Clarifying the biological nature of the interaction between the systems-based epigenetic landscape and the epigenome

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Abstract

The epigenetic landscape concept initially proposed by Conrad H. Waddington has become a powerful tool to quantitatively address constraints underlying cell differentiation and morphogenesis. In theoretical and experimental terms, this has been enabled by grounding gene regulatory network models on experimental data. Such models have, in turn, led to proposing epigenetic landscape models that entail functional and structural constraints of cell differentiation and morphogenetic dynamics, and thus the understanding of development from a systems–based perspective. Therefore, it is mainly in the context of the study of development where the epigenetic landscape has been anchored as a conceptual support. On the other hand, nonetheless, given the recent understanding of gene control by epigenomic modifications and the capacity to profile these modifications using high–throughput molecular techniques, the notion of epigenetics has been mainly related to non-genetic heritable modifications of the genome. Therefore, this approach, which until now has not been based on a systems–based dynamical treatment, has given proximal epigenomic modifications a central role in understanding development. The latter, has left the dynamic view of epigenetic landscape aside. In this paper we aim at establishing a conceptual link between both conceptualizations of epigenetic regulation.

1 Introduction

The popularity of epigenetics among the scientific community and the lay public has strongly increased during the last decades [10] and we believe public interest in epigenetics can be attributed to two main reasons: 1) the agreement on the fact that genetic information is not enough to understand how an organism is formed and 2) the possibility brought by next generation sequencing technologies to profile epigenomic marks on chromatin [34]. The abuse in the use of the term "epigenetics" comes with the risk of canceling its value in the effective
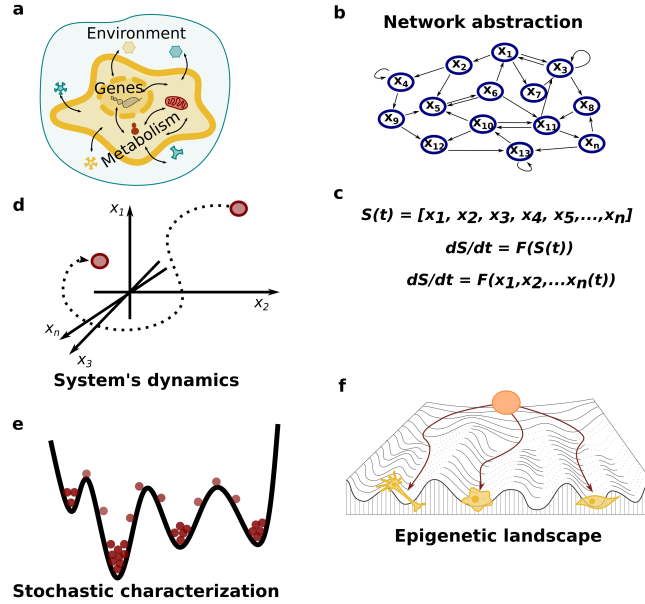
Figure 1: **Dynamical systems modeling of the epigenetic landscape.** The epigenetic landscape theoretical framework seeks to understand a cell as (a) a multidimensional system in which the molecules involved in its behavior are represented as (b) a network of interacting elements. (c) The behavior of this network is analyzed via mathematical formalization. (d) The complete set of possible system states define a state space. (e) Introducing stochasticity to the model grants the characterization of the system states in terms of relative stability, and (f) the intuitive interpretation of the associated epigenetic landscape.

