

Chapter 16

Morphogenesis, Structural Stability and Epigenetic Landscape

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This chapter offers a commentary on the correspondence exchanged between René Thom and Conrad Hal Waddington in 1967, concerning the interpretation in terms of catastrophe theory of the concepts of epigenetic landscape and chreod, introduced by Conrad Hal Waddington since the 1940s.

It is intended to provide some elements of reflection on the difficulties encountered in exchanges between a mathematician and a biologist on the subject of the mathematization – in this case by means of a “dynamical systems” approach – of a theoretical question in biology, expressed in images by the compound metaphor of epigenetic landscape. One interpretation of the disagreement between the two scholars is based on the difference between their mathematical cultures, making it difficult to establish a shared dictionary (this was René Thom’s view). But another aspect must be taken into account to understand the difficulties of dialogue between the two scientists: the choice of variables (and the timescale specific to each of them) used to construct a mathematical model of the epigenetic landscape.

16.1 The Correspondence

Catastrophe theory, originating in René Thom’s research into the topology and differential analysis of the problem of structural stability, was conceived by its author as a mathematical theory of morphogenesis.

The paper “A dynamic theory of morphogenesis”, written by Thom in 1966 and published in 1968 in *Towards a Theoretical Biology I*, under the direction of Conrad Hal Waddington [7], is generally considered to mark the birth of catastrophe theory. In it, René Thom argued that embryology, and in particular the concepts of epigenetic landscape and chreod invented by Waddington, is both a source and a field of application of catastrophe theory. To illustrate his argument, he chose as an example of morphogenesis the model of cell differentiation developed by Max Delbrück in

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1949 [2], and showed how it could be applied in the context of catastrophe theory. This choice sparked off a correspondence between Waddington and Thom, some of which was published in 1980 as an annex to the French version of the paper in the collection *Modèles mathématiques de la morphogenèse* (five letters, dated between 25 January and 23 February 1967) [8]. This correspondence reveals disagreements between the two authors about the relevance of the example chosen by Thom to the question of cell differentiation in the context of development.

Waddington made two criticisms of the first version of Thom's paper. The first concerned the paternity of the biochemical interpretation of cell differentiation, which he claimed for himself. He questioned the following phrase in Thom's text ([8], p. 23, our translation):

The biochemical interpretation (due to Delbrück and Szilard) of cell differentiation.

The second criticism was more subtle. It concerned the use (by Delbrück and Szilard) of steady states, instead of time-extended chreods, when treating the question of cell differentiation. According to Waddington, the following phrase in Thom's text was problematical ([8], p. 23, our translation):

All cell specialisation being — according to the idea of Delbrück and Szilard — characterised by a stable regime of the metabolism, that is to say an attractor A of the local biochemical dynamics.

This suggested that Thom supported the idea of a description in terms of steady states. For Waddington, the expression "*stable regime*" was synonymous with *steady state*, and he therefore asked Thom to change it. On the subject of the first point, he wrote ([8], p. 23):

I had stated the main point as early as 1939.

And concerning the second ([8], p. 23):

I got it right, and spoke of alternatives between time-extended chreods (though I did not yet call them that), whereas Delbrück and Szilard had the simpler and basically inadequate idea in the context of development of an alternative between steady states.

In response to these remarks, Thom proposed the following changes ([8], p. 24, our translation):

This idea of interpreting cell differentiation in terms of "a stable regime of the metabolism", i.e. of an attractor of the biochemical kinetics, is often attributed to Delbrück and Szilard. In fact it was stated — under its local form, which is the only correct one — in C.H. Waddington, *Introduction to Modern Genetics*, 1939.

And secondly ([8], p. 24, our translation):

All cell specialisation being characterised by a stable regime of the local metabolism.

But concerning his second, more conceptually important criticism, Waddington preferred ([8], p. 25):

... by a stable but evolving regime of the local metabolism.

