.* (1987^{a,b}) only represent a geometrical aspect of the complex forms underlying the pattern. The most important function of a pattern of patches and stripes is to make the animal less visible in a certain environment, called 'mimicry'. 'Positional information' has been necessary to produce that pattern, for the geographical constraints imposed on the mechanisms of natural selection make part of the conditions for the appearance of that type of organization. To understand the functioning of the mammalian fur however, as, for instance, the fur's insulation, these color patterns probably represent one of the least important features. Indeed, it has been shown that for a wide range of mammalian furs with colors from white to black, the emissivity, i.e. a physical parameter that determines the magnitude of heat radiation, is almost equal to unity in all cases (HAMMEL, 1956). Hence, color patterns are rather unimportant features to heat radiation. Ironically, an equivalent of reaction-diffusion theory might offer the tools for understanding some of the insulation properties of mammalian furs, for the heat transfer processes are described in terms of conduction

(diffusion)-convection-radiation (HUTCHINSON and BROWN, 1969). As schematically represented in Fig. 3A the heat transfer processes depend on both environmental parameters and structural elements of the integument. The latter example illustrates the relevance of 'positional information' to understand insulation phenomena in

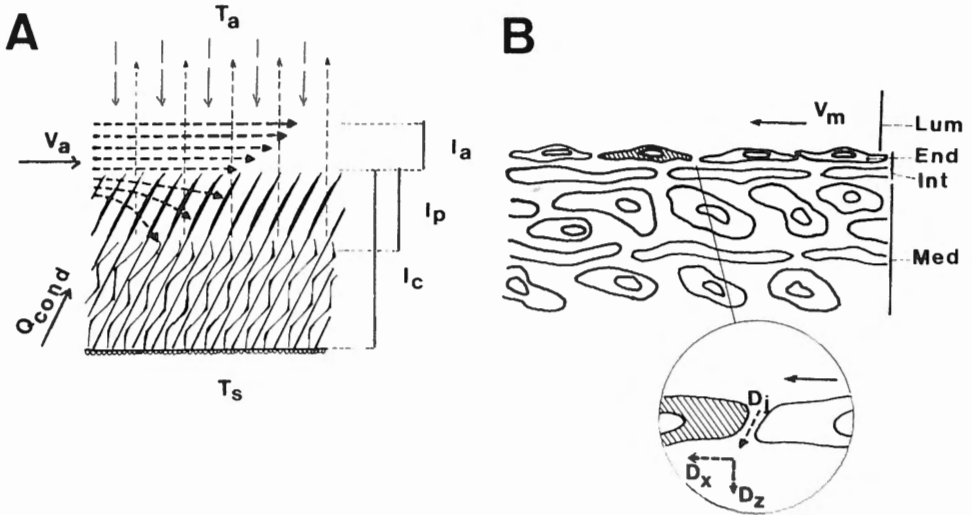


Fig. 3. — A. — Scheme representing the main constituents of a mammal's coat (skin, protective hairs and wool hairs), the main environmental factors affecting thermal insulation (T_a , V_a) and the main components of the insulating barrier (I_a , I_p , I_c). A 'gestalt switch' enables one to see the insulating phenomenon in a different way, by describing the transport processes (conduction, irradiance and air transport) rather than the insulating barrier [sum of components I_a , I_p and $(I_c - I_p)$].

I_a : (thermal) insulation of air cushion; I_p : 'penetrance' of the fur (after HUTCHINSON and BROWN, 1969); I_c : total insulation of the coat; T_a : radiating (absolute) temperature of the air; T_s : radiating temperature of the skin; Q_{cond} : conductive heat transfer across the fur; V_a : velocity of air motion outside the fur; $\cdots\cdots\rightarrow$ irradiance from environment; $\cdots\cdots\leftarrow$ irradiance from fur; \longrightarrow transport of air, outside and inside the fur.

B. — Scheme of transport phenomena occurring in a blood vessel wall (modified after WEN *et al.*, 1988). A simplified anatomical reconstruction of the vessel wall indicates the following parts: Lum: lumen; End: endothelium; Int: intima (inner layer of vessel wall); Med: media (outer layer of vessel wall). The main components of the latter two parts are the smooth muscle cells and elastic laminae. Some endothelial cells are currently undergoing mitosis (hatched), resulting in the formation of a leakage site with respect to the neighbouring endothelial cells that form 'normal' junctions with each other (WEINBAUM *et al.*, 1988; WEN *et al.*, 1988). An 'environmental' factor imposed on the molecular transport across the vessel wall is the fluid motion in the vessel lumen (V_m). The diffusion process is characterized by the 'effective' diffusion coefficients of the intra-endothelial cleft (D_j) and of the sub-endothelial medium in lateral (D_x) and normal direction (D_z). These effective diffusion coefficients are function of the molecular species and local 'microviscosity' of the medium. Hence, reaction-diffusion theory here accounts for diffusional motion and molecular adhesion effects.

biological materials, for indeed this can be considered as a boundary-condition problem in reaction-diffusion theory.