understanding of important biological phenomenology. From the current viewpoint, the term "epigenetics" is used as a new universal explanation for almost any biological question that cannot be explained by classical genetics. It is used to characterize distinct phenomena such as cellular differentiation and development, inter–generational transmission of acquired traits, response to environmental stress, and the origin of complex diseases [3, 32]. Nowadays, the most common use of the word epigenetics is to refer to a diverse set of phenomena associated with biological information not encoded in the genome, ranging from transcriptional regulatory mechanisms, DNA methylation, and histone covalent modifications to RNA editing [16]. This variety of uses stems from the etymological origin of the word: the prefix "epi–", meaning above, and "genetic", referring to information encoded in the DNA sequence. Following this idea, epigenetics is used as a general term referring to anything that has some effect over the genetic information [35]. The semantic ambiguity associated with the word 'epigenetics' might arise from the issue that its current most widely used interpretation is different from the one Conrad Hal Waddington had in mind when he coined the term [36]. He conceived epigenetics as a discipline focused on studying the processes mediating between genotype and phenotype; under the assumption that there is a multiplicity of factors involved in this matter and that the interrelations between these factors should be studied in order to understand development [35]. It is important to highlight that at the time when Waddington conceived his ideas, there was no knowledge yet of molecular signatures on the genome that today are known as

epigenetic marks. In this sense, Waddington defined epigenetics as a general term referring to the processes linking genotype and phenotype. Currently there is a much wider knowledge about the molecular processes involved in organismal development. Still, it is worthwhile considering if a better understanding of the general process of development could be attained by incorporating current knowledge on molecular mechanisms of development that can be integrated into earlier theoretical models. In this paper we evaluate if the two scientific common understandings of epigenetics, namely one referring to molecular modifications of the genome and the other referring to developmental processes relating genotype and phenotype, can be brought together.

2 Modern understandings of epigenetics

There are two main understandings of the word epigenetics: i) the entire series of interactions that mediate between genotype and phenotype (*i.e.* dynamical epigenetics), and ii) the study of heritable modifications in gene function that cannot be explained by changes in DNA sequence (*i.e.* molecular epigenetics) [33]. The former definition comes from Waddington's conception of epigenetics and its focus on developmental processes [18]. The latter one derives from molecular biologists focus on entities determining gene activity, its use is more extended among the molecular biologists and bioinformaticians [17]. This popularity is firmly anchored in the cultural hegemony that computing technology has achieved, which has led to the widespread, and sometimes abusive, use of computational metaphors to address numerous aspects of the structure and functioning of living matter [6]. In part, the difference in these two definitions is a consequence of the historical contexts in which they were conceived. When Waddington introduced his ideas, molecular biology was a recent branch of biology, DNA structure and the biochemistry of transcriptional regulation were still unknown. Something different happened when the term epigenetics met the environment of molecular biology, which grew dramatically in a relatively short time. This is due to the development of new technologies oriented to the investigation of biological phenomenology at the biomolecular level based on the use of the achievements of computing [38]. Thus, the most recent definitions, often built around terminologies inherited from the recent past, were formulated during a time of great technological and conceptual advances in molecular biology, giving this branch of biology a primary role in the explanation of biological phenomenology [24]. Taking apart the differences in the definitions of the word epigenetics, both perspectives intend to find a non–genetic mechanisms for the memory of a phenotypic state. Molecular epigenetics looks for a material entity (DNA methylation, histone covalent modifications, chromatin structure, etc.) that explains phenotypic memory. On the other hand, dynamical epigenetics seeks a memory based on dynamical systems theory, with phenotypic memory emerging from the complex regulatory relationship among genes, cellular, organismic and environmental elements [33]. In this way, the search for information not found on the genome mediating key processes of biological phenomenology has led to the use of the same term, epigenetics, in two different contexts. Advances in molecular biology have made it possible to characterize molecular epigenetic marks in a context dependent manner, giving a much more precise knowledge of the proximate molecular mechanisms that control gene function [34]. These advances have lead some scientists to think that exhaustively characterizing these molecular details would be enough to understand both organismal development and cellular differentiation [21]. Thus, the concept coined by Waddington was taken up by molecular biology and this, as it grew, became interested in answering the questions raised by him, *putting aside his perspective*. Still, it is necessary to evaluate if profiling epigenetic marks is sufficient to understand cellular differentiation and if they give a better understanding of development than that given by the conceptual theory first proposed by Waddington.