For Waddington, the specification "local state", by implicit contrast to "global state", was not explanatory. He felt that the distinction should be made between a stable regime, invariant over time (which he believed to be the case in the Delbrück model), and a regime that is ([8], p. 25):

at any moment, stable, but which changes progressively as time passes.

Thom then suggested ([8], p. 33, our translation):

... an attractor of the biochemical kinetics tangent to the point considered.

This response shows how Thom was seeking the best expressions, in mathematical terms ("local form", "kinetics tangent to the point considered"), to meet Waddington's requirements. The next instalment in the correspondence shows that Waddington did not find this wording completely satisfactory; but this is nevertheless what Thom kept in the final version of his article.

One interpretation of this terminological disagreement between the two scholars is based, on first analysis, on the difference between their scientific cultures, especially in the field of mathematics. They suggested this idea themselves. Thus, René Thom presented this correspondence as a typical example of difficulties in understanding, or even of misunderstanding, between mathematicians and biologists, caused by a difference in the requirements of mathematical rigour with which the concepts are defined. For René Thom, it is the property of structural stability that provides the link between his catastrophe theory and the concept of chreod introduced by Waddington: a chreod is none other than those parts of the domain of parameter space for which a process is structurally stable. Consequently, according to Thom, the property of *homeorhesis*¹ invoked by Waddington follows quite naturally from the very definition of chreod. According to Waddington, the disagreement arose from the fact that Thom, as a mathematician, did not appreciate the particular value of the time variable in the analysis of development, wrongly considering it to be a variable that could be equated, for example, to concentrations² ([8], pp. 33, 34):

Delbrück in 1949 was talking about the alternatives of driving round and round the Place de la Concorde, or round and round the Étoile; and that is only a degenerate case of what I had been talking about in 1940, which is the alternative of taking the bus from the Aéroport des Invalides to the Aéroport Orly or the Aéroport Le Bourget. The only way to eliminate this difference between Delbrück and myself would be if you are so "pure" a mathematician that you acknowledge no difference between a dimension devoted to a material variable, such as concentration, and one devoted to time. But this is a level of abstractness at which mathematics loses touch with the real-world problems of biologists.

¹ Waddington coined the term *homeorhesis* to describe the property of stability (in modern parlance we would call it robustness) of the processes of development when subject to perturbations. For Waddington, it was essential not to confuse this property of equilibrium along a trajectory of development (which he called the *chreod*) with the property of homeostasis, indicating an equilibrium around an unchanging state.

² As we shall see in Sect. 16.2, to interpret in mathematical terms the problem of cell differentiation as presented in the Delbrück model, Thom wrote a differential law in which the variables are concentrations.

To clarify the terms of this disagreement, it will be useful to examine the underlying issue: Delbrück's model.

16.2 Delbrück's Model

This model was introduced by Max Delbrück at a conference on genetics held in Paris in 1949, during which a proof was presented for the heritability of certain phenotypic traits in paramecia and other ciliates over a large, but finite, number of generations [2]. This could be taken as evidence against the chromosomal transmission of these traits. G.H. Beale then advanced the hypothesis of the existence of populations of cytoplasmic genes, or plasmagenes, that would be transmitted through a finite number of cell divisions before disappearing, and which would be responsible for the existence of these traits. Delbrück wanted to show that the same observations could be explained without resorting to genes or plasmagenes. To this end, he put forward the following argument ([2], p. 33, our translation):

... many systems in flow equilibrium are capable of several different equilibria under identical conditions. They can move from one equilibrium state to another under the influence of transient perturbations.

