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ARGUMENTS OF STABILITY IN THE STUDY OF MORPHOGENESIS[1]

Argumentos de estabilidad en el estudio de la morfogénesis

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ABSTRACT

Arguments of stability, intended in a wide sense, including the discussion of the conditions of the onset of instability and of stability changes, play a central role in the main theorizations of morphogenesis in 20th century theoretical biology. The aim of this essay is to shed light on concepts and images mobilized in the construction of arguments of stability in theorizing morphogenesis, since they are pivotal in establishing meaningful relationships between mathematical models and empirical morphologies.

Key words: Morphogenesis; Stability; Metastability; Equilibria; Competence; Epigenetic Landscape; Catastrophe Theory; Semiophysics.

RESUMEN

Los argumentos de estabilidad, entendidos en sentido amplio, incluyendo la discusión de las condiciones del inicio de la inestabilidad y de los cambios

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de estabilidad, juegan un papel central en las principales teorizaciones de la morfogénesis en la biología teórica del siglo XX. El objetivo de este ensayo es arrojar luz sobre conceptos e imágenes implicados en la construcción de argumentos de estabilidad en la teorización de la morfogénesis, ya que estos resultan fundamentales para establecer relaciones significativas entre modelos matemáticos y morfologías empíricas.

Palabras clave: Morfogénesis; Estabilidad; Metastabililidad; Equilibrio; Competencia; Paisaje epigenético, Teoría de catástrofes; Semiofísica.

Arguments of stability, intended in a wide sense, including the discussion of the conditions of the onset of instability and of stability changes, play a central role in the main theorizations of morphogenesis in 20th century theoretical biology.

Thus, Alan Turing (1912-1954) in his work on the chemical basis of morphogenesis establishes a link between the study of the onset of instabilities in a system of reaction-diffusion equations with phenomena of pattern formation. On another side, René Thom (1923-2002), in the framework of catastrophe theory, is not only interested in the asymptotic stable states of the studied dynamics (attractors), but also in the changes of structural stability of the same dynamics *i.e.* in the changes of the attractors of the dynamics, that he associates to morphological changes in the substratum.

Both these approaches to morphogenesis, despite their differences and specificities, share the fact of having being inspired by the research of the experimental embryologist and promoter of theoretical biology Conrad Hal Waddington (1905-1975), whose experimental work, theoretical constructions and open questions have been concerned, in turn, with questions of stability.

The aim of this essay is to shed light on concepts and images mobilized in the construction of arguments of stability in theorizing morphogenesis. These arguments are pivotal in establishing meaningful relationships between mathematical models and empirical morphologies. A synoptic view of these questions can thus provide a perspective from which to look at the renewal of morphological thinking that, from theoretical biology spread, or could spread, into other domains.

1. Looking for the onset of instability

In the opening of "The Chemical basis of Morphogenesis" Turing declares of being interested in writing "a mathematical model of the growing embryo"[2]. However, he immediately recognizes that he has to limit his interest on the chemical aspect only of this phenomenon, leaving aside, for the moment, the mechanical one. He is thus concerned with the diffusion dynamics of two interacting chemical substances (Turing calls them "morphogens") on a tissue, that he translates into a two variables system of non-linear partial differential equations (known as a reaction-diffusion equations). As Turing explicitly states, the "investigation is chiefly concerned with the onset of instabilities"[3]. Mathematically studying the onset of instability of this system in different situations, Turing shows that it presents spontaneous pattern formation through symmetry breaking.

From the point of view of biology, Turing's contribution can be seen as an example of a too abstract and purely mathematical model, in the tradition of modeling typical of mathematical physics, but regrettably disconnected form biologists concerns[4]. The main reasons of this appreciation are due to the fact that Turing does not attribute a decisive role to genes in the phenomenon of pattern formation. Genes are in fact supposed to have only a catalytical function in Turing's model, whereas in general they are, and were already in Turing's time, considered to play an essential role in explanations of biological phenomena. However, despite his unconventional position regarding genes role, we think that Turing has the ambition to connect his proposition to questions coming from theoretical biology of his time. In order to defend this point of view, it is necessary to consider the main actors of Turing's reaction-diffusion model, the interacting chemical substances diffusing on a tissue that define his system, that Turing calls "morphogens." Morphogens are defined as follows: "These substances will be called morphogens, the word being intended to convey the idea of a form producer"[5]. Turing precises that the term "morphogen" "is not intended to have any exact meaning, but it is simply the kind of substance concerned in this theory"[6]. A morphogen is thus a chemical substance that enters in a certain relation with another chemical substance (another morphogen), relation that can be described through reaction-diffusion equations, the study of the onset of instability of which allows to understand pattern formation with

2. Turing, A. M., "The chemical basis of morphogenesis", *Philos. Trans*. B, 237, 641 (1952), pp. 37-72.

3. *Ibid*., p. 37.