2.1   Epigenetics from a dynamical systems perspective: the epigenetic landscape

With his idea of epigenetics, Waddington proposed that a "concatenation of processes linked together in a network" guides development through the coordinated action of multiple genes and environmental factors causing the system to reach specific stable end states [36]. He depicted his idea in his popular diagram of the 'epigenetic landscape', which represents the process of cells passing from an immature undifferentiated stage to distinct stable adult conditions. Although nowadays this picture is widely used, it is not strange to find references to it that do not seem to understand it as a diagrammatic representation of the idea of development as a multidimensional dynamical system defined by the interactions among genes and environment [4]. So, to get things clear, how is development explained as a multidimensional dynamical system? A theory of development should answer several questions, for example: How is it that a single cell gives rise to hundreds of different cell types? What makes terminally differentiated cell types stay in that state and not transform to other cell types? Where is the information for the developmental process encoded? The dynamical systems theory of development tackles these questions considering the organism as a complex dynamical system composed of multiple elements (genes, cytoplasmic, organisimic, and environmental factors) interacting among each other with certain regulatory logic, as shown in Figure 1–(a). Classical dynamical systems theory seeks to understand the way a system will behave through time. There are different ways a system can be formally treated mathematically and the method used to model a system depends on the degree of detail that is pursued, as shown in Figure 1–(b). At the center of the theoretical approach that concerns the study of dynamical systems is the concept of state, see Figure 1–(c): a minimum set of descriptive variables that correspond to a kind of memory that is constantly updated. Then, the system can be described at any point of time by the vector of states of its constituent elements. From a very general point of view the system can stay in the same state it is or change to a different state. When a system reaches a state that does not change in time, this state is known as an *attractor* state and the system's regulatory logic will make it remain there. Some systems known as multistable systems can have several attractor states. This means that the way their elements are related allows them to exist in different combination that make the system state remain unchanged. As an illustration consider a two–dimensional system, every possible combinations of its two constituent elements can be represented in a Cartesian plane, each dimension corresponding to a constituent element, which is to say to a state variable. This representation is known as the system's state space and contains all the possible states the system can have. Depending on the interacting rules defining this system, its behavior at any given time is determined and the system dynamics can be represented as trajectories which will eventually reach an attractor state. This abstraction can be expanded to dynamical systems of any number of dimensions, as depicted in Figure 1–(d). Going back to developmental biology, considering a cell the system under study, its constituent elements are interacting genes, proteins, signaling molecules, environmental factors, and any other molecular species that has an effect on it's behavior. Each state variable, at a given time has a level of activity that corresponds to the specific concentration of an associated product and the interactions among them is in fact the molecular network Waddington conceived underlying the epigenetic landscape [37]. The set of attractor states of such a complex multidimensional system correspond to the different cell types attained during development, *i.e.* the motion of the organism's cells through a specific attractors landscape. The dynamical systems framework provides a conceptual way to formally take into account the possibility of the system to leave a given steady state and reach another attractor, corresponding to cell type transitions observed in development. This change may be due to both the intervention of exogenous and endogenous

signals that modify the state of activity of the nodes of the network in question. Dynamic modulation of transition processes can involve deterministic (such as trigger signals) as well as stochastic influences [29]. By adding stochasticity to the a regulatory network model, the probability to leave an attractor can be measured, as shown in Figure 1–(e). This probability is known as the *attractor's relative stability*, and from Waddington's epigenetic landscape idea it is analogous to the inverse of the valley's depth [9]. In this way, the integration of stochastic noise to the regulatory network model results in a probabilistic landscape that captures the possibility of transitioning between attractors and relates directly to Waddington's diagram of the epigenetic landscape, see Figure 1–(f).