Delbrück thus proposed a model of interacting metabolic pathways, as illustrated in Fig. 16.1, but without explicitly writing the associated equations. A_1, A_2, B_1, B_2 represent different types of enzymes within the cell (represented by the circle). a_1 and b_1 are substances in the environment, while a_2 and b_2 are intermediate metabolites produced from a_1 and b_1 under the influence of A_1 and B_1 . They are, in turn, the substrates of enzymes A_2 and B_2 , which transform them into a_3 and b_3 , which are waste products. In a constant environment, this model always remains in a stable state. But at this point, Delbrück added the hypothesis that there exist mutual interactions between the two series of enzymatic reactions (shown in the diagram as

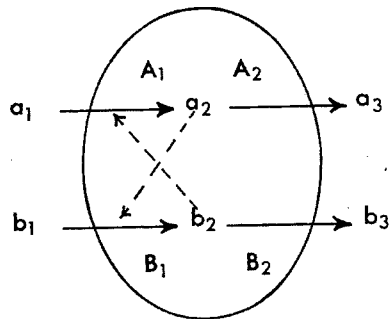


Fig. 16.1 Delbrück's model. A_1, A_2, B_1, B_2 are different types of enzymes inside the cell (which is represented by the circle). a_1 and b_1 are substances in the environment. a_2 and b_2 are intermediate metabolites produced from a_1 and b_1 under the influence of A_1 and B_1 . They are in turn the substrates of enzymes A_2 and B_2 , which transform them into a_3 and b_3 , waste products. After [2]

dotted arrows). Now there exist three possible equilibria for the same conditions of the environment: two stable states and one unstable state ([2], p. 33, our translation):

To sum up, our cell model is capable of existing in two functionally different states of flow equilibrium, without that entailing any change in the properties of the genes, plasmagenes, enzymes or any other structural units; transition from one state to another can be provoked by transient modifications in the conditions of the environment.

Commenting on this model and the role it has played in the development of developmental biology, Evelyn Fox-Keller observed that it has undergone a series of semantic shifts according to the contexts in which it has been considered. She also suggested that it has acted more as a metaphor than as a model [3]. To illustrate, but purely qualitatively, an application of catastrophe theory, Thom wrote an explicit system of differential equations inspired by this model/metaphor, introducing k chemical substances s_1, s_2, \dots, s_k with respective concentrations c_1, c_2, \dots, c_k :

$$\frac{dc_i}{dt} = X_i(c_1, \dots, c_k) \quad (\text{differential law for concentration variations}). \quad (16.1)$$

He then extended the model by taking into account its spatial extension, through the introduction of a system of coordinates (x) over the domain U occupied by the system:

$$\frac{\partial c_i(x_i, t)}{\partial t} = X_i(c_i, x, t) + k\Delta c. \quad (16.2)$$

where the Laplacian term $k\Delta c$, assumed to be small compared to X , can be neglected.

16.3 Structural Stability and Morphogenetic Field

In the very broad sense of the term adopted by Thom, "morphogenesis" describes any process that creates (or destroys) forms, without specifying anything about either the nature (material or immaterial) of the substrate of the forms considered, or the nature of the forces causing these changes. The key concept allowing Thom to link his view of morphogenesis in terms of catastrophe theory with Waddington's concepts of chreod and epigenetic landscape is structural stability. The idea is that a function F is *structurally stable* if, for a sufficiently small perturbation of that function, the perturbed function $G = F + \delta F$ keeps the same topological form as the initial function F .

Andronov and Pontrjagin had formulated a more technical definition in 1935 [1]. They asked what properties a dynamical system (a model) must have to correspond to a physical system. One cannot take into account all the factors that influence a physical system; moreover, there is nothing to guarantee that the factors considered will remain perfectly constant during the evolution of the system. Whence the following concept of structural stability ([9], p. 48):

For a dynamical system defined by the vector field X on the manifold M , we say that this system (M, X) is structurally stable if, for all fields X' topologically close enough to X , there exists a homeomorphism h_x of M to itself, which transforms any trajectory of X into a trajectory of (M, X') . In other words, the total decomposition of M into orbits does not change topological type when X is perturbed into X' .

According to Thom, a morphogenetic field on an open set U of space-time resides in a pre-existing "universal model", of which the particular process under study is a copy. Such a process will unfold in accordance with the universal model given *a priori* and will therefore be structurally stable.

