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On the institutional and intellectual division of labor in epigenetics research: A scientometric analysis

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Abstract

While numerous qualitative social scientific analyses of (environmental) epigenetics have been published, we still lack a macro-level, quantitative assessment of the field of epigenetics as a whole. This article is aimed at filling this gap. Mobilizing an extended version of the Web of Science, we constituted a corpus of 199,484 documents (articles, reviews, editorial material, etc.) published between 1991 and 2017 and performed several scientometric analyses to map out the development and structure of the epigenetics field. Three main results were drawn from these investigations. First, contradicting the hope expressed by some social scientists that their disciplines will find solace in epigenetics' social biology, it is striking that the scientists, journals and institutions that drive most of the research in the field are overall little concerned with social and environmental dimensions of gene expression. Second, and confirming existing qualitative analyses, we find that epigenetics is constituted by diverse networks of scholars, institutions and research specialties that enjoy relative autonomy from each other and approach epigenetics through different thematic interests, from cognitive functions to cancer, to DNA methylation in plants and molecular biology. Third, findings obtained from the bibliographic coupling showed that these different networks

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became more and more autonomous over the last decade, which suggests that we are currently witnessing the constitution of a scientific archipelago akin to that of behavior genetics (Panofsky, 2014: 33) rather than to a discipline *per se*. At the same time, this differentiation was less pronounced conceptually speaking, as we also observed a clear standardization of the keywords used in epigenetics articles between 1991 and 2017, with DNA methylation and RNAs serving as rallying signs for different communities of researchers.

Keywords
bibliometrics, biology, biosocial, epigenetics, genetics, heterogeneity, scientometrics

Résumé

Si de nombreuses analyses socio-scientifiques qualitatives en épigénétique (environnementale) ont été publiées, il nous manque encore une évaluation quantitative du champ que constitue l'épigénétique dans son ensemble. Cet article a pour but de combler cette lacune. En mobilisant une version augmentée de *Web of Science*, nous avons constitué un corpus de 199,484 documents (articles, comptes rendus, matériel éditorial, etc.) publiés entre 1991 et 2017 et avons réalisé plusieurs analyses scientométriques pour cartographier le développement et la structure du champ épigénétique. Trois principaux résultats sont ressortis de ces recherches. Tout d'abord, contredisant l'espoir de certains chercheurs en sciences sociales que leurs disciplines puissent trouver un appui dans la biologie sociale de l'épigénétique, il est surprenant que les scientifiques, les revues et les institutions qui concentrent la majorité de la recherche dans ce champ soient en grande partie peu concernés par les dimensions sociale et environnementale de l'expression génétique. Deuxièmement, confirmant des analyses qualitatives existantes, nous avons constaté que l'épigénétique était constituée de divers réseaux de chercheurs, institutions et spécialités de recherche, qui profitent d'une relative autonomie les uns par rapport aux autres et qui approchent l'épigénétique à partir d'intérêts thématiques différents, des fonctions cognitives au cancer, en passant par le méthylation de l'ADN chez les plantes et la biologie moléculaire. Troisièmement, les résultats obtenus à l'aide du couplage bibliographique ont montré que ces différents réseaux étaient devenus de plus en plus autonomes au cours des dix dernières années, ce qui laisse penser que nous sommes actuellement en train d'assister à la constitution d'un archipel scientifique, semblable à celui de la génétique comportementale (Panofsky, 2014 : 33), plutôt qu'à celle d'une discipline en soi. Néanmoins, ce processus de différentiation était moins prononcé s'agissant des concepts employés, car nous avons également constaté une nette standardisation des mots-clés utilisés dans les articles sur l'épigénétique entre 1991 et 2017, où la méthylation de l'ADN et les ARN servaient de signes de ralliement pour les différentes communautés de chercheurs.

Mots-clés
bibliométrie, biologie, biosocial, épigénétique, génétique, hétérogénéité, scientométrie

Introduction

The paternity for the biological concept of 'epigenetics' is generally attributed to English embryologist Conrad Waddington, in particular for his book *Organisers and Genes* first published in 1940 (Jablonka & Lamb, 2002; Pickersgill et al., 2013; Van Speybroeck, 2002). According to Waddington, epigenetics could be defined as 'the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being' (Waddington, 1968). To be clear, Waddington did not just invent the concept of epigenetics. In fact, he approached epigenetics as a way to put forth a novel conceptualization of embryological development that would bridge together genetics, ecology, development and evolution. More precisely, Waddington paid a particular attention to the intriguing uncoupling of genetic and phenotypic variations. In a famous paper published in *Nature* in the early 1940s, he thus used the example of the drosophila to underline the fact that the great variations observed in gene expression between different individuals were particularly difficult to understand given the lack of alteration in the underlying genotype (Waddington, 1942: 564).