Examples are easily found within other domains of the biological sciences, where equivalents of reaction-diffusion theory offer the appropriate tools for the understanding of the functioning of certain morphologies. We recently used diffusion theory to treat the problem of the transport of a certain hormonal signal through a tissue-like configuration of cells obtained from the pituitary gland (ALLAERTS *et al.*, 1990). Moreover, reaction-diffusion theory has some value in quantification of cell functioning, such as hormone secretion, at the level of individual cells (ALLAERTS *et al.*, 1988). Other examples have recently been described, using a combination of diffusion and forced flow to study the permeability of blood vessels to macromolecules (Fig. 3B), resulting in a renewed theory on the genesis and functioning of the blood-brain barrier (WEINBAUM *et al.*, 1988 ; WEN *et al.*, 1988). Transport functions within living organisms are indeed the subject of growing interest. One special example, the transport of neoplastic cells through an organ at metastasis, is only one of the challenging problems facing the medical enterprise of today.

Can the 'functioning' of biological forms be defined in ontological terms ?

Essentially, the two following functions can be recognized in the examples presented above : that is 'insulation' in the first example and 'transport' in the second example. These are not merely arbitrary and independent examples, for the function of 'insulation' also implies 'insulation against transport', and 'transport' implies 'movement across an insulating barrier'. Both functions are related just as 'movement' is related to 'inertia'. The only difference with the latter duality, is that it requires the presence of a medium of matter. The nature of the substance being transported might be 'heat' (i.e. in the case of thermal insulation), or a chemical substance (i.e. in the case of insulation against molecular diffusion). In both cases the mathematical formulation of the transport process is approximately the same, i.e. the transport processes are described by the same differential equations. Therefore, the standard work of CARSLAW and JAEGER on « Heat conduction in solids » (1959) is also a standard work for physicists investigating molecular diffusion. The importance of 'insulation' for living organization is not only known by cellular biologists (cfr. the role of the cell membrane), but is also reflected in the following passage from Vladimir Nabokov's « Pnin » :

« I do not know if it has ever been noted before that one of the main characteristics of life is discreetness. Unless a film of flesh envelops us, we die. Man exists only insofar as he is separated from his surroundings ».

The above idea of insulation or discreetness found its way into physiology and cellular biology, as for instance the notion of compartmentalization was considered as an important feature in tissue homeostasis (ABBOTT, 1988), and compartmentalization of the extracellular matrix was proposed to play an important role in directing gene expression at the cellular level (BISSELL *et al.*, 1982).

If insulation and transport are two major aspects of the functioning of biological forms, can we then define them in ontological terms? According to THOM, the «logos of living organisms» appears as a «quasi-universality of certain functions and certain morphologies» (THOM, 1974; p. 207). One might feel somewhat uneasy with the Platonic definition of a «morphology that in the time tends towards a stable and invariant limit form» (THOM, 1974; p. 13), a definition used by THOM to designate the concept of «asymptotic chreode», which was introduced to extend the notion of chreode first formulated by WADDINGTON (1940). In the terminology of THOM (1974), a morphology is represented by the closed environment of catastrophes (discontinuities) in the product space of 'Space box' (\mathbf{B}) x 'time' (\mathbf{T}). The chreode then is postulated to account for the isomorphism between morphologies, for the open environment (\mathbf{U}) on $\mathbf{B} \times \mathbf{T}$ supporting a morphogenetic field (\mathbf{F}) can be depicted by the relation $\mathbf{G} : \mathbf{B} \times \mathbf{T} \rightarrow \mathbf{V}$ upon the abstract space (\mathbf{V}) with same dimensions as \mathbf{U} , in which a standard closed environment of catastrophes (\mathbf{J}) is provided. In that case the morphogenetic field is called a chreode (THOM, 1974; p. 13). A Platonic element in Thom's concept of morphology, is that he defines the isomorphism of the closed environment \mathbf{K} of catastrophes as being the inverse image \mathbf{G}^{-1} of the standard environment \mathbf{J} or $\mathbf{K} = \mathbf{G}^{-1}(\mathbf{J})$. Or, the observed 'form' (\mathbf{K}) is the inverse image of a standard (ideal) (!) form (\mathbf{J}), just as the inverse images appearing on the wall of Plato's cave.