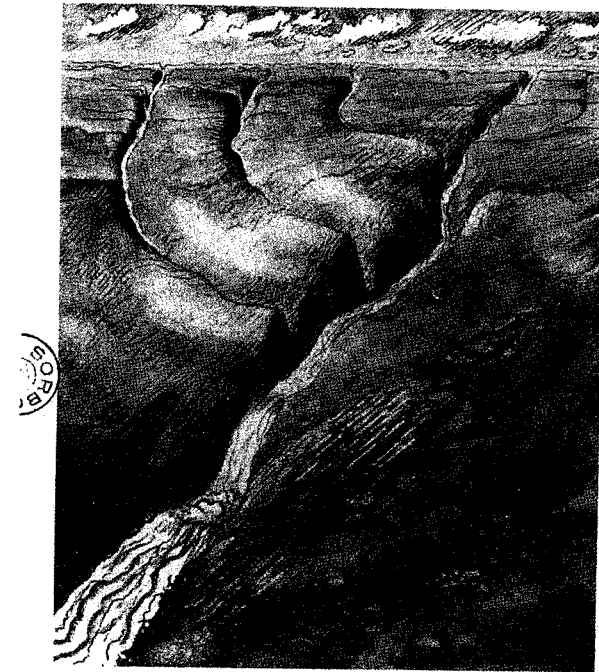
16.4 Epigenetic Landscape: A Mental Picture, a Metaphor . . . of What?

In *The strategy of the genes* [12], Waddington explicitly called for a mathematization of the processes of development on the basis of their geometrical rather than algebraic properties. In the chapter "The cybernetics of development", he argued that the processes of development cannot be modelled in terms of alternatives between several steady states, as they were, according to him, in Delbrück's model. He knew the property of sensitive dependence on initial conditions, which he called "the exaggeration of initial differences" ([12], p. 16). He drew this knowledge from the biomathematical work of Lotka [5], Kostizin [4] and others. And in an appendix to his book, he included a treatment of autocatalytic reactions written by Kacser. According to Needham [6], Waddington had been searching since the 1930s for a way to represent the course of embryonic determination in terms of a succession of choices between unstable equilibria, in the tradition of embryology research ([6], p. 58 *et seq.*). The analysis of different types of equilibrium in the study of living matter had already been taken into consideration by Lotka in the domains of epidemiology and population dynamics, where he succeeded in plotting the integral curves for systems with two variables. Needham ([6], p. 61), proposed a three-dimensional plaster model to represent these curves. The similarity to the hilly contours of the epigenetic landscape is obvious. Waddington knew these studies and he knew Lotka's results. And it is possible that he drew on them for the mental pictures he evoked with his landscapes. The thing that remained difficult to achieve, and which Waddington did not in fact achieve, as he never got any further than proposing metaphors, was to transfer the techniques of mathematization (and of the study of equilibria) from the biology of populations to the domain of development.

By breaking down the compound metaphor into its three significant aspects, we shall now see which variables Waddington believed ought to be taken into account.

i. Cell differentiation (Figs. 16.2 and 16.3)

Figure 16.2 is the first pictorial representation of the epigenetic landscape. It dates back to 1940. It is a landscape with a river flowing towards the sea (on the horizon, under the clouds) and branching into different valleys, at the ends of which we can



THE EPIGENETIC LANDSCAPE

From a drawing by JOHN PIPER

Looking down the main valley towards the sea. As the river flows away into the mountains it passes a hanging valley, and then two branch valleys, on its left bank. In the distance the sides of the valleys are steeper and more canyon-like. (See p. 91.)