While some natural scientists would use the term epigenetics in the way Waddington intended during the next decades, it would not be until the 1990s that this area of research would really take off and, paradoxically, also begin to be redefined (Jablonka & Lamb, 2002: 87–88). For instance, molecular biologist Robin Holliday proposed to redefine epigenetics as 'the study of the changes in gene expression, which occur in organisms with differentiated cells, and the mitotic inheritance of given patterns of gene expression' (1994: 453), while other scientists suggested that we abandon the term altogether and replace it with what they see as less confusing concepts (Lederberg, 2001). In the aftermath of the *Human Genome Project*, this already heterogenous research field has been further complexified by the apparition of 'epigenomics,' which proposes to study epigenetic phenomena at the genome level: 'While epigenetics refers to the study of single genes or sets of genes, epigenomics refers to more global analyses of epigenetic changes across the entire genome'[1]. The *Roadmap Epigenomics Project*, funded by the National Institutes of Health (NIH), and the *International Human Epigenome Consortium* (IHEC), both aimed at mapping the human epigenome, are some of the main manifestations of this movement.

The sociological dimension of epigenetics is worth emphasizing, as it is a common feature of emerging scientific movements to be operating a boundary-work,[2] and insist on the novelty and originality of their approach not only vis-à-vis normal science, but also vis-à-vis alternative, concurrent conceptions (Frickel & Gross, 2005; Gieryn, 1983). This is quite clear in the case of epigenetics. Already in the early 20th century, 'epigenetic theories of development were adopted in direct conflict with the particulate, preformationist understanding of the organism' (Sapp, 1987: 7). In his *Nature* paper, Waddington thus introduced his epigenetic theory as a way to settle 'the battle, which raged for so long between the theories of evolution supported by geneticists on one hand and by naturalists on the other', and that he thought had 'gone strongly in favour of the former' (1942: 563). Nowadays, debates on epigenetics that are internal to the field of molecular biology can be summarized by two archetypical positions, 'with some arguing that epigenetics is nothing but another aspect of gene regulation, and others enthusiastically

proclaiming a paradigmatic shift in developmental biology' (Niewöhner, 2011: 279). Interestingly, variations in the understanding of the role and function of epigenetics are partially attributable to larger divisions of labor in biological research, with different communities promoting different visions of epigenetics. As Harvard biologist David Haig (2004: 1) underlined:

> Molecular biologists are probably most familiar with a definition of epigenetics as 'the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence' (Riggs et al., 1996). For them, epigenetic mechanisms would include DNA methylation and histone modification. Functional morphologists, however, would be more familiar with a definition such as that of Herring (1993), for whom epigenetics refers to 'the entire series of interactions among cells and cell products which leads to morphogenesis and differentiation.

Hence, the apparently unified and consensual epigenetics label actually dissimulates more or less important disagreements and differing practical uses among scholars (Morange, 2002), which we shall argue only confirms the pertinence of a macro-level study of the entire field. Moreover, the brief history of past and present epigenetics that we outlined clearly shows that epigenetics is not merely a set of disembodied ideas but is likely to impact the structure of the biological field itself, that is the repartition of resources and credit within the scientific field (Bourdieu, 1991). Indeed, the theoretical implications are potentially immense, as the development of epigenetics might, according to some authors, lead to a return and reappraisal of Lamarckian evolution (Jablonka & Lamb, 2002: 92–95; Ward, 2018), among other things.[3] Relatedly, with its emphasis on gene-environment interactions, reversibility and transmission of acquired features, epigenetics seems to threaten the gene-centric views that have long animated an important portion of biological research.[4]

To be clear, such phenomena are still highly debated and far from being settled among scientists. Hence, while a few select experiments, including the case of the Dutch Hunger Winter (Heijmans et al., 2008), are sometimes interpreted as definite evidence that social processes influence humans' biology across generations, social scientists must remain wary vis-à-vis too-quickly-drawn conclusions (Dubois et al., 2018: 87–88). The fact that certain researchers are trying to implement what sociologist Maurizio Meloni termed a 'social biology' (2014), does not necessarily mean that every biologist adheres to the idea that environmental factors can have lasting impacts on biological processes.[5] As Kasia Tolwinski (2013) forcefully demonstrated using in-depth interviews with epigenetics researchers, only a subgroup of them, 'the champions', believe that epigenetics represents a paradigmatic change for biological research. Yet, some social scientists – albeit fewer (Dupras et al., 2019) – tend to investigate the field as if it was riddled with champions, thus forgetting along the way the more middle grounded and skeptical researchers who do not hold such views. Evelyn Fox Keller's diagnostic is symptomatic of this sort of sampling bias, when she wrote a few years earlier that 'there is little doubt that its discovery [that of epigenetic inheritance] and its integration into mainstream genetics is indeed rocking the foundations of that science' (2014: 2423).