The study of organisms as dynamical systems has had great advances. It has been demonstrated that gene regulatory networks have associated stable states [20], cell types have been associated to these attractor states [19], and empirical gene regulatory networks have been successfully inferred, simulating their dynamical behavior, and explaining the observed phenotypes in several developmental processes by grounding gene regulatory network models on experimental data. [2]. This evidence has led to the conception of the epigenetic landscape as an *experimentally and mathematically grounded theory of development*. Under the dynamical systems perspective, the phenotypic memory epigenetics seeks to explain is grounded in the interrelationships among the system's elements that sustain the stable states existence and guide the trajectories in the state space. From these ideas, the memory of the system cannot be associated to a given gene or epigenetic mark, instead all the interacting elements in a given situation account for the system's behavior. In this vein, in what follows we address an important question that is related to the insufficiency that characterizes epigenomic marks when addressing the understanding of cell differentiation.

2.2 Molecular epigenomic marks are not sufficient to understand both cell differentiation and biological development

Molecular epigenomic marks are a very useful subject to study non–genetic memory because their presence has been demonstrated to exert control over gene function and they do not imply any change in the DNA sequence. Several evidences underscore the importance of epigenomic marks in the maintenance of cell fate; mainly, it has been shown that changes in cellular identity are associated with changes in the epigenomic profile and alterations in the chromatin modifying enzymes cause switches in cell fate [1]. This has lead to the idea that epigenomic modifications are instructions "written" over the DNA sequence to provide an additional level of gene regulation that in many cases is heritable [15]. The main epigenomic marks profiled in mammals are DNA methylation and covalent modifications of the amino–terminal tails of histones, but the collection of epigenomic marks is sometimes extended to include RNA editing, prions, and modifications in non–histone proteins such as microtubules [14].

With the increasing breadth of epigenomic marks, it is usual to find studies assuming that these provide a sufficient explanation of the observed patterns of gene activation/silencing. This kind of explanations take for granted that the proximate molecular effectors of gene regulation are enough to understand why a cell is in a given state, as illustrated in Figure 2. However, as stated by the Roadmap Epigenomics Consortium [8], "Despite these technological advances, we still lack a systematic understanding of how the epigenomic landscape contributes to cellular circuitry, lineage specification, and the onset and progression of human disease." The problem is that even a detailed genomic/epigenomic profile of a given cell informs about which genes are activated or silenced, it does not explain why those epigenomic marks are there. It is a fact that epigenomic marks contain information about the regulatory state of a given cell,
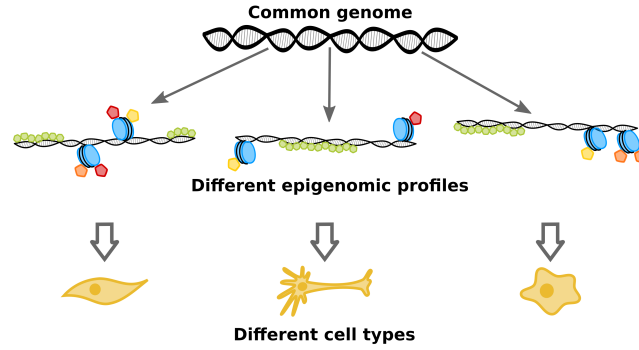
Figure 2: **Molecular epigenomics grants epigenomic marks an explanatory condition for cell phenotypic differences.** The differences in phenotype among cell types from a same organism are explained by the differences in the configuration of their epigenome.

but is this information intrinsic to the mark or is the epigenomic mark and the information it carries a result of the developmental process itself [31]? Considering epigenomic marks as the bearers of information and explanation for cellular differentiation entails two big problems: i) the enzymes that modify them lack sequence specificity and ii) they are highly dynamic and reversible [7, 1]. The absence of DNA-binding domains in the enzymes responsible for DNA methylation and histone modifications makes it necessary for them to cooperate with transcription factors (TFs) to guide their activity on the genome [24]. The involvement of TFs seems to be a way to overcome problem of sequence specificity, but this brings up yet another problem for understanding epigenetic control of gene function: are TFs drivers and epigenetic enzymes follow their activity placing epigenomic marks on the genome, or on the contrary epigenomic marks drive TFs activity determining the places where they can bind the genome [22]? The relationship between TFs and epigenomic marks has been shown to be a complex one, with cases in which DNA methylation inhibits TF binding [11] and other situations in which TF binding causes local loss of DNA methylation [13]. A similarly complex relationship exists between DNA methylation, histone modifications, Polycomb mediated silencing and their control over gene expression [24].

The second problem we referred to is the reversibility of epigenomic marks. As mentioned above, chromatin modifying enzymes are responsible for the addition of chromatin marks on the chromatin, these enzymes can also remove previous marks from it. So, the stable presence of epigenomic marks on the chromatin depends on proteins placing them there and not removing them. These evidences together have led to the idea that, although epigenomic marks are involved in regulating gene expression they are another set of the interacting elements involved in development. From a Systems Biology view, this information arises from the complex relationships among TFs, chromatin modifying enzymes, metabolic factors in the cytoplasm, and the whole transcriptional machinery regulating cellular behavior [33]. This view recovers the dynamical systems conception of epigenetics originally framed by Waddington, with the epigenomic marks being yet another factor in the complex system underlying development. In order to integrate epigenomic marks to the conceptual framework proposed by Waddington, it is necessary to approach the way their regulatory mechanisms can be integrated into the epigenetic landscape.

3   Bridging the gap

First, we want to explore how context dependent epigenomic profiles can be interpreted from the epigenetic landscape perspective. Epigenomic profiling allows the inference of genome–wide coverage of epigenomic marks in a condition specific manner. Different high–throughput techniques make it possible to evaluate the distribution of DNA methylation, histone modifications, chromatin accessibility, or genome architecture in different cell types or environmental conditions [34]. With these sets of data and the knowledge of the functional effects these marks have on the surrounding genes, it is possible to translate these information into chromatin states and deduce the activity states of genes [8]. We consider that this information should be interpreted as a representation of the system's state, complementary to its usual description as the transcriptional pattern of the genes expressed by a cell [19]. Assuming that the epigenomic marks depend on the dynamics of the underlying regulatory interactions, their distribution along the genome reflects the particular system's state. Still, it is difficult to determine if the transcriptional environment of a cell sets up a given epigenomic marks distribution, or if on the other hand a pre–existent epigenomic environment determines the transcriptional activity of the cell [15, 7]. This "chicken and egg" problem might be solved through more studies on the interplay between TFs and epigenomic modifiers. Nevertheless, we firmly believe that an ultimate clear cause and consequence relationship will remain elusive. We support the idea that transcriptional and epigenomic elements of the cell have a dialectical relationship. This means that the role a particular element plays cannot be determined *a priori*, because it is dependent on the state of the system at that particular moment [25, 31]. We must point out that epigenomic profiling also allows the inference of condition–specific regulatory interactions, those actually taking place in a given cell state, in the form of state–specific regulatory networks [27]. If we consider the epigenomic state of a cell as a feature of the cellular state (system's attractor) as stated above, the particular condition–specific network topology inferred from these epigenomic data would also be a description of the system state. Taking into consideration that condition–specific networks represent regulatory interactions, they can be considered a dynamical system with an associated dynamic of their own. Here it is important to think about the difference in stability and timescales between the epigenomic and the transcriptomic regulation. Despite epigenomic marks being reversible, in general they have a stable expression in a given cell type [8]. On the other hand, condition–specific networks represent transcriptional regulation dynamics which have shorter timescales. What this idea points at is a process in which during development the system reaches stable states with an associated epigenomic profile, which in turn define a more constrained regulatory network by defining regions of the genome accessible or inaccessible to regulatory interactions. Accordingly, chromatin protein modifications processes are a way in which transcriptional programs are incorporated to the regulatory network, consequently becoming independent of the conditions that first brought them about [30].

   Having in mind the ideas presented above, let's consider now how they can be applied when thinking about mammalian development. Starting from zygote fertilization, the developmental process starts with the removal of the gametic epigenetic marks from the newly formed zygote [23]. The process of zygotic epigenomic reprogramming and preimplantation embryo development reaches the blastocyst stage, where embryonic stem cells are found [39]. Embryonic stem cells, defined by their capacity to self renew and differentiate into any adult cell type [12], have a characteristic DNA organization, different from the one that characterizes adult cell types [28]. Their chromatin appears to be more "open" with dispersed heterochromatin, enrichment of histone modifications associated with transcriptional activity, and reduced DNA methylation [5]. During embryonic development, differentiating cells acquire epigenomic modi-
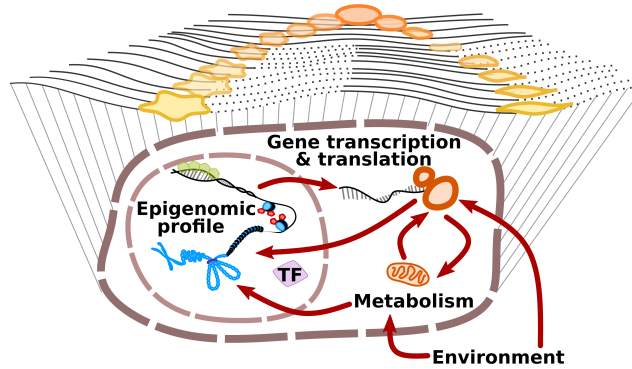
Figure 3: **Integrating epigenomics to the epigenetic landscape.** To understand the emergency and the specific instantiating of different cell types during cell differentiation and development, epigenomic marks should be integrated to the network of regulatory elements of the cell. Their presence derived from the regulatory interactions of the rest of the system and influencing the whole system's dynamics.

fications that "silence" certain parts of the genome and restrict their transcriptional capacities, in fact defining them as differentiated cell types [26]. Thus, it can be hypothesized that the step–wise acquisition of epigenomic marks during differentiation has the effect of stabilizing the systems dynamics in the adult cell types, progressively limiting the system's dynamics to the corresponding lineage attractors. This would add up to the directionality and the almost irreversibility of the differentiation process, because before switching lineages or reprogramming cell fates it would be necessary to rewire the epigenomic profile [22].

4   Conclusions and final comments

Knowing the distribution of the epigenomic marks on the genome does not explain why that given cell type has that particular distribution and not other or why are there different epigenomic profiles in the first place. The deep understanding of the basic generic principles that causally explain biological development and cell differentiation will hardly come solely from the study of the patterns present in the databases built with the epigenomic information. We firmly believe that epigenomics urgently requires a systems–based mechanistic perspective. We argue that the analysis of organisms as multidimensional nonlinear dynamical systems, as proposed initially by Conrad H. Waddington, is still the best theory to tackle the deep understanding of development, cellular differentiation and the reasons that causally explain the existence of different epigenomic profiles. Based on what we have discussed, we proceed to hypothesize how recent knowledge about epigenomic regulation can be incorporated into the conceptual framework of the epigenetic landscape. We propose then that the effects that epigenomic marks have on the dynamic network can be understood as changes in the topology and, consequently, as modifications of the dynamics of the regulatory network, as graphically depicted in Figure 3. In this way, the epigenomic modifications would act as a regulatory loop linking the system's transcriptional state with its regulatory dynamics. We believe this idea could bring together and enrich the two fields of epigenetics that coexist separately in these days. On one side, it

gives a systemic comprehension of epigenomic profiles by recognizing they are determined by the underlying regulatory system and as such a characteristic of the steady states this system can reach. On the other hand, accepting that epigenomic marks can exert an influence over the system's network topology and dynamics gives the systems theory of development another layer of control in which the system can influence its own dynamics and stability.

Acknowledgements

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