Fig. 16.2 Waddington's epigenetic landscape. This river flowing towards the sea (on the horizon), and the valleys that form along its sides, was Waddington's first pictorial representation of the epigenetic landscape. From [10]

imagine the different products of cell differentiation. In 1957, Waddington proposed a more explicit image of the epigenetic landscape (Fig. 16.3). The interpretation of Fig. 16.3 as a metaphor of cell differentiation is based on the concept of sensitivity to initial conditions ([12], p. 16 *et seq.*). At the end of the hilly landscape, we must imagine the different tissues or organs produced by differentiation. The initial position of the marble at the top of the hill represents one of the different cytoplasmic states occupying the different regions of the egg. Waddington thus showed that he had well understood the property of sensitivity to initial conditions, which he cited as being responsible for progressive cell differentiation ([12], p. 29):

Or we could represent the various different initial conditions by imagining various degrees of bias on the balls which are to run across the surface.

ii. Robustness, chreod, homeorhesis

The different paths that the ball may take are stable pathways of development, or chreods – guarantees of the robustness of the process. If we adopt the hypothesis

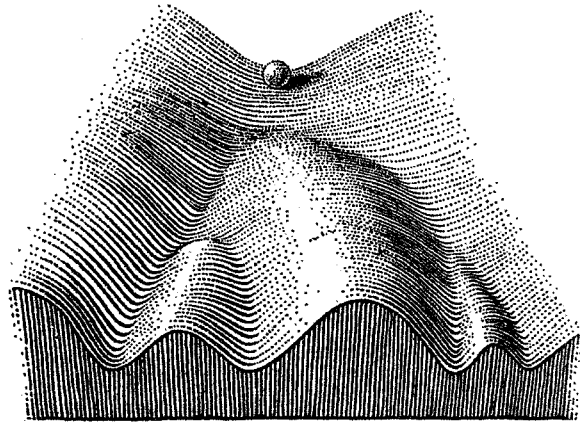


FIGURE 4

Part of an Epigenetic Landscape. The path followed by the ball, as it rolls down towards the spectator, corresponds to the developmental history of a particular part of the egg. There is first an alternative, towards the right or the left. Along the former path, a second alternative is offered; along the path to the left, the main channel continues leftwards, but there is an alternative path which, however, can only be reached over a threshold.

Fig. 16.3 In 1957 Waddington gave this representation of the epigenetic landscape, in the form of a hilly landscape down which a ball is rolling. The path followed by the ball corresponds to the history of the development of a given part of the egg. From [12], p. 29

that Lotka's work on different types of equilibrium gave Waddington the idea for this image of the epigenetic landscape, then Waddington's conception marks a shift in thinking, at the level of the chreods. Whereas in Lotka's work the hilly plaster model was no more than a three-dimensional representation of integral curves, and therefore a consequence of the study of equilibria, Waddington focused directly on the chreods, believing that he was thereby "inventing" a new type of equilibrium, specific to the study of living matter, because it could guarantee an equilibrium that evolves over the course of time, along a stable path of development. From this point of view, Thom seems to be right in affirming that Waddington did not fully appreciate the scope of a dynamical systems approach. But my thesis is that the reasons for their mutual misunderstanding go far beyond this. What I find even more remarkable in Waddington's ambition, which was certainly very high, was the idea of combining this image, already suggesting two metaphorical interpretations, with a third image, which Thom did not explicitly take into account in his modelling.

iii. Influence of gene interactions on the process of (epigenetic) development

For Waddington, epigenetics studies the effect of causal relations originating in the genes on the genotype-phenotype transition [11]. Waddington wanted to express the idea that it is the genes and their interactions that determine the form of the epige-