Still, it remains that the biological field is not the only one which might be reconfigured along the development of epigenetics. Another important implication of experiments such as the Dutch Hunger Winter study is to demonstrate how social scientists might be expected to contribute to the understanding of health inequalities and gene expression more generally (Dubois et al., 2018; Landecker & Panofsky, 2013). Indeed, although the context of, and the data drawn from, the Dutch Hunger Winter were quite exceptional, several research projects conducted in medical sociology have already convincingly demonstrated that nutrition and other health-relevant variables were dependent on social factors such as Socio Economic Status (SES) and race (Williams & Sternthal, 2010).

Moreover, the emergence since the 2000s of an array of biosocial movements within the social sciences, from neuroeconomics (Monneau & Lebaron, 2011) to neuromarketing (Wannyn, 2017), to biosocial criminology (Larregue, 2018a) and genopolitics (Larregue, 2018b), demonstrate the growing appeal of biology to social scientists and the need expressed by some of them to rethink the relationship between natural, psychological and social processes. The rise of interest in environmental epigenetics contributes to this movement, at the same time that it might challenge certain genetic, deterministic visions of human behavior that have been paradoxically instrumentalized by scholars from the social and human sciences with the aim of challenging dominant environmental theories (Bliss, 2018; Larregue, 2018a; Panofsky, 2014).

Overall then, the potential lasting impact of epigenetics in various areas of the scientific field renders it particularly important to get a better understanding of this stream of research. Although illuminating qualitative analyses have already been published about specific aspects of, and particular issues related to, environmental epigenetics (Buklijas, 2018; Dubois et al., 2018; Jablonka & Lamb, 2002; Landecker, 2011; Lloyd & Müller, 2018; Mansfield, 2012; Meloni & Testa, 2014; Niewöhner, 2011; Pickersgill et al., 2013) and the so-called postgenomic era (Richardson & Stevens, 2015), we still lack a macro-level, quantitative assessment of the field of epigenetics as a whole. Previous attempts at mobilizing scientometric data to investigate epigenetics are scarce and tend to rely on simple rankings and descriptive statistics that say little about the constitution of the field (Haig, 2012).[6] We argue that a more sophisticated scientometric approach might help us to answer some of the following questions: What is the level of institutionalization of epigenetics and what form does it take? For instance, is epigenetics becoming a clear-bounded, autonomous discipline? Or is it more like an archipelago composed of distinct, yet communicating communities, akin to behavior genetics (Panofsky, 2014: 33)? More generally, what forms of division of labor are at play in epigenetics research?

In so doing, we do not aim to limit ourselves to any specific area of epigenetics but rather to map out the development and structure of the field as a whole by analyzing a corpus of 199,484 documents (articles, reviews, editorial material, etc.) published between 1991 and 2017. Our scope is thus considerably larger than the one generally adopted by existing qualitative investigations focusing on restricted portions of environmental epigenetics. Still, it does help to grasp the centrality, or, in this case, lack thereof, of such environmental approaches in the broader field of epigenetics, as we found that only approximately 1% of epigenetics articles published every year mentioned environment-related keywords in their title. This means that the Science and Technology Studies

(STS) literature on epigenetics was first and foremost mobilized to guide our hypotheses and research questions; however, since most of our findings concerned areas yet largely unknown to social scientists, the STS literature was less instrumental to the interpretation of our findings.

This article proceeds in six steps. We first outline the scientometric methods that we mobilized and the data that we gathered to shed light on the development of, and division of labor in, epigenetics. The second section is devoted to presenting a panorama of the development of epigenetics across time and disciplines. We then turn to the institutional networks supporting the field, including the Boston area which serves as a hub for epigenetics research. The fourth section uses bibliographic coupling to map out the intellectual diversity of epigenetics as measured by the different areas of researchers' interests (cancer, molecular biology, cognitive functions, etc.). Next, we analyze the keywords used in the 199,484 documents to gauge the conceptual standardization of epigenetics over time. We finish by discussing the main contributions and limits of our paper.

Methods

Scientometric methods are regularly mobilized to analyze the development and structure of scientific fields of research, from synthetic biology (Raimbault et al., 2016) to economics (Claveau & Gingras, 2016), to criminology (Nadeau et al., 2018) and information science (White & McCain, 1998). Using an extended version of the Web of Science license to the *Observatoire des sciences et des technologies* (Université du Québec, Montreal), we constituted a corpus of peer-reviewed articles in the domain of epigenetics. This extended version of the Web of Science contains approximately 60 millions of documents and 1.1 billion of references published between 1900 and 2017, which makes it one of the most comprehensive scientometric databases and thus a satisfactory tool to analyze the development of scientific fields.

A particular difficulty in the constitution of our corpus was related to the selection of keywords. One fear was to reify and naturalize dominant conceptions of epigenetics and to consequently underestimate the importance of certain networks and subcommunities that may be more peripherical and/or in opposition with the more visible ones. In order to be comprehensive and wide-ranging, we thus proceeded in two successive steps. First, we began by performing an exploratory request using the prefix 'epigen*,' allowing us to identify 77,289 articles. This corpus was not entirely satisfactory because many epigenetics researchers publish articles that do not mention 'epigenetics' in the title, abstract and/or keywords, which is of course the case of any disciplines. The same way that sociologists do not constantly mention 'sociology' or that physicists do not write 'physics' every two words, epigenetics researchers do not constantly remind their readers that their research fall into this category. Hence, we performed a second Web of Science query by using a wider set of keywords. The keywords were selected because of their direct relevance to epigenetics research and after having been validated by a molecular biologist:

> TS='epigen*' OR 'DNA methyl*' OR '(methylation AND (gene OR CpG))' OR 'DNA hydroxymethyl*' OR 'hydroxymethylcytosine' OR 'histone marks' OR 'histone retention' OR 'histone modification' OR 'histone *acetyl*' OR 'histone *methyl*' OR 'histone *sumoyl*'

OR 'histone phosphoryl*' OR 'histone ribosyl*' OR 'histone ubiquitin*' OR 'small non coding RNA' OR 'small noncoding RNA' OR 'endogenous small interfering RNA' OR 'microRNA' OR 'piRNA' OR 'miRNA' OR 'piwi-interacting RNA' OR 'lincRNA' OR 'lncRNA' OR 'long non coding RNA' OR 'long noncoding RNA'

Overall, these two steps led us to identify 199,484 documents (articles, reviews, editorial material, etc.) published between 1991 and 2017. From this extended corpus of documents, we were able to extract data regarding 8 main variables: articles themselves, but also journals, disciplines, research specialties, countries, institutional affiliations, authors and references. Such data was not only descriptive but also relational, thus allowing to investigate research networks at the institutional and cognitive levels.

This approach, as any, has some limits. First, because the database we used only references journal documents, our corpus logically excludes any other types of documents, including books and book chapters. We did however conducted manual explorations using Google Scholar to identify popular books on epigenetics (Carey, 2012; Moore, 2015; Ward, 2018). A second limitation is that our approach – and the size of the corpus – renders it impossible to distinguish between what we could call primary articles, that is epigenetics research *per se*, and secondary articles that investigate epigenetics itself, for instance through a sociological or epistemological lens. A third limit is that compared to more fine-grained approach, our focus on macro-level and large-scale tendencies might tend to obfuscate nuances and fractures that could be considered as essential by epigenetics researchers. Hence, our article should not be read in an isolated manner but rather understood as an attempt to parallel and complement the qualitative analyses mentioned earlier.

The growing visibility of epigenetics

As mentioned earlier, the methods described above lead us to identify 199,484 documents (articles, reviews, editorial material, etc.) containing the prefix 'epigen' and/or other epigenetics-related keywords (methylation, histone, microRNA, etc.) published between 1991 and 2017 (Figure 1). The rationale for limiting our corpus to this period is that while the first paper that we identified was published in 1905 in *Les comptes rendus hebdomadaires des séances de l'Académie des sciences*, the vast majority of epigenetics papers were published from the 2000s.[7] In 2014 alone, 8011 papers containing the prefix 'epigen' were published, which is almost as much as the number of publications containing this same prefix on a century (1905–2005: 8,065 articles).

Disciplinary speaking, epigenetics is now first and foremost a biomedical matter (Table 1). To be even more precise, four main research specialties concentrate the bulk of epigenetics research: biochemistry & molecular biology (32,116 articles), oncology (28,950 articles), general biomedical research (20,414 articles) and genetics & heredity (19,443 articles). On the other end of the spectrum, we find the social sciences and humanities, whose interest in epigenetics is understandably very relative when compared with the figures found in biomedical research. For instance, sociology journals have published 14 articles on this topic, philosophy journals published 29, while economics journals published only 5.

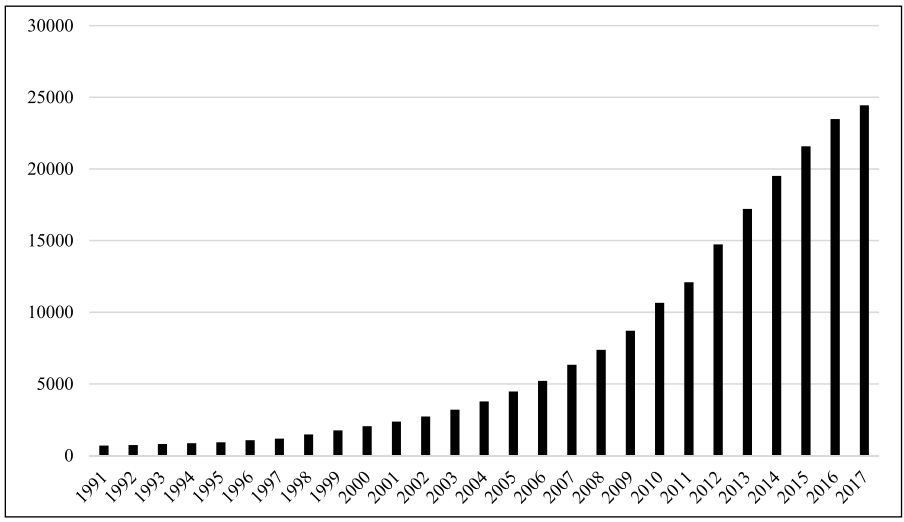

Figure 1. Evolution of the number of articles containing epigenetics-related keywords, 1991–2017 (*n*=199,484).

This repartition tells us something about the sociopolitical expectations surrounding epigenetics. The current understanding of epigenetics as an area studying the activation and silencing of genes has a lot to do with the hopes that studying the epigenome will lead us to successfully fight a large array of pathologies, from psychological disorders to cancer. As we shall see, the centrality of cancer is not only visible in the research outputs of epigenetics researchers, but also – and logically – related to the institutional networks of the field. Overall then, disciplinary hierarchies that are internal to the scientific field come to resonate with expectations expressed by scientists, physicians, politicians, activists and lay people alike.

At the same time, the growing number of epigenetics articles since the 1990s must be put in perspective and compared to disciplinary publication trends overall. For instance, it might be possible that epigenetics is *relatively* less important in biomedical research today than it was in the 1990s if the general publication rate of the latter discipline evolved more rapidly than the publication rate of epigenetics researchers did. Hence, sheer numbers are not sufficient to draw reliable conclusions, and one must take a look at proportions. As Figure 2 clearly demonstrates, the *proportion* of epigenetics articles in biomedical research has been growing steadily between 1991 and 2017, which comforts our hypothesis that the important visibility of epigenetics is not merely an artefact of broader publication patterns.

Converging institutional networks: The Boston area as a hub for epigenetics research

Now that we have documented the disciplinary structure of the epigenetics field, we can turn to another aspect, namely geography and institutional networks. Where is epigenetics research produced? Table 2 presents the main institutions contributing to

Table 1. Main research specialties (1,000 articles and more) of the journals publishing epigenetics articles, 1991–2017.

Research specialty	Articles
Biochemistry & molecular biology	32,116
Cancer	28,950
General biomedical research	20,414
Genetics & heredity	19,443
Cellular biology cytology & histology	9,739
Pharmacology	7,742
Neurology & neurosurgery	6,507
Pathology	4,766
Botany	4,605
General & internal medicine	4,515
Immunology	4,353
Endocrinology	3,309
Hematology	2,976
Gastroenterology	2,619
Microbiology	2,610
General Chemistry	2,096
Cardiovascular system	1,950
Virology	1,845
Embryology	1,190
Fertility	1,179
Physiology	1,160
Nutrition & dietetic	1,156
Miscellaneous biology	1,064
General biology	1,032

epigenetics research, that is represented in our corpus of 199,484 articles. Harvard University is by far the most active institution in epigenetics, with 4,559 articles published, followed by the Chinese Academy of Sciences (3,090 articles) and Johns Hