CHAPTER 7

The landscape metaphor in development

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Introduction

Sewall Wright's graphical visualization of the *fitness landscape* (Wright, 1932) is reputed to be one of the most famous metaphors in the history of biology (Dietrich & Skipper, 2012). On that hilly landscape, populations of organisms are represented as occupying a specific position (or a set of positions, one for each individual) in a space of descriptors, which depends on their genetic or phenotypic constitution. Different positions of this space are characterized by distinct fitness values, which collectively describe a fitness surface whose shape affects the future evolution of the population itself. Evolutionary change is visualized as the population change in the occupancy of the fitness landscape.

Wright's metaphor has met with criticism from both philosophers and theoretical biologists, who pointed out its ambiguous interpretation, the complications with translating it into rigorous mathematical models, and the inability of its standard three-dimensional visualization to capture the properties of real multidimensional fitness functions (Gavrilets, 2004; Kaplan, 2008; Pigliucci, 2012; Pigliucci & Kaplan, 2006; Provine, 1986). Meanwhile, other scholars have defended the value of the landscape metaphor in spite of technical difficulties with its application, at least as a heuristic (Plutynski, 2008; Ruse, 1996; Skipper, 2004; Skipper & Dietrich, 2012).

Where all agree is that during the last eighty years the fitness landscape metaphor has played a central role in the formal mathematical modelling of adaptation and speciation and in the didactics of the basic principles of evolutionary theory (Svensson & Calsbeek, 2012). Furthermore, the notion of fitness landscapes, aptly modified and expanded, has found numerous applications outside evolutionary biology, as for instance in biochemistry, computer sciences, engineering, and economics (Gavrilets, 2010). More importantly here, it inspired Conrad Hal Waddington (1939, 1940) to adopt a landscape visualization in a different biological discipline which, at a different temporal scale, also deals with time dynamics, i.e. development. This chapter reviews and discusses the use of the landscape metaphor in development, rather than in evolution, analysing its relationship with experimental work and theoretical modelling.

We start by defining a landscape as a function of multiple variables and show how this can be interpreted as a dynamical system. From the perspective of dynamical systems modelling, we move to analyse Waddington's 'epigenetic landscape' and landscape representations in current developmental biology literature. Then we delve into the problem of models and metaphorical representations in science, which stands out as a crux for assessing the use of landscapes in development, and analyse the somewhat parallel stories of Wright's and Waddington's landscapes. We conclude with some ideas on developmental landscapes in the context of visualization in science, with a focus on theoretical work in developmental biology.

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What is a landscape?

A precise definition of 'landscape' is the necessary starting point for any investigation on this visualization in scientific research.

Let us define a landscape as a mathematical function which associates the values of a set of independent variables (*indV*s) to the value of one numerical dependent variable (*depV*) over an ordinary Euclidean space. In technical terms, a landscape is thus a *function of multiple variables*.

For a set of *n indV*s, such a function describes a *hypersurface* of dimension *n* (the same number of dimensions of the space of *indV*s) embedded in a multidimensional space of $n + 1$ dimensions. In the special case of just one *indV* ($n = 1$), the function can be represented as a one-dimensional curve in a two-dimensional space (the Cartesian plane; Figure 7.1a). When $n = 2$, the function assumes the form of a two-dimensional surface in an ordinary three-dimensional Cartesian coordinate system (Figure 7.1b).

The latter case provides the analogy with geographic landscapes. The two *indV*s are interpreted as geographic coordinates whose values specify a position in a two-dimensional space (e.g. the surface of an ideal globe), while the value of the *depV* represents the elevation with respect to the mean sea level. This analogy, by extension, gives reason for the use of the label 'landscapes' for these kinds of functions, irrespective of the number of *indV*s and of the actual possibility of visualizing the relationship as a geographic landscape. Note that, although in mathematics a function can also be termed a *map*, it is not true that any function is a landscape, as the homonymy with (topographic) maps, which are representations of geographic landscapes, might suggest. For instance, a function which associates each point of its domain to a set of values (rather than only to one) is a map that is not a landscape, under the above definition.

A key property of landscape functions (henceforth, landscapes), as we have defined them, is that they are *scalar fields*, i.e. functions that assign a real numerical value to every point in a space. In the regions of the domain where the scalar field is differentiable, this is associated with a *vector field*, that is, its *gradient*. The gradient of a scalar field is a function that assigns to every point of its domain a vector which points in the direction of the greatest rate of increase of the scalar field and has a magnitude equal to the rate of that increase (Figure 7.2). In other words, the vectors indicate the direction and degree of inclination of the maximum slope at each point in the landscape.

Landscapes and dynamical systems

Because of the association of scalar fields with vector fields, landscapes have close connections with dynamical systems.

As a mathematical formalization, a *dynamical system* consists of a rule that governs the temporal evolution of a set of *system variables*. At any given time, a dynamical system has a *state*, defined by the values of its system variables, and the *temporal*

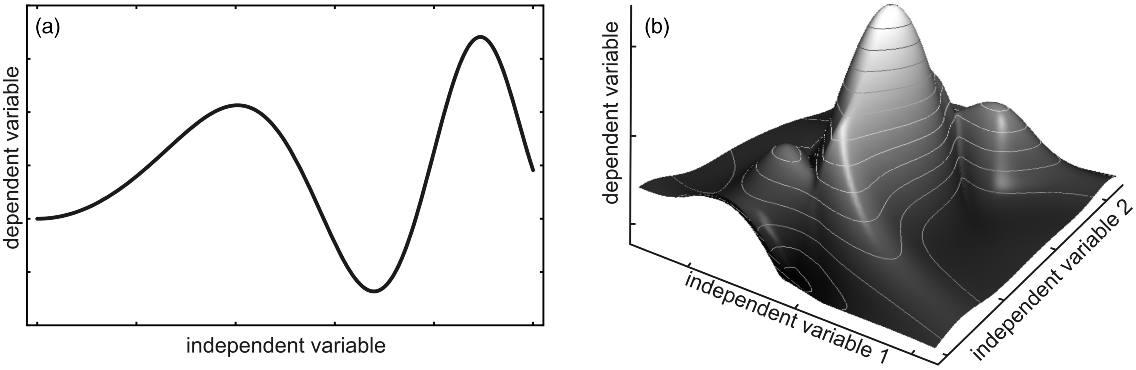

Figure 7.1 Landscape functions in (a) two- and (b) three-dimensional space.

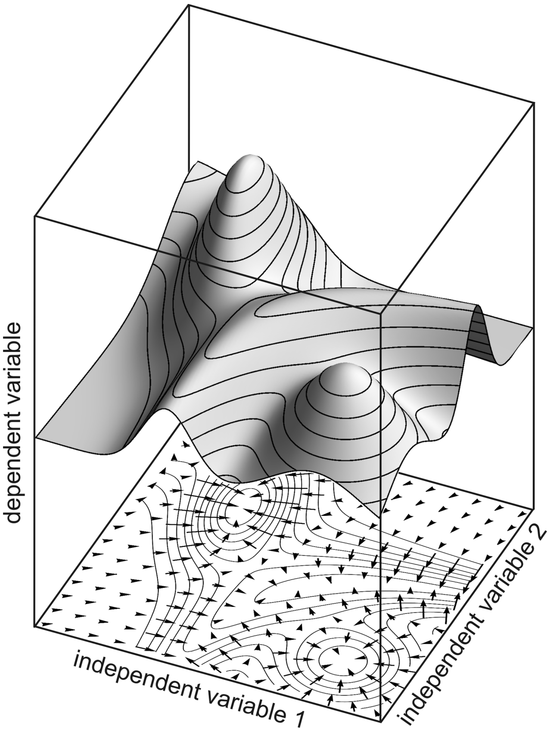

Figure 7.2 A scalar field in two variables (the landscape surface) with the associated vector field that is its gradient. This is depicted as a projection on the bottom plane.

evolution rule makes it possible to derive from that state the past and future states of the system. The state of the system can be represented by a specific point position in an appropriate *phase space* (or *state space*), the axes of which represent the system variables. Dynamical systems customarily take the form of systems of differential equations or systems of finite difference equations, and at low dimensionality (number of system variables ≤ 3), they are graphically portrayed as curves that show the time trajectories of the system in the phase space (*phase portrait*; Figure 7.3).

The key point for the discussion that will follow is that the equations defining a dynamical system describe a vector field which, under certain conditions, can be seen as the gradient of an associated scalar field. In physics, such a scalar field is known as *potential function* (also *scalar potential* or *potential surface*), and a system governed by a potential function has the property that the rate of change of its states is proportional to the derivative of the function (in other words, proportional to its gradient), while the minima and maxima of the function are equilibrium states.

Dynamical systems whose expression is the gradient of a potential function (actually, by convention, with opposite sign) are called *gradient systems* (Hirsch et al., 2004), but there are dynamical systems that do not have a potential function, as it is the case of most real physical systems, which are far from thermodynamic equilibrium. In other words, there are dynamical systems, often called *non-equilibrium* systems, which cannot be faithfully represented as landscapes, while in general any ordinary landscape can potentially be interpreted as a dynamical system. As we will see, the asymmetric relationship between landscapes and dynamical systems has profound implications for an understanding of the use of landscape visualizations for the modelling of developmental processes.

One can also note that the interpretation of a landscape as a dynamical system is generally coupled with a supplementary graphical contrivance. The landscapes which simply depict the relationship between a set of variables and that do not describe the time evolution of any system (e.g. a genotype–phenotype map), which we can call *static*, are depicted as 'uninhabited lands'. On the contrary, the landscapes loaded with a dynamical system interpretation, which we can call *dynamic*, are depicted as 'lands inhabited by entities' whose movements are governed by the shape of the landscape itself. In the classic iconography, not only in biology, these are landscapes populated by rolling balls (e.g. in chemistry) or by swarms of climbing points (e.g. in evolutionary biology) which describe the temporal evolution of the modelled system. In addition, or as an alternative, the surface of the landscape is covered by arrows or stream symbols which show the time evolution of the system from different points in the space. 'Dynamic landscapes' are the kind of landscape put to work in the study of developmental processes.

Waddington's landscapes

Undoubtedly, the most famous application of a landscape visualization in thinking about development is Conrad Hal Waddington's (1940, 1957)

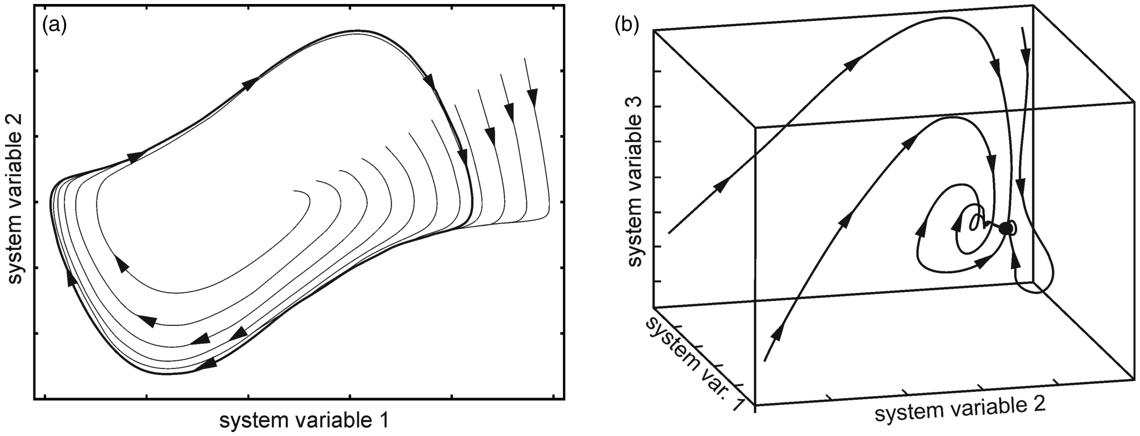

Figure 7.3 Dynamical systems of (a) two and (b) three variables represented in their phase space. In (a), several of the system trajectories lead to the same limit periodic stable attractor, a limit cycle (Van der Pol oscillator, adapted from Wikimedia Commons). In (b), several system trajectories lead to the same stable point attractor.

'epigenetic landscape' (Figure 7.4a), which served as a pivotal concept in his attempt to conceive an explanatory framework encompassing the organizational processes of development ('epigenesis', in contrast to 'preformationism', Maienschein, 2012) and the activity of genes ('genetics'). Today, the term 'epigenetic' tends to be used with a different meaning with respect to that intended by Waddington, i.e. to indicate phenomena of heritable changes in gene expression that are not due to changes in DNA sequence (Eccleston et al., 2007). To avoid ambiguities we will refer to 'Waddington's landscape'. As we will see, this label is further justified by the fact that in contemporary literature, in particular on cell differentiation, landscape visualizations are often accompanied by specific reference to Waddington's work.

Waddington himself, in successive works (1939, 1940, 1956, 1957), gave different interpretations of his landscape visualization (for careful historical reconstructions and philosophical scrutiny see Baedke, 2013; Caianiello, 2009; Fagan, 2012; Gilbert, 1991, 2000; Peterson, 2010; Slack, 2002). Here we summarize the main issues of his concept, which are of particular relevance with reference to its current use in the context of a dynamical system approach to the study of development. Indeed, several authors have seen in Waddington's work a pioneer application of the dynamical systems theory (Franceschelli, 2009, 2011; Kauffman, 1987; Saunders, 1989, 1993; Slack, 2002).

A picture of Waddington's landscape, first described in words (1939), appeared in *Organisers and Genes* (1940) in the form of a painting in the frontispiece of the book. In this book Waddington conceptually examined the embryological knowledge of his time: grafting experiments and other manipulations had demonstrated that the 'organizer', a specific region of the embryo, could deviate contiguous regions of the developing embryo towards forming different tissues and organs. However, in order to be effectively influenced, those parts of the embryo had to be in a specific state of 'competence' which gets progressively lost during development.

Relying on a solid tradition of visualization in embryology (Gilbert, 1991; Griesemer & Wimsatt, 1989), Waddington first envisioned the development of any 'embryo part' as a cascade bifurcation diagram, where, through a sequence of developmental decisions, the part is driven from an undifferentiated state towards one of its alternative possible fates, represented by the tips of the diagram. In this view, the action of the organizer is more a sort of 'evocation' than an 'induction', the emphasis being on the potency and competence of the embryo part that only needs specific triggers at particular times.

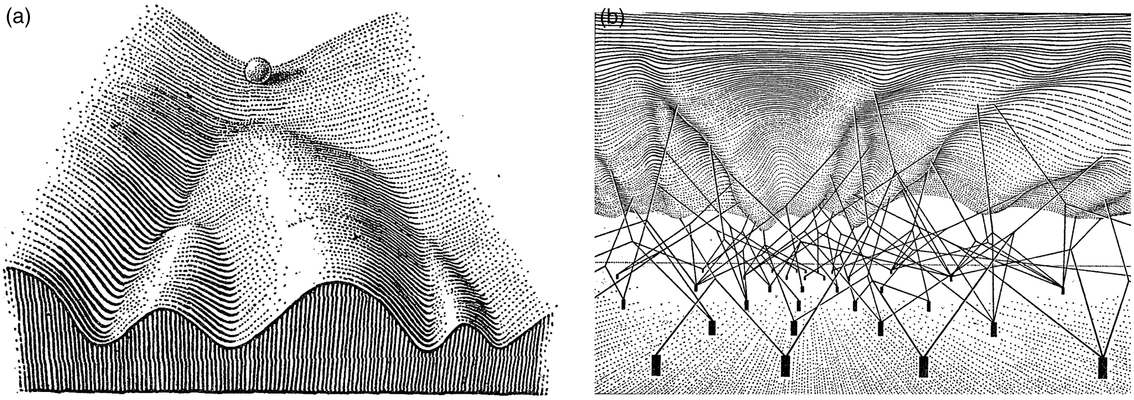

Figure 7.4 Waddington's (1957) depiction of his 'epigenetic landscape' (reprinted with permission). (a) The marble represents a biological system (e.g. a cell) at the verge of taking a developmental path toward one of a set of alterative more differentiated states represented by the three ending depressions at the base of the slope (Waddington, 1957: 29). (b) A vision from behind an epigenetic landscape. The shape of the slope is determined by tension of several interconnected guy-ropes (interacting gene products) that are attached to pegs stuck in the ground (genes) (Waddington, 1957: 36).

Waddington's landscape is clearly a reduction to three dimensions of this first intuition, through the transformation of a branching-track diagram into a system of bifurcating valleys. This transformation allowed Waddington to animate the track graph with notions like equilibrium, disequilibrium, and disturbance. The familiar behaviour of water streaming by gravitation provided Waddington with the means of conjugating several ideas, namely that embryo's parts (i) are in dynamic disequilibrium (like water running downstream) with a progressive loss of potential, (ii) follow a developmental track which, as a whole, is more or less stable ('the normal developmental track is one towards which a developing system tends to return after disturbance' (Waddington, 1940: 93)), and (iii) generally decrease their sensitivity to disturbances, from periods of high sensitivity where regulation is possible ('a valley with gently sloping sides') to periods of strong canalization ('the valley as having vertical sides'). These concepts, with different degree of importance, survived in later developmental biology studies (Gilbert, 2000).

Looking for the 'evocator', i.e. the key causal factor within the organizer, Waddington argued for its chemical nature. He further argued for a chemical explanation of development in general, where concentrations of different chemicals are causally relevant to developmental pathways and decisions. In Waddington's view, chemical compounds were gene products, and what we today would call gene expression profiles, in their turn dependent on other molecules, were thought of as the proximal cause of developmental trajectories. The dependence of gene product concentrations on 'the dosage of the genes' (allele dosage) represented a key passage in his attempt to relate genes and development. By giving a pioneering image of development regulated by chemical interactions involving gene products, Waddington grasped the intuition of gene regulatory networks with a view strikingly similar to that in modern systems biology (Fagan, 2012).

Waddington's landscape was described in more detail in *The Strategy of the Genes* (1957), where its most famous graphical instances are found (Figure 7.4). In the image, which can be considered the 'icon' of the developmental process of differentiation (Figure 7.4a), the graphic represents a tilted moulded surface, down which a marble is going to roll. The rolling marble's path corresponds to the development of some part of an organism from an early undifferentiated state to a mature differentiated state. The landscape topography presents a system of diverging valleys that become shallower and coalesce towards the top, while becoming deeper and fanning out towards the bottom of the slope. The bottom edge sees a series of depressions representing alternative differentiated states of the system. The particular shape chosen for the slope also conveys other ideas about development. The progressive reduction of the number of possible final differentiating states that occurs as the marble rolls downslope represents the progressive restriction of competence and potency of the system that accompanies differentiation. The progressive increase in the elevation of the crests that separate the different developmental pathways represents the process of canalization, the fact that the system becomes increasingly buffered against development disturbances. The different developmental options available at the beginning of the slope could be followed in response to evocating factors that are not represented in the landscape, like some environmental factors, producing a typical representation of the phenomenon of developmental plasticity. Although it is often assumed that the rolling marble represents a developing cell, in fact, and in Waddington's view, it can represent any developing system under the effect of a number of relevant factors, such as gene products or inducing signals.

Waddington's (1957) landscape is a genuine representation of a developing system described in a space of state variables. For a differentiating cell, the height of the surface is proportional to some potential variable ('developmental potential') associated to each combination of the underlying descriptive variables (e.g. concentrations of different substances or gene products) in the cell. The tilt of the surface shows the spontaneous tendency for the system to change its state along one of the available pathways. Although in this graphical representation the surface is in some way external to the marble/cell, in the modelled system the slope is actually determined by the characteristics of the developing cell, while non-represented (*hidden*) variables that play the role of external perturbations or induction may be either inside or outside the developing cell.

Even when unanimously interpreted as the representation of a dynamical system, the metaphor is still open to different understandings. For instance, for Slack (2002), the axes represent concentrations of all the substances, or all the gene products, in the cell, but because of the existence of inducing signals (not represented in the landscape), which can only influence a cell's development while the cell is competent to respond (i.e. uphill), different cells/marbles will roll down different pathways to end up at different states of terminal differentiation. Instead, for Fagan (2012), the horizontal axis projecting outward to the viewer represents time, the horizontal axis parallel to viewer represents the phenotype, and the vertical axis represents the 'order of development'.

In an effort to make the metaphor more explicative, Waddington (1957) provided a view of the 'underside' of the landscape, to show its supposed relationship to the genes (Figure 7.4b). The shape of the surface is determined by the pull of numerous guy-ropes which are in their turn controlled by genes, represented as pegs fixed to the ground. Guy-ropes represent gene products, and their connections represent their reciprocal interactions, which form a network that directly determines the shape of the landscape, i.e. of the dynamic of development.

Summing up, with his landscapes Waddington provided a simple mechanical analogy for the complex biochemical and genetic dynamics that occur in organisms during development (Slack, 2002). The surface embedded in the state space of an organism's molecular components is an effective representation of a dynamical system, potentially able to describe the change in time of a developmental system at any level of biological organization, from the cell (or even from systems within a cell) to the whole organism.

Subsequent modelling in developmental biology, although not directly stemming from Waddington's approach, nonetheless continues to put forward his graphical representations and to refer to his pioneer work.

Landscapes in current developmental biology

Current primary literature in developmental biology makes use of a diversity of graphical visualizations, depending on the specific subject (e.g. cell differentiation, pattern formation, gene expression) and the arena of the argumentation (e.g. experimental report, local dynamic modelization, theoretical generalization). Beyond their predictable occurrence in developmental biology textbooks, if only for historical reasons, Waddington's landscapes can also be found in the current primary literature, in both experimental and theoretical developmental biology papers. They have been brought into play in studies on pattern formation (Lepzelter & Wang, 2008), cell signalling (Sekine et al., 2011), and programmed cell death (Zinovyev et al., 2013); however, they mainly tend to occur in cell differentiation studies, with a further focus on stem cell biology (see below). This is a direct consequence of the landscape model's connection with dynamical systems.

Mathematical modelling in developmental biology, in particular at the level of specific developmental processes, like cell differentiation or pattern formation, is largely implemented through a dynamical system approach. Here developmental biology enters an intimate relationship with *systems biology* (see Jaeger and Sharpe, this volume), an emerging interdisciplinary approach to the study of biological systems which focuses on the complex interactions among different components of the system. The system, in essence, is seen as a network of relations, with gene expression, metabolic networks and cell signalling networks as well-known examples. The formal representation of the system can take several alternative formalizations, from ordinary differential equations to directed graphs, Boolean networks, and Bayesian networks (Fagan, 2012; Klipp et al., 2009). All these different formalisms have a specific scope and range of application. For instance, differential equations define continuous, deterministic models, while other kind of formalisms make it possible to cope with discrete deterministic models or with stochastic models. The different scope of these formalizations is not of particular relevance for the argument we are developing here, and we can limit ourselves to simply note that the use of differential equations is the most common formalization for dynamical systems in general and biology dynamical systems in particular.

In many papers the mathematical modelling of the dynamical system, typically as a system of equations, is accompanied by either or both of two kinds of graphical representations: wiring diagrams and phase portraits. Wiring diagrams are conventional pictorial representations of networks. Network nodes represent interacting entities (e.g. molecules or genes) while the connecting edges represent the interactions among the different nodes, generally with a simple symbolism to discriminate different kinds of relations (e.g. activation vs repression). Quantitative aspects of the interactions and spatial organization of the interacting entities are generally not represented. Wiring diagrams provide a means to grasp the topology of the interactions, that is, the interdependence of system variables which are detailed in the equations, while avoiding the possibility of getting lost in the complex expression of the latter. However, while the wiring diagram represents the system 'machine' behind a given developmental process, it does not make it possible to see how the system changes in time. Thus wiring diagrams are generally accompanied with a different representation of the same system, i.e. the phase portrait. Phase portraits are geometric representation of the trajectories of a dynamical system in its phase space (Figure 7.3). Each curve represents the time evolution of the system starting from a different set of initial conditions (a different point in the phase space). The trajectories reveal the existence of system *attractors*, i.e. the sets of states towards which the systems tend to move over time. An attractor can be a point, a finite set of points, a curve, or even a complicated set with a fractal structure known as a strange attractor. The zone of the phase space where the system is driven towards the attractor is called its *basin of attraction*. Within the limits of the three-dimensional illustration (not easy to overcome on a paper sheet), phase portraits can represent a diverse bestiary of systems behaviours, which is wider than the set representable with a landscape. First, in a three-dimensional phase portrait, three system variables can be represented, rather than two as in a three-dimensional landscape plot, in which the vertical axis is needed to represent the associate potential value of variable value combinations. Second, there are dynamical behaviours of the systems that cannot be faithfully accounted for by a landscape, such as limit cycles and chaotic behaviours (see 'Landscapes and dynamical systems').

Nonetheless, frequently phase portraits are followed by a landscape representation, or by a hybrid visualization which mixes phase portrait and landscape together. To understand their precise role in the current literature, we will start from a few illustrative examples of recent studies on cell differentiation. Actually, the use of Waddington's landscapes is not exclusive to such area of study (see Baedke, 2013).

However, since the aim of this contribution is not a meta-analysis of the current use of the landscape visualization but rather a close examination of the rationale behind its involvement in ‘development thinking’, limiting the selected examples to cell differentiation does not affect our general argument.

In a review on stem cell dynamics, Enver et al. (2009) are explicit in that they make a ‘metaphorical’ use of the landscape representation (Figure 7.5a). Using the traditional imagery of a marble rolling down a slope, they give the vertical dimension a thermodynamic interpretation as the free energy of the system in different states. However, in their opinion the valleys of Waddington’s landscapes ‘missed the scope for relatively stable, if transitory, intermediate cell types observed during the differentiation’ (Enver et al., 2009: 388). The valleys (actually barely perceivable) of their landscape are thus punctuated by shallow depressions, representing as many intermediate temporary stable states. Mathematically, all the depressions are seen as attractors, i.e. equilibrium states towards which the dynamical system tends to move. However, as is apparent from the trajectories of the system represented in the graph, although certain paths are more likely than others, the authors specify that for a cell ‘the possibility must also exist of moving in the reverse or alternative directions’ or that a cell can ‘move from one attractor to another by different routes’ (Enver et al., 2009: 389).

In a methodological study on mathematical modelling of stem cell differentiation, Wang et al. (2010) do not consider the landscape representation as an accessory metaphor, but they have to go beyond the original landscape concept in order to make it significant in rigorous modelling. While they recognize that the idea of a potential function is particularly useful for equilibrium systems, where the potential is knowable a priori, non-equilibrium systems (in practice, most biological systems) cannot, in general, be modelled as the gradient of a potential. The intuition of some potential, although widely used metaphorically, does not make it possible to move to a precise mathematical formalization. However, at the same time, standard dynamical system analysis cannot account for the fact that developmental processes exhibit, at certain scales at least, a consistent directionality in time. In their words, the ‘“arrow of time” in the collective change of gene expression across multiple stable gene expression patterns (attractors) is not explained by the regulated activation, the suppression of individual genes which are bidirectional molecular processes, or by the standard dynamical models of the underlying gene circuit which only account for local stability of attractors’. Thus, to capture the global dynamics of this non-equilibrium system and gain insight in the time asymmetry of state transitions, they compute a ‘quasi-potential landscape’ of the stochastic dynamics of gene circuits that govern cell-fate commitment. This is a function which combines a gradient potential with another force (‘curl flux’) that stem from the non-integrability of the system. In a fol-

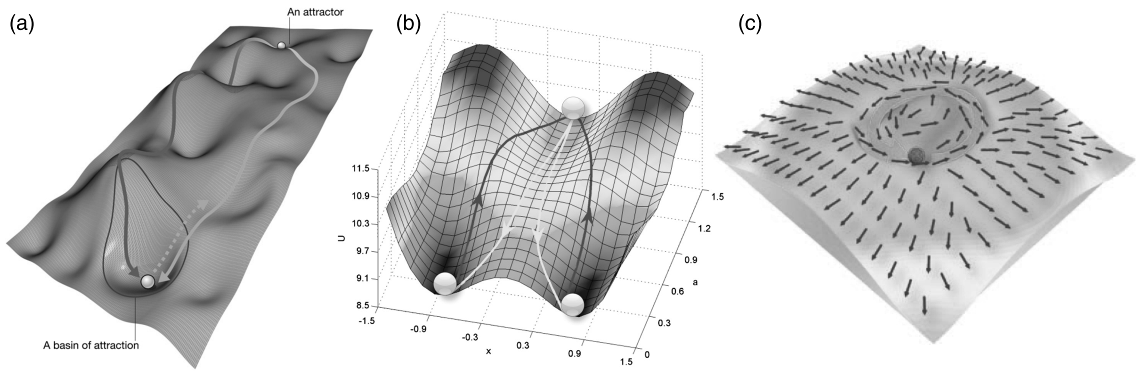

Figure 7.5 A few examples of contemporary developmental landscapes (reprinted with permission): (a) from Enver et al. (2009); (b) from Wang et al. (2011); (c) from Furusawa and Kaneko (2012). In all cases, the behaviour of the developing systems does not faithfully follow what would be expected under a strict gravitational analogy (see text).