4. See on this point Fox Keller, E., *Making Sense of Life. Explaining Biological Development with Models, Metaphors, and Machines,* Cambridge MA, Harvard University Press, 2002, pp. 95-100.

5. Turing, A. M., "The chemical basis of morphogenesis", *op. cit.*, p. 38.

6. *Ibid*., p. 38.

respect a previous homogeneous situation. The definition of morphogen is thus merely relational and any substances behaving as the ones defined by Turing's system can potentially be considered as morphogens. Turing thinks that genes, since they do not diffuse, can be considered as morphogens of a particular kind that exercize only an indirect action (a catalyzing action). They do define the reaction rates and, "Insofar, for organisms with the same genes, they can be eliminated from discussion"[7]. What is at the core of Turing theoretical proposition, and captured by the form of his system of equations, is the fact that one has to look for the onset of instability. The connection with theoretical biology of his time comes from the fact that Turing explicitly refers to "evocators," a notion introduced by Waddington, as examples of morphogens: "The evocators of Waddington provide good examples of morphogens (Waddington 1940). These evocators diffusing into a tissue somehow persuade it to develop along different lines from those which would have been followed in its absence"[8].

Among the several concepts and the corresponding neologisms created by Waddington in the course of his career, we are thus going to discuss, for its link with arguments of stability, the concept of "evocator," introduced during the 1920s.

2. From "evocator" as a chemical substance to "competence" as an unstable system

Waddington creates the concept and the term of "evocator" in the framework of his experimentations in embryology on "induction," following the research line opened by the work of the embryologists Hans Spemann (1869-1941) and Hilde Mangold (1898-1924) on "induction" and on "organizers"[9]. Experimental research in embryology consisted in studying the effects on development of the grafting of embryos, or of regions of embryos, in other embryos or regions of embryos. "Induction" was for Spemann and Mangold the process through which the identity of certain cells influences the developmental fate of the surrounding cells. An "organizer"

7. *Ibid*., p. 39.
8. *Ibid*., p. 38.
9. For more details on Waddington's works, in the context of his time research at the interface of genetics and embryology, one can report to Gilbert, S.F., "Induction and the Origins of Developmental Genetics", in: Gilbert, S.F. (ed.), *A Conceptual History of Modern Embryology*, New York, Plenum Press, 1991, pp. 181-206, on which I rely here for what concerns the definitios of "induction" and "organizer".

was considered a region of the embryo producing an induction on other, surrounding regions. Waddington, working among others with the biochemist Joseph Needham (1900-1995), wanted to understand the role played by organizers during the process of induction.

In this research context, Waddington and Needham consider an "evocator" as a chemical substance responsible for induction in the creation of tissue in a living organism: the evocator as a substance is present throughout the whole embryo and is activated in one particular region, the organizer center, by way of a gradient system. The point that mostly concerns us in the framework of this research on the arguments of stability, more than the material identity of evocators, is the fact that their activation is realized means a *gradient system*. Waddington defends the idea that each induction process depends both on the properties of the inductive agent and of the material that undergoes induction. This idea is better expressed by another Waddington's concept: "competence." For Waddington a material that is capable of reacting to a given inducing stimulus is said to be "competent" for that process of induction[10]. For Waddington "a competent tissue should be thought of as an *unstable system* with two or more ways of change open to it, the decision as to which way it actually follows being taken by the relevant organizer"[11].

Summarizing, Waddington's work expresses the idea that the phenomenon of induction could/should be interpreted through the attribution of the property of competence to certain tissues (t.i. a property of instability with two or more changes open to it). When Waddington writes in 1940 his *Organisers and genes*, it is clear that he considers genes as evocators and this allows him to translate his idea of competence coming from embryological experiments into the language of contemporary genetics, implying genes and gene-products as controllers of the switches between different ways of change. However, his attention seems more directed towards the dynamical state of the complex of considered reactants than towards the nature of the same reactants (genes or genetic products); in fact, this analogy between dynamic equilibria is what allows Waddington to think embryology *and* genetic through the *same* conceptual scheme of competence: "We had described competence as a state of disequilibrium in a complex

10. Waddington, C.H., "Experiments on the Development of Chick and Duck Embryos, cultivated in vitro", *Philos. Trans. Roy. Soc.* B (London) 221 (1932), pp. 179-230.

11. Waddington, C.H., "The Origin of Competence for Lens Formation in the Amphibia", *J. Exp. Biol.*, 48 (1936), pp. 86. Italics in the quotation is mine.

systems of reactants, and had suggested that the reactants are ultimately genes or gene-products"[12].