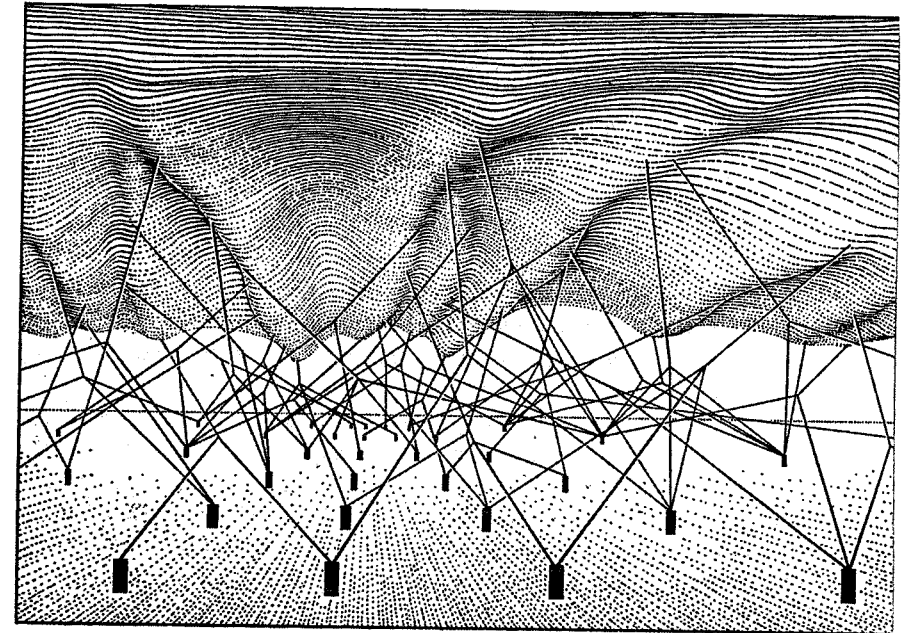


FIGURE 5

The complex system of interactions underlying the epigenetic landscape. The pegs in the ground represent genes; the strings leading from them the chemical tendencies which the genes produce. The modelling of the epigenetic landscape, which slopes down from above one's head towards the distance, is controlled by the pull of these numerous guy-ropes which are ultimately anchored to the genes.

Fig. 16.4 In the same work ([12], p. 36), Waddington adds this image, representing the system of interactions woven between the genes underlying the epigenetic landscape

netic landscape (Fig. 16.4). For him, the surface of the epigenetic landscape, which governs the course of cell differentiation, can be seen, if we change the timescale, as a metaphor for the resultant of gene interactions ([12], p. 34, 35):

It is important to realise that the comparatively simple orderliness of the epigenetic landscape – its restricted number of valleys with their branching point and characteristic contours – is a property of higher order dependent on an underlying network of interactions which is vastly more complicated. The cells proceeding along any development pathway must have a metabolism of some corresponding complexity. [...] But genetics still gives us more insight into the real complexity of apparently simple epigenetic processes than does biochemistry. [...] Since each gene must be regarded as a distinct chemical entity, the path of development as it is observed by the anatomist must be viewed as the resultant of all the very numerous processes in which these genes are involved in the cells concerned.

It was this desire to represent phenomena taking place at different scales that prevented Waddington from being completely satisfied with Thom's proposition ... Of

course, as Waddington made very clear, these were only mental pictures. But if we are prepared to reason in terms of images, what Thom proposed did not account for the process of cell differentiation, within Waddington's metaphorical context. At most, it can account for the genesis of chreods!

16.5 Interpretations

To sum up, this commentary brings to light two possible interpretations, which are not mutually exclusive, for the disagreement between the two scholars.

The first is based on the difference between the scientific cultures of the two authors, especially their requirements in terms of mathematical rigour. This amounts to saying that Waddington did not have enough mathematical knowledge to understand that the terminology used by Thom simply gave explicit expression to the properties implicit in the concept of chreod, of which the characteristic and essential trait is that it represents the domain (in parameter space) of a structurally stable process, a trait from which all its other traits ensue. In addition, and again from Thom's point of view, Waddington did not understand that if Delbrück's model was expressed in a very general form, in mathematical terms, that did not mean that it could be reduced to a choice between alternative steady states.

The second is based on the existence of a theoretical problem, underlying the compound metaphor formed by these different metaphorical images of the epigenetic landscape, which Thom failed to take into account: how to model mathematically two processes taking place over different timescales (one slow, the timescale of evolution, acting at the level of gene interaction, and one fast, the timescale of development, acting at the level of the different cytoplasmic states in different regions of the egg). Such modelling would involve writing a dynamical system with time-dependent variables. Or describing the dynamics on a network (underlying the landscape, which would be an emergent property of the network). The variables of this dynamics would be the different cytoplasmic states, and the nodes of the network would be the genes ...

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