lowing paper from the same research group (Wang et al., 2011), underlining the fact that due to the *qualitative* nature of Waddington's landscape it is not very clear how to connect it to the results of experimental work, the authors suggest a formalization which aims at 'quantifying' Waddington's landscape. Focusing on cell differentiation, they use the analytical tool based on the combination of a gradient with a curl force devised in their previous works (Wang et al., 2008, 2010) to construct a 'quantified Waddington landscape' (Figure 7.5b). However, despite superficial similarity, a number of differences between the new landscape and the original Waddington's landscape must be pointed out: (i) in the quantified landscape the temporal stabilization of the uncommitted stem cell state is permitted; (ii) cell-fate decision does not necessarily happen at the hilltop, as developmental paths can start bifurcating even when the system is in a basin of attraction; (iii) 'developmental paths clearly do not follow gradient paths that the gravity driven metaphor of Waddingon would predict', as the curl force makes the developmental path deviate from the steepest descending gradient path; and (iv) while in Waddington's landscape the possible reverse path is supposed to be the same as the forward path, in this quantified landscapes 'the developmental paths are clearly distinct from the retrodifferentiation paths'.

In a dynamical systems perspective on stem cell biology, Furusawa and Kaneko (2012) argue that some core property of 'stemness', like differentiation from a stable state, 'cannot easily be described by Waddington's landscape'. Through a dynamical systems approach, they describe a model in which fluctuating and oscillatory gene expression, 'the essence of stemness', are accounted for. To explain the difference between the traditional view of cell differentiation and the one suggested in their work, they make use of a landscape visualization (Figure 7.5c). On these landscapes, however, the streams of vectors indicating the direction of the system in each state are not always in conformity with the curvature of the landscape, as one would expect if these were to be intended as its gradient field.

As noted by Fagan (2012) and exemplified by the case studies above, landscape visualization does not represent a predictive tool, but rather a visual aid for the derivations of the model. In other words, model construction of cellular systems does not start from the definition of a potential function (the landscape), as is the case under certain condition for fitness landscapes (but see Rice, 2004).

Summing up, landscape visualizations are still present in the current literature, although they come in different 'flavours' and with a great disparity in their interpretative load. This varies from allegoric pictures, like in the editorial commentary (Iovino & Cavalli, 2011) of an experimental work of Thomson et al. (2011) in the same journal issue, where landscapes are not even mentioned, to their full rehabilitation as models, conditional on their mathematical quantification, in the works of Wang et al. (2008, 2010, 2011).

Landscapes, between models and metaphors

Contemporary modelling research in developmental biology, in particular on cell differentiation, makes frequent reference to Waddington's landscape. On the one hand, historical continuity is emphasized. On the other hand, this is supplemented by a statement of progress with respect to Waddington's ideas, and many authors identify such progress with the move from a 'mere metaphor' to a more sound conception. For Ferrell (2012), 'Waddington's landscape [. . .] is more than just a metaphor', but at the same time he argues that the classical shape of its surface, with diverging valleys, is correctly illustrative of some developmental processes but not others, like cell-fate induction, for which he proposes an alternative general shape. Furusawa and Kaneko (2012) claim that today to 'characterize the attractors of stem and differentiated cells quantitatively' we need not just further experiments but also 'theoretical formulations that go beyond Waddington's epigenetic landscape'. For Wang et al. (2011), 'The Waddington landscape is no longer a metaphor. It is physical and quantifiable by the underlying probability landscape.' And Huang (2012) emphasizes that the 'quasi-potential landscape with attractors' is 'a mathematical entity that has a molecular basis and is not a mere metaphor'. It seems that the qualification of a landscape as either a metaphor or a mathematical model is a crucial passage for any evaluation of the use of landscapes in developmental biology.

In everyday discourse, as well as in some philosophy of science studies, the most natural counterpart of metaphors are models: there is an intuitive difference between representations that are 'only metaphors' and others that are 'models in their own right'. However, there is little consensus on any diagnostic feature to distinguish between the two. Mathematization has been proposed as a distinctive feature of models (Lewontin, 1963), but scientific models come in many kinds, including visual and material objects (Downes, 1992), and even organisms (Ankeny & Leonelli, 2011). A narrow selection of represented aspects of the world and the lack of testability were proposed as distinctive marks of metaphors (Kirchner, 1990), but extreme simplification can be found in mathematical models too (Lewontin, 1963), and the application of such models to the world can always be seen as a metaphorical re-description (Hesse, 1966). A famous analysis by Levins (1966) emphasized that model building requires making certain trade-offs between realism, precision, and generality. Levins' scheme can be used to accommodate several kinds of representation as models without the need of setting metaphors apart (Calcott, 2008 vs Pigliucci & Kaplan, 2006 on adaptive landscapes).

In the case of developmental landscapes, we think that the most suitable framework to set the model/metaphor contrast is one based on a criterion technically known as *autonomy*. Morgan and Morrison (1999) emphasize the autonomy of models with respect to both theory and observational data. Models are seen as 'mediators', and their autonomy consists in the possibility of performing intensive research on the model itself, elevated to a 'stable target of explanation' (Keller, 2002: 115). For instance, mathematical analysis of models built through a dynamical systems approach (see 'Landscapes in current developmental biology') has brought about discoveries about dynamical systems themselves, quite independently from the original questions to which they were applied. The produced knowledge can be brought back, at different times, to the 'representational target' that had inspired the model but also to a changing 'representational scope' that can be much wider than the original target (Ankeny & Leonelli, 2011), as exemplified by the fact that the same mathematical model can apply to completely unrelated real systems. A model M can thus be defined as a representation of the system S that can be worked upon with significant autonomy from S and can be usefully employed for answering questions on S and, with every probability, also on a wider set of systems S_i. The set S_i, the representational scope of model M, can change as science progresses. In contrast, the distinctive mark of a metaphor is not that it conveys a very limited set of aspects of the represented system (although, of course, it does), but rather that it cannot be investigated, deepened, and modified independently to accrue knowledge. It can be further amended and/or complemented only as the empirical or theoretical understanding of S progresses. The constitutional subordination of metaphors with respect to the system they represent is not in contrast with the positive heuristic function emphasized by some theorists. Indeed, summarizing, stimulating, and guiding research upon target systems, as opposed to upon themselves, is all metaphors can do. Constitutional subordination further implies that internal consistency is neither a requirement nor an assumption of metaphors. Models, unlike metaphors, need some kind of internal consistency that is at the basis of their constitutional autonomy.

The degree of autonomy criterion is a suitable framework for addressing the problem of landscapes in development. However, it produces a continuum of representations, from the most rigorous of formal models to the most allegoric of metaphors, rather than providing a clear boundary between the two categories (see Kaplan, 2008 for an opposite view). Both models and metaphors are representations of real systems, both emphasize some feature of the real world while deliberately neglecting others, both are good for specific purposes only, and both are potentially misleading in that accepting a specific representation necessarily influences and defines the questions that are considered to be important (Gavrilets, 2004, 2010).

Further insights on the model/metaphor relationship can be gained by looking into the parallel histories of the two major landscape metaphors in biology. At the beginning of the chapter, we mentioned fitness landscapes in evolutionary biology, their success, and the debates that surrounded them in recent years. Historical reconstructions of Waddington's work (Caianiello, 2009; Gilbert, 1991) demonstrated that Waddington's landscape was inspired by Wright's work (1932) through Joseph Needham (1936). Such connection was motivated by Waddington's search for relating development to genetics (Gilbert, 1991).

Beyond historical links between landscapes in development and evolution, we highlight here a curious form of antisymmetry between the history of the two ideas since their respective introduction in scientific literature. Evolutionary landscapes were introduced by a mathematician, Wright, as a pictorial representation of a mathematical model. Then, generations of students of evolution, working in totally different fields, from genetics to palaeontology (Dobzhansky, 1937; Simpson, 1944), adopted the figure as a basis for their non-mathematical theorizations. Some commentators describe the employment therein as a useful heuristic (Ruse, 1996; Skipper, 2004; Skipper & Dietrich, 2012). In contrast, developmental landscapes were introduced by an experimental embryologist as a depiction of his empirical observations to serve as a conceptual tool. The figure was then taken up by biologists and biophysicists with more mathematical skills as a complement to their formal models and simulations about specific developmental processes. Both Wright and Waddington were partly responsible for the later uses of their respective intuitions. Wright (1988) approved the usage in contexts as different from the native context as palaeontology and was charged with levity for that (Pigliucci, 2008). Waddington (1957) himself moved to systems theory and presented his landscape in a completely different context with respect to his previous work (1940). At that time, powerful mathematical and theoretical tools were already available (although without the computational power we have today), but the empirical knowledge, e.g. on genes and their role in development, was by far insufficient for model construction in development.

Interestingly, the two landscape metaphors are opposites in terms of what concerns their native context. Wright's model was a logico-mathematical system of Mendelian populations, with huge dimensionality that was reduced to a three-dimensional representation (Serrelli, 2011). The landscape metaphor here is thus a partial representation of a complex mathematical model, which, however, cannot capture the properties of real multidimensional landscapes, as shown by more recent theoretical work (Gavrilets, 2004, 2010). Waddington, instead, originally had no mathematical models to select from, and the messages entrusted to the metaphor were directly derived from empirical observations of competence, evocation, equilibrium, disequilibrium, disturbance, discrete end-states, and the like in developing tissues of embryos of different species.

In the studies examined in this chapter, developmental landscapes, despite being potentially misleading, nonetheless correctly orientate the attention of the reader towards specific messages chosen by the researcher. Landscape visualizations are metaphorical in that they are not autonomous objects of research and inference, and they show a limited selection of features of the developing systems, although at the same time they are the best visual approximation for the equations that describe them.

Landscapes and 'vision'

Our perusal of recent literature, although far from being exhaustive, has shown that Waddington's landscape is 'alive and well in contemporary developmental biology' (Gilbert, 2000: 734). However, contemporary developmental landscapes differ profoundly from the original representations. It is a semantic question to ask if these 'new landscapes' are still 'Waddington's landscapes', but asking how much of a landscape there is in them is not. On these strange landscapes, or 'quasi-landscapes', one is not authorized to see a marble rolling down the slope. Strange things can happen on such surfaces: marbles emerging from a pit, taking a path different from the one with maximum slope, going uphill, moving from one place just to be back some time later. In addition, the landscape surface is only a part of the graphical representation of a dynamics. This needs to be complemented with vector arrows or stream signs that can even be at odds with the shape of the landscape on which they sit. On this landscape one has to relax the natural spontaneous gravitational interpretation of the represented dynamics, but at the same time it is exactly the fact that everybody has a personal experience of the gravitational force that makes this representation so eloquent.

This is a little-appreciated, misleading trait of landscape representations in general, not only in visualizations of development. The landscape representation deceptively suggests that the phenomenon/system could be described in terms of a potential function that is maximized/minimized at equilibrium; however, this function does not always exist (Rice, 2004). Another, mostly neglected and potentially misleading trait is that, even if a landscape faithfully represents the directions of change of the system from any state, the kinematics of a rolling marble does not necessarily apply. For instance, while a marble in a gravitational setting would increase its speed rolling down a constant slope, the marble of Waddington's landscapes would roll down the same trajectory at a constant speed. At a local minimum of the landscape, a gravitational marble would stop accelerating, whereas Waddington's marble would stop moving (Ferrell, 2012).

Nevertheless, landscape graphical representations are able to convey information not immediately apparent in a phase portrait. For instance, they can effectively express the directionality of the process at large scale, the degree of stability of local equilibria, and the fact that certain trajectories are more probable than others. Some dynamical systems can still be represented as landscapes, for instance stipulating that a 'stable state' is not necessarily exactly a point, but can also be a periodic or aperiodic oscillation within a comparatively small region of their phase space.

In general, a landscape cannot be a faithful representation of a real system. This is especially true of open systems (i.e. systems open to matter and/or energy flow), such as a developing organism or a part of it. But this is not new, as Waddington himself described with words dynamics and interactions which could have never been portrayed on his landscape. Indeed, to stress his view on the role of genes in development, Waddington (1957) produced a second graph (Figure 7.4b). However, whereas in the most famous graph (Figure 7.4a) the figure can still be ideally translated into a formal model, providing specific identity to the three axes, in this second graph this possibility is lost. The ropes traverse the space inserting at the base of the space (why there?) and under the surface. Actually, the ropes (genes products, cell metabolites) should already be represented by the axis of the space, while their insertion points have no physical value; and they are supposed to exert forces that are not represented in the space. Thus Waddington's attempt to convey more explicit reference to the generative forces (or relevant factors) for the particular shape of the landscape results in a less accurate representation.

One can search the reasons behind the persistency of the landscape metaphor in the scientific literature. It appears that the idea of a landscape is floated every time there is the need to talk about a map, an association between quantities, irrespective of the mathematics one can develop on it or the actual possibility of giving precise physical meaning to the axes of the space. Reasons for that can possibly be found in the architecture of our cognition system, or in our difficulty in giving up the tradition of a cherished metaphor. We refrain from pushing these speculations further, and suggest instead a parallel with a historic controversy, partially still ongoing within mathematics. This is about the role of geometric vision in mathematics.

The French school known by the collective name of Nicolas Bourbaki was the leading group of mathematicians who aimed at a complete algebraization of geometry and analysis through the construction of extremely abstract theories, in which the possibility of 'visualizing' mathematical objects is considered to be unnecessary. In contrast, other schools of thought remained more closely linked to an intuitive and geometric vision of mathematics. For example, Vladimir Arnol'd (1998), the author of fundamental works on differential equations and dynamical systems, argued that geometry algebraization, inflated axiomatization and abstraction as an end in itself, leads mathematics to nowhere. In his opinion, the geometric and physical vision of mathematics has a constructive role in the process of mathematical discovery. This is not only a question of method, as there are fundamental mathematical theorems, as for instance the classification theorem for surfaces, which are an achievement of both mathematics and physics together. This discussion was central for most of the last century; however, today the need for a geometric vision of problems, before, during, and after their algebraic differential development, goes beyond all these contrasting arguments. The centenarian development of differential geometry and its centrality as a discipline are no longer in question (Alekseevskij et al., 1991); on the contrary, they are both reputed determinant players in the construction of a 'new geometry' that has yet to come (Yau & Nadis, 2010).

Conclusion

It seems that the landscape metaphor will continue to stay with us, at least for a while. However, it is more difficult to envision its future role in exploring more inclusive levels of abstraction and theorization, as for instance in the search for a comprehensive theory of development. In fact, cell differentiation, in the study of which landscapes have been chiefly employed, cannot be assumed to be a general model for the dynamics of other developmental processes, like cell proliferation, movement, and death, production and consumption of extracellular material, morphogenesis, pattern formation, and growth.

As we have seen, Waddington originally introduced the landscape metaphor in developmental biology as a tool for unifying under the same explanatory framework different developmental processes and their control. Can this be considered an attempt to search for a general theory of development? The answer, not surprisingly, depends on the meaning one attaches to the word 'theory'. Unfortunately, philosophy of science offers more problems than solutions about the nature of theories, in particular about any meaningful distinction between 'theories' and 'models'. Despite a recent rise of interest in defining what theories are (Griesemer, 2013; Morrison, 2007), after several decades during which the philosophy of biology has been mainly focusing on models and modelling in theorizing (Downes, 1992), a reasonable consensus has certainly not been achieved yet. Pragmatically, avoiding venturing into the question of what a scientific theory is or should be, which is far beyond the scope of the present chapter, most would probably agree that Waddington's general model of development fits into what we could call a 'minimal concept of theory', that is, a rational abstract generalization of a set of natural phenomena. However, his conceptualization would not pass the test for a more demanding 'paradigm concept of theory', which requires a theoretical edifice with strong explanatory power for a very large set of natural phenomena as well as high predictive performances to the level of very detailed observations and measures. In common understanding, a general model of a natural phenomenon does not as such qualify as a theory of that phenomenon.

As a matter of fact, independently from the epistemological evaluation on what Waddington was historically aiming at, landscapes have proven to be effective visualization tools for investigating only specific developmental processes, without allowing straightforward formalization into mathematical models. Overall, landscapes seem to be too limited a form of abstraction to stand as a pivotal metaphor in the search for a comprehensive theory of development. However, only future research will be able to assess whether the landscape metaphor can effectively extend its scope to other developmental processes or have any role in a conceptualization of development as a whole.

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