Considered the networks of waddingtonian concepts to which belongs the one of "evocator," and the importance of arguments of stability and instability within this network, Turing's search for the onset of instability in a reaction-diffusion system seems a quite pertinent theoretical attitude with respect Waddington's questions. In fact, Waddington expresses his interest in Turing's approach in a letter of September 1952[13]: "It is very encouraging that some really competent mathematician has at last taken up this subject". However, he thinks that the kind of processes described by Turing plays certainly a role in pattern formation ("in the arising of spots, streaks and flecks of various kinds in apparently uniform areas such as the wings of butterflies, the shells of molluscs, the skin of tigers, leopard, etc."), but he doubts that the kind of processes described by Turing plays "a very important role in the fundamental morphogenesis which occurs in early stages of development". Waddington thinks in fact that the new fertilized egg does not satisfy the condition of homogeneity that Turing's model supposes. The new fertilized egg for Waddington "always possesses some element of pattern of its own, although this may be to some extent labile". We quote extensively the rest of the letter, since it details Waddington's desiderata that mathematical models adapted to describe the early stages of embryological development should satisfy. These desiderata correspond to a property of development that Waddington calls, elsewhere, "canalization".

3. Canalization as buffering against perturbations

> The problem of embryological interest which I should most like to see tackled from a mathematical point of view is the following: *Development is particularly characterised by the fact that it produces a finite number of quite definitely distinct tissues and organs and does not produce all intermediate types of tissues between the kidney and the liver for instance*. If one imagines a series of synthetic chemical processes, probably autocatalytic and interfering with or stimulating one another, for instance by competing for substrates or in other ways, *under what conditions will the system have a finite number of distinct paths, which it may follow?* What sort of alterations would be

12. Waddington, C.H., *Organisers and Genes*, Cambridge, Cambridge. The University Press, 1940 (1947), p. 92.

13. Letter from Waddington to Turing, 11 September 1952, from the Turing Digital Archive, AMT/D/1TLS (images 19-20).

> necessary to cause the development to click over from one path into another alternative?[14].

Waddington clearly expresses an interest in the kind of mathematical models Turing proposes ("autocatalytic, interfering with or stimulating one another"), but he thinks that Turing's model itself is not able to represent a process presenting a finite number of distinct alternative paths, without possibility of intermediate solutions. This Waddington's commentary gives a privileged access to the understanding of the difficulties of translating, in mathematical terms, concepts describing biological processes. Even if Waddington does not use the term, what is in question here is the possibility of mathematical expressing the notion of "canalization," notion that Waddington had introduced in 1942 and that is, from its introduction, deeply intertwined both with arguments from natural selection and from genetics. In his paper "Canalization of development and the inheritance of acquired characters"[15] Waddington introduces "canalization" as a property of developmental reactions that depends from the nature of the same reactions; since developmental reactions occur in organisms submitted to natural selection, they are, for Waddington, canalized: "That is to say, they are adjusted so as to bring about one definite end-result regardless of minor variations in conditions during the course of the reaction"[16].

From this point of view, Waddington's neologism "canalization" seems to indicate a property of "robustness," that in contemporary complex systems language indicates the property of a system to withstand different kinds of failures and perturbations. However, while discussing canalization, Waddington, does not use the term "robustness" and does not express himself on the possibility to mathematically model this property. The inability in mathematical expressing the property of canalization does not characterize Turing's approach only. It is a difficulty that has been acknowledged, several decades later, by René Thom, too. In a late inventory of Waddington's concepts he provides in 1989, René Thom stresses that the mathematical concept of structural stability is unable to express canalization:

> [Canalization] describes any kind of process whose temporal evolution is buffered against external perturbations. There is apparently no strict mathematical equivalent to this concept, as the classical "structural stability" is

14. Waddington, C.H., *Organisers and Genes, loc. cit.* Italics is mine.
15. Waddington, C.H., "Canalization of development and the inheritance of acquired characters", *Nature*, 3811 (1942), pp. 563-565.
16. *Ibid*., p. 563.

of global topological nature, whereas "canalization" has a metric and local character[17].

This consideration deserves our attention in the framework of this quest about arguments of stability in the study of morphogenesis. If structural stability, which is the mathematical concept founding (since the end of the 1960's) Thom's approach to morphogenesis through catastrophe theory, turns out to be admittedly inadequate to express canalization, what can be the pertinence of the same catastrophe theory in understanding morphogenesis? In order to better appreciate this question let us now turn to the role of arguments of stability in the definition of an important source of inspiration of Thom's catastrophe theory, the "epigenetic landscape", a set of mental images introduced by Waddington to think to embryological development since the end of the 1930's.

4. Properties of the equlibria of the epigenetic landscape

Waddington first introduces conceptually the main traits of the epigenetic landscape, without introducing the expression itself, in his *Introduction to Modern Genetics* (1939)[18]. The first pictorial illustration, realized by the painter John Piper, one of Waddington's friends, appears the following year in the frontispiece of *Organisers and Genes* (1940)[19]. The painting depicts a river flowing towards the sea. From the description Waddington gives of the epigenetic landscape, the centrality of arguments of stability for the constitution of this image emerges:

> The system of developmental paths has been symbolysed in two dimensions as a set of branching lines. Perhaps a fuller picture would be given by a system of valleys diverging down an inclined plane. The inclined plane symbolizes the tendency for a developing piece of tissue to move towards a more adult state. The sides of the valleys symbolize the fact that developmental tracks are, in some sense, equilibrium states. The meaning which must be attached to this term in such a context may at first sight not be obvious, since the

17. Thom, R., "An Inventory of Waddingtonian Concepts", in: Goodwin, B./ Saunders, P. (ed.), *Theoretical Biology. Epigenetic and Evolutionary Order from Complex Systems*, Edinburgh University Press, 1989, p. 3. I whish to thank Peter Saunders for having attracted my attention on this Thom's inventory.

18. Waddington, C.H., *Introduction to Modern Genetics*, New York, Macmillan, 1939.

19. Waddington, C.H., *Organisers and Genes,* ed. cit.

> developmental processes move along the tracks and do not stop anywhere in their course. It is not meant, however, that any point on the track is a position of equilibrium; it is the track as a whole which, compared with any other line lying between the tracks, is a description of an equilibrium. The equilibrium is a moving one and the state of the system changes as time passes. But it is an equilibrium in the following two senses. Firstly, it is a definite, and normally repeatable, result of a whole complex of factors. […] Secondly, the normal developmental track is one towards which a developing system tends to return after disturbance. […] This symbolic representation of developmental processes can be spoken of as the "epigenetic landscape"[20].

In this first description of the epigenetic landscape is already expressed the idea that a *whole track* is the description of an equilibrium, a *moving equilibrium* through the course of development. This will be later conceptualized, and expressed in an extended form in *The Strategy of the Genes* (1957), through the notion of "homeorhesis" ("same flow"), which is the term Waddington introduces to qualify this particular equilibrium of the developing embryo, manifesting itself along a developmental track. To indicate such a developmental track, Waddington creates another neologism: "creod" (t.i. a "necessary path" of development)[21]. These neologisms are introduced in the chapter "The Cybernetics of Development", in which Waddington provides a new figurative version of the epigenetic landscape. Here the landscape, that Waddington himself qualifies of "mental picture" to help in thinking the developing embryo, is defined by an undulated surface, on which a ball is ready to move along one of the paths opened in front of it[22]. The landscape is completed by a "hidden" part, underlying the undulated surface: a network of pegs fixed in the ground, interconnected by guy-ropes and strings[23]. Waddington writes that the undulated surface represents the fertilized egg. The path followed by the ball represents the developmental history of a particular part of the egg. As far as the underlying part, on the basis of an analogy –between the pegs and the genes, and the strings and the chemical tendencies produced by the genes– it offers the possibility of understanding how the surface itself is modeled:

20. *Ibid*., pp. 92-93.
21. *Cf.* the description of the epigenetic landscape that Waddington gives in Waddington, C.H., "The Cybernetics of Development" (ch. Two), in: *The Strategy of the Genes*, London, Allen and Unwin, 1957, pp. 11-58.
22. For the image see *Ibid*., p. 29.
23. Waddington, C.H., "The Cybernetics of Development", ed. cit., p. 36 (for the image of the underlying part of the epigenetic landscape).

> *The complex system of interaction underlying the epigenetic landscape*. The pegs in the ground of the figure represent genes; the strings leading from them the chemical tendencies which the genes produce. The modeling of the epigenetic landscape […] is controlled by the pull of these numerous guy-ropes which are ultimately anchored to the genes[24].

The mental figure of the epigenetic landscape translates into images the dynamical desiderata of the process of embryological development as already described by Waddington in terms of competence as an unstable state. The epigenetic landscape, in fact, "makes one reflect that there may be regions at upper levels which are almost flat plateaus from which two or three different valleys lead off downwards. These, in fact, correspond to what we know as states of competence, in which embryonic tissues are in a condition in which they can be easily brought to develop in one or other of a number of alternative directions"[25].

Waddington also reaffirms the considerations already expressed in the quoted letter to Turing about the form that mathematical expressions of the property of canalization of development should take. He thinks that this phenomenology can be instantiated by autocatalytic reactions producing threshold effects, multiple steady states, and exaggerated responses in small changes in the initial concentrations, quoting at this regard, as examples coming from other fields of theoretical biology, the work of mathematical biologists of populations such as Alfred James Lotka (1880-1949) and Vladimir Alexandrovic Kostitzin (1883-1963). The reference to Lotka is not trivial, also in light of some qualitative considerations expressed by Waddington concerning the necessity to switch from an algebraic to a geometric mode of expression of the solutions of the sets of equations defining these developmental pathways. Waddington observes in fact that it is usually impossible to integrate these sets of equations, even if for some particular systems (and here Waddington evokes Turing) it is possible to compute numerical solutions. Due to the general impossibility to integrate this kind of equations, Waddington suggests the introduction of a representation in "phase space" as follows: "A system containing many components can be represented by a point in multidimensional space, the co-ordinates of the point in each dimension representing the measure of a particular component. A space of this kind is known as phase space"[26].

In the attempt of depicting a phase space for development, Waddington writes: "The *true representation* of this, as has been stated, is a multidimensional

24. *Ibid*., p. 36, from the original caption.
25. *Ibid*., p. 30.
26. *Ibid*., p. 27.

space, subdivided into a number of regions, such that trajectories starting anywhere within one region converge to one certain end point, while those starting in other regions converge elsewhere"[27]. The statement that immediately follows presents the image of the epigenetic landscape itself as a model of this "true representation:" "I have tried to give a simple model in three dimensions which will correspond with this to some extent"[28].

This illuminating commentary, establishing a connection between the epigenetic landscape and phase-space, leaves nevertheless a non-obvious open question: is the epigenetic landscape to be intended as a simple model in three dimensions of a "true representation" of development *in* phase-space, or as a simple model in three dimensions of a "true representation" of the *phase-space of development* itself? In other terms, is phase-space to be considered an external container in which to depict the epigenetic landscape, or it is to be considered a solidary space to the epigenetic landscape itself, and as such, something which is not totally pre-given?

This is a crucial question for the pertinence and fruitfulness of images of epigenetic landscape to think morphogenesis well outside theoretical biology, as the reader will himself appreciate, and for that reason we've mentioned it here. However it is not the purpose of this essay to try to answer this question. We are on another hand going to proceed to another question, following the thread of the use of arguments of stability in the study of morphogenesis. How possibly Waddington came to think to development in terms of a *hilly landscape* and, more specifically, to a hilly landscape defined by the arrangement of different equilibria and alternative pathways and end states in phase-space? If the concepts of competence and canalization Waddington introduced in the previously decades are compatible with representations in terms of a hilly landscape, these representation themselves are certainly underdetermined by these concepts, and the question whether Waddington has been under the influence or the inspiration of other theoreticians having used the image of a hilly landscape to study and represent equilibria is fully justified. The motivation of this question goes far beyond the historical interest for the paternity of an idea, being justified by the conviction that finding the source, or a possible source, of the images of the epigenetic landscape could provide an access to the understanding of its theoretical aspirations to depict developmental processes. Through an archeological enquiry that, through Needham's *Order and Life* (1936), goes back to the work of Alfred Lotka,

27. *Ibid*., pp. 27-28. Italic is mine. Cfr., the image p. 28, Waddington gives to illustrates a phase-space diagram of development.
28. *Ibid*., pp. 28-29.

we will see in the following that the landscape can be interpreted as the set of integral curves in phase space, charted thanks to a qualitative study of the instability of the equilibria of a given dynamics expressed by a set of non-linear equations.

5. Landscapes and metastability

Collaborator of Waddington, and sharing with him the interest for theoretical biology, the biochemist Joseph Needham in his *Order and Life* (1936) devotes a chapter to theories of morphogenesis in embryo development and to images representing some key concepts of these theories[29]. In general, what Needham discusses in this chapter are not images of embryo development itself, but representations of concepts that should grasp the mechanisms of this development and illustrate the concept of "determination" as used in embryology at his time, *i.e.*, "the fixing of the fates of parts of the embryo at a definite time in development"[30]. Through the lens of determination, development is defined by Needham as "a progressive restriction of potencies by determination of parts to pursue fixed states"[31]. For Needham this state of affairs can be pictured in the manner of a series of equilibrium states as he illustrates through a diagrammatic way of representing the course of embryonic determination that he calls "Waddington's cones" and that Waddington suggested, without graphically representing it, in its already quoted article of 1932 where he discusses competence[32]. Needham describes as follows Waddington's cones:

> At the top of the uppermost cone there is a ball in a position of extremely unstable equilibrium. It will tend to fall along the side of the cone at some one of the 360° degrees of the cone's circumference. Here it will again find itself in a position of unstable equilibrium, only with respect to a second stage of determination, and will again be pushed in one direction or another, again to occupy a passing equilibrium, and so until the final stage of absolute stability is reached; i.e. the plan of the adult body[33].

29. Needham, J., *Order and Life*, Cambridge MA, MIT Press, 1936.
30. *Ibid*., p. 49.
31. *Ibid*., p. 58.
32. Waddington, C.H., "Experiments on the Development of Chick and Duck Embryos, cultivated in vitro", ed. cit., p. 221.
33. Needham, J., *Order and Life*, ed. cit., p. 58.

For Needham the understanding of the passage from unstable to stable equilibria is the key point to describe embryological development and it offers opportunities for advances in the mathematization of embryology. Clearly motivated by providing a visual representation of this process, he proposes himself a picture of a plaster model representing a hill resting on a flat soil. The walls of the hill descending towards the soil present, irregularly, several plateaus that can be seen as local states of equilibrium. Needham defines this plaster model as "a qualitative three-dimensional model of embryonic determination, illustrating the passage from unstable to stable equilibria"[34]. Discussing further this model, he explains that "the state of harmonious equipotentiality would then correspond to the summit point, where the instability is maximal, and a point could descend to the successive levels of instability not in one direction only, but in many, according to its position ad other relations to the organizer region"[35].

Even from Needham's discussion are absent Waddington's considerations on the role of the genes as switches of different pathways of development, since Needham is only concerned with visual representations of development determination, without genetic or epigenetic considerations, Needham's plaster model seems to be a very relevant source for what became Waddington's images of the epigenetic landscape. There is another striking aspect in this Needham's contribution: he presents his plaster model as an intuitive representation of an unstable equilibrium coming from a study of Alfred Lotka on the use of equilibrium-concepts in biology.

In his treatment of equilibria in biology, a subject extensively developed in his *Elements of physical biology* (1925)[36], Lotka chooses to look at the kinetic conception of equilibria: a stationary state is defined as a state in which certain velocities vanish. Thus general condition for equilibrium (intended, for Lotka purposes, as a stationary state) is obtained by equating to zero the velocity of growth of each component of the system. This furnishes in general n independent equations, determining one or more sets of values of the variables X_i.

In order to obtain a graphic representation of the different types of equilibrium, Lotka does not seek for solutions of the fundamental equations expressing the variables X_i as a function of time t. He eliminates t from this system of equations, which leads to a new system defining a family of curves passing

34. *Ibid*., p. 60.
35. *Ibid*., p. 61.
36. Lotka, A.J., *Elements of Physical Biology*, Baltimore, Williams & Wilkins, 1925, pp. 143-155.

through the equilibrium points. The study of equilibrium points (their kind and their topography) is realized by Lotka through methods of qualitative analysis of the singular points of differential equations[37].

If only two variables are in question, the integral curves may be plotted on rectangular co-ordinates. As an example, Lotka figures the topographic chart of the Ross malaria equations[38], which describe the course of events in the spread of malaria in a human population by the bites of certain breeds of mosquitos infected with malaria parasite. Lotka shows that there are two singular points, one unstable, and one stable. The stream lines of the chart suggest the construction of a qualitative three-dimensional model. Lotka gives a graphical representation of this model. He notices that in this model, that he calls *landscape*, the unstable point is represented by a *col* (a "notch") in *the landscape*, and one stable, represented by a pit in the *landscape*.

We see thus how, through a perfectly rigorous, even if qualitative, mathematical study, Lotka obtains the representation of a three-dimensional landscape depicting the integral curves as lines of flow of a system of differential equations of two coupled variables[39]. If we remember Waddington's considerations about the necessity of switching to a geometric instead of an algebraic approach to the representation of the solutions of the equations of a developmental system in phase space, it seems pertinent to think that this Lotka's landscape influenced not only Needham, but Waddington as well.

A further Lotka's consideration is remarkable in this analysis of arguments of stability: discussing the unstable equilibrium, Lotka precises that it is as a case of "metastable" equilibrium. Thermodynamically, the characteristic of a metastable equilibrium is that the thermodynamical potential of the system, though a minimum, is not an absolute minimum. Lotka affirms that this is the common characteristic of growth of a living system (autokinetic character):

37. Regarding this question Lotka refers to a specialized mathematical literature (Picard, E., *Traité d'analyse*, 1891, and Liebmann, H., *Lehrbuch der Differential gleichungen*, 1901). Even if Lotka does not quote explicitely Poincaré, he uses his qualitative methods and terminology for the study and classification of singular points.

38. Ross, Sir R., *The Prevention of Malaria* (2d ed. 1911), p. 679 ; also Lotka, A.J., "Contribution to the analysis of malaria epidemiology", *Am. Jour. Hygiene*, 3 (1923 January suppl.), pp. 1-121.

39. For a discussion of Needham's and Lotka's landscapes with respect Waddington's epigenetic landscape, in particular concerning the difference in involved variables, see Franceschelli, S., "Morphogenèse, stabilité structurelle et paysage épigénétique", in: Bourgine, P./Lesne, A. (ed.), *Morphogenèse. L'origine des formes*, Paris, Belin, 2006, pp. 298-308 (Eng. Tr. *Morphogenesis. Origins of Patterns and Shapes*, Berlin and Heidelberg, Springer Verlag, 2011).

> Growth is initiated by a nucleus of the same species of matter that is added by the growth. Conversely, in the entire absence of any nucleus of a particular species of living matter, growth of that species cannot take place, even though all other conditions for such growth may be satisfied, even though the system may be, as it were, supersaturated with regard to that species of matter. In these circumstances an equilibrium may be presented which is unstable in the sense that, upon the introduction of a suitable nucleus, growth immediately sets in[40].

Now, another Lotka's remark is retained in Needham's chapter from *Order and Life* from which we started our inquiry: inorganic systems, in an analog manner, can present metastable equilibria, for example in the case of supersaturated solutions or vapors that are brought to crystallization or to condensation by the introduction of a suitable nucleus. This consideration allows Needham to emit the hypothesis that the term metastable could be applied to the plateau-states occurring in his plaster model of embryonic determination, allowing him to establish an audacious analogy between crystallization and embryo development that leads him to suggest that the "appropriate organizer would then correspond to the nucleus which ends the state of supersaturation in an inorganic system […] Just as inorganic metastable systems are stable in the absence of their nucleus, so, in the absence of the organisers, normal development and differentiation will not occur […]"[41].

In conclusion of this section we can summarize by saying that the association of images of landscapes and arguments of stability, accompanied by a quest for a pertinent mathematization of developmental or growing processes, is not a particularity of Waddington's approach. It is, in the case of Lotka, the result of a rigorous study of the qualitative dynamics of a set of non-linear equations and it allows, in the case of Needham, to establish analogies between crystallization and embryo development. In the three cases, images of landscapes are able to grasp conceptual issues in a synthetic manner and help in establishing fruitful analogies. We will see in the next section that images of landscapes are at the core of René Thom's approach, too.

6. From structural stability to landscapes again

It is well known that the image of the epigenetic landscape has inspired Thom for the creation of catastrophe theory as a mathematical theory

40. Lotka, A.J., *Elements of Physical Biology*, ed. cit., p. 151.
41. Needham, J., *Order and Life*, ed. cit., pp. 62-63.

morphogenesis - Thom himself declares it in the *princeps* article in which he first presents catastrophe theory[42]. It is interesting to observe that the same image continued to inspire him till the end of his career, in his attempts to go beyond catastrophe theory as a general mathematical theory for morphogenesis through the elaboration of his "semiophysics" and the notion of "pregnance".

Thom adopts a very broad sense of "morphogenesis": to him this term describes any process that creates or destroys forms, without taking into account neither the nature (material or not) of the substratum of the considered forms, nor the nature of the forces causing these changes. With catastrophe theory Thom proposes a new kind of modeling for the natural sciences. As Jean Petitot stresses (2015)[43], catastrophe theory is not properly speaking a theory, but a method leading to an "art of modeling" (an "art des modèles")[44]. At the core of this art of modeling is the property of "structural stability", that allows Thom to link his view of morphogenesis through catastrophe theory to the waddingtonian notions of epigenetic landscape and creod. The intuitive idea is that a mathematical function is structurally stable if, for a sufficiently small perturbation of that function, the perturbed function keeps the same topological properties of the unperturbed function. The technical definition used by Thom has been introduced in the framework of the Andronov's school of non-linear oscillations during the 1930's[45], and has been influential for the development of dynamical

42. See Thom, R., "Une théorie dynamique de la morphogenèse", in : Waddington, C.H. (ed.), *Towards a Theoretical Biology I*, Edinburgh, University of Edinburgh Press, 1968, pp. 152-166 (reprinted in: Thom, R., *Modèles mathématiques de la morphogenèse*, Paris, Christian Bourgeois, 1980; eng. trans.: *Mathematical Models of Morphogenesis*, Chichester, John Wiley and sons, 1983.

43. Petitot, J., "Les premiers textes de René Thom sur la morphogenèse et la linguistique: 1966-1970", <hal-01265180> 2015. For a history of catastrophe theory the reader can report to Aubin, D., *A Cultural History of Catastrophes and Chaos: Around the Institut des Hautes Études Scientifiques, France 1958-1980*, Ph. D. thesis (Princeton University), UMI #9817022. See also, on modeling practices related to catastrophe theory, Aubin, D., "From Catastrophe to Chaos: The Modeling Practices of Applied Topologists", in: Dahan Dalmedico, A./Bottazini, U. (ed.), *Changing Images in Mathematics: From the French Revolution to the New Millenium*, London, Routledge, 2001, pp. 255-279.

44. Thom, R., *Stabilité structurelle et morphogenèse. Essai d'une théorie générale des modèles*, Massachusetts, W.A. Benjamin, Inc., Reading, 1972, p. 324.

45. Andronov, A. A./Pontryagin, L.S., "Coarse Systems", *Dokl. Akad. Nau. SSR*, 14 (1937), p. 247.

systems theory[46]. The question at the origin of the concept of structural stability is: how a mathematical model can be a good model to represent a system of the physical world? The question is relevant, since when writing a mathematical model one cannot take into account all the factors that influence a physical system; moreover nothing guarantees that these factors will remain constant during the evolution of the system. The idea of structural stability is that certain topological properties are shared by classes of mathematical models. This means that one thinks that what is important in order to represent a certain target system does not depend from all the mathematical details of a particular mathematical system. Focusing on *families* of mathematical models instead of *a particular* mathematical model, the notion of structural stability introduces an important epistemic modification in the relation between mathematical models and empirical systems. For Thom, the stability properties of the creods composing the epigenetic landscape are expressed by the mathematical property of structural stability, in the sense that a creod is not but a region of the parameters space for which a process is structurally stable (t.i., roughly, it does not depend from small enough variations of its parameters). However, when Thom exposes these ideas in his article, that has first been published as a chapter in the volume *Towards a Theoretical Biology I* (1968) edited by Waddington, he is criticized by Waddington. Waddington considers that homeorhesis, the property of moving equilibria characterizing creods as pathways of living processes, is not satisfactory represented by Thom's mathematical approach. For Waddington, structural stability is only able to express homeostasis, as the tendency to maintain a stable state, and not homeorhesis, as a moving equilibrium along a pathway of development (a creod). This misunderstanding has aroused a correspondence partially published as an annex to the French version of Thom's article as a chapter of the book *Modèles mathématiques de la morphogenèse* (1982), showing that the two scientists did not really find a definitive agreement[47]. Despite the convincing arguments Thom provided in favor of the pertinence of the property of structural stability, the polysemy of "stability"and its irreducible vagueness when attributed to living systems have accompanied his intellectual entreprise in the following decades.

46. The reader can report to Roque, T., "The role of *genericity* in the history of dynamical systems theory", in: Chemla, K./Chorlay, R./Rabouin, D. (ed.), *The Oxford Handbook of Generality in Mathematics and in the Sciences,* Oxford, Oxford University Press, 2016.

47. For a more detailed commentary of this correspondance, see Franceschelli, S., "Morphogenèse, stabilité structurelle et paysage épigénétique", *loc. cit*.

In his *Esquisse d'une sémiophysique* Thom intends to take up the succession of "natural philosophy"[48]. For Thom "Semiophysics is concerned in the first place with the seeking out of significant forms; it aims to build up a general theory of intelligibility"[49]. The neologism "Semiophysics" has been inspired by an expression used by Jean Petitot, presenting the use of models of catastrophe theory as a "physics of meaning" (*physique du sens*)[50]. For Thom, this general intelligibility could be provided though the development of a theory of *saliances* and *pregnances*. How is this theory related to catastrophe theory?

For Thom a "salience" or a "salient form" is "any experienced form clearly separate from the continuous background against which it stands out"[51].

This notion can be seen as encompassed by the program of catastrophe theory, which is, in fact, a theory of the genesis of salient forms. Catastrophe theory says us that when the structural stability of a phenomenon changes, *i.e.* when we attend to a change of attractor of the dynamics under study, a new salient form appears.

At a first look, it is more difficult to recast the notion of "pregnance" in terms of catastrophe theory. "Pregnances" are in fact defined as "non-localized entities emitted and received by salient forms"[52]. "Pregnances" or "pregnant forms" carry a biological significance: "Among these are the forms of prey for the (hungry) predator, of the predator for its prey, of a sexual partner at the appropriate time. The recognition of these forms gives rise to a very ample reaction in the subject: the freeing of hormones, emotive excitement, and behavior designed to attract or repulse the inductive form"[53]. The relation of pregnances to saliences is at the core of Semiophysics, but does not seem to offer an immediate connection with catastrophe theory: "When a salient form seizes a pregnance, it is invaded by this pregnance and consequently undergoes transformations in its inner state which can in turn produce outward manifestations in its form: we call these *figurative effects*"[54].

However a clarification comes from a further distinction between physical, or objective pregnances and biological, or subjective pregnances,

48. Thom, R., *Esquisse d'une sémiophysique*, Paris, InterEditions, 1989 (eng. trans. *Semio physics: a sketch*, Redwood City, CA, Addison-Welsey, 1990).

49. Thom, R., *Semio physics: a sketch*, ed. cit., vii

50. Petitot, J., *Morphogenèse du sens*, Paris, Presses Universitaires de France, 1985, Vol.1, p. 293.

51. Thom, R., *Semio physics: a sketch*, ed. cit., p. 3.

52. *Ibid.*, p. 16.

53. *Ibid.*, p. 6.

54. *Ibid.*, p. 16.

which allows Thom to affirm that structurally stable forms are physically pregnant forms.

Thom proposes also a formalization of subjective pregnances: the structure of a pregnance is depicted as potential well, more exactly as an "epigenetic landscape" in Waddington's sense of term"[55], where the source forms are at the bottom of the potential well. As if René Thom had never stopped to come back to the initial sources of embryology and in particular of Waddington writings, that had been at the origin of catastrophe theory, the discussion of the properties of the epigenetic landscape in the elaboration of semiophysics is relevant, too. But in this case the landscape, as the formalization of a subjective pregnance –a concept that largely exceeds the domain of embryological development– must possess further properties of stability or of instability, included the ones of being able to propagate and to be modified in its proper morphology.

55. *Ibid.*, p. 10.