It is important to mention that in the terminology of THOM, the concepts of form (morphology) and function are closely related. Though THOM unfortunately choose a bone as an example of a 'stable limit form', the above definition of «logos of living organisms» indicate that the stability resides in the entity that appears either as 'form' or as 'function'.

The latter idea is also found in the paper of GOODWIN (1987) on «The Stability of Nature», where the author expresses astonishment concerning the morphological stability of ciliate protozoa of the genus *Tetrahymena*, but however all are distinguishable with respect to macromolecular composition. This example and others make GOODWIN conclude that similarity of form does not necessarily depend upon similarity of molecular composition, just as the «characteristic spiral motion of a liquid flowing down a plughole does not depend on whether the liquid has molecular composition H_2O or C_6H_6 or $\text{C}_2\text{H}_5\text{OH}$ » (GOODWIN, 1987; p. 326).

Indeed, as was emphasized by THOM, the stability of form cannot be explained in terms of the composing elementary particles, but resides in an entity, designated as 'algebraico-geometric', «endowed with the property of structural stability with regard to the incessant perturbations affecting it» (THOM, 1974; p. 205). THOM here refers to the metaphor of Heraclitus, regarding the universe as the πάντα 'φεί, the universal motion depicted as a stream of water. The metaphor resurges in morphogenetic theory in the formulation of EDELMAN (1984) as «the stream flowing over a rock which is below the freezing point : accumulation of ice at first disturbs the stream only in minor ways, but eventually splits it into two branches». The functioning accompanies the form, just as the bed and the rock guide the stream of water (cfr. EDELMAN), or the plughole guides the spiral motion of water flowing down through it (cfr. GOODWIN). A 'Gestalt switch' is necessary to separate

form and functioning, or in abstract 'Thomistic' terms, to separate 'signifying' and 'signified/signification' (THOM, 1974 ; p. 197) (see Appendix).

Concerning the functions mentioned above, namely 'insulation' and 'transport', it is now clear that they can only be described in terms of 'insulation/transport within/through a certain environment', i.e. they can only be described in terms of 'positional information'. We may conclude that positional information not only is necessary to understand the emergence of biological forms, but also to understand the functioning of biological forms.

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APPENDIX : Definition of biological function in topological terms

It is important to clarify some of the misunderstanding that may arise from the interpretation of « function » as (biological) « effect ». In our opinion, this viewpoint is expressed in the assertion that « form precedes function » (De Loof, 1993). From the writings of THOM (1969, 1974), it is clear that « stable limit forms » are not primarily to be interpreted as the result of some biological process after differentiation and/or maturation of a biological object, being a macromolecular complex, a cell or an organ. A better understanding of the function notion is gained from the concept of « reification », used by JI (1988) to indicate the effectuating of the genetic information at the cellular level, and that is also called the intracellular dissipative structure (for a discussion of JI's argument see also ALLAERTS, 1992).

In general, biological functions can be related to the concepts of aptation and fitness (PRANGER, 1990), which approach allows for the incorporation of evolutionary-biological principles and causal reference into the biological function notion (NISSEN, 1970, 1971 ; PRANGER, 1990). In topological terms, and referring to THOM's (1974) definition of an asymptotic chreode, the biological function notion is related to an inverse mapping relation \mathbf{G}^{-1} , imaging aptations (\mathbf{A}_i) onto the developmental process represented in the subspace \mathbf{W} of space-time \mathbb{E}^4 :

$$\mathbf{G}^{-1} : \{\mathbf{A}_i\} \rightarrow \mathbf{W} : \mathbf{W} \subset \mathbb{E}^4 \quad (1)$$

As biological phenomena can be parametrized in a local domain $\mathbf{B}^3 \times \mathbf{T}$ of space-time \mathbb{E}^4 , the developmental representations (\mathbf{F}) of biological phenomena are in turn characterized by the mapping relation :

$$\mathbf{F} : \mathbf{B}^3 \times \mathbf{T} \rightarrow \mathbf{V} : \mathbf{V} \subset \mathbb{E}^3 \quad (2)$$

where \mathbf{V} is the notation for the « unfolding space », spanned by a number of external variables (THOM, 1969 ; p. 318).

Two important implications result from the combination of the expressions (1) and (2), namely, that the biological functions thus defined have implicit reference to goals, as was mentioned by NISSEN (1971 ; p. 256). On the other hand, it ensues that biological functions are neither identical nor topologically equivalent (homeomorphic) to the developmental representations of the biological phenomena in space-time, obtained by so-called retraction from space-time onto some domain of the unfolding space, a well-known type of mapping relation in topology (ARMSTRONG, 1979). In turn, this implies that in terms of topology no chronological order can be established between biological form and function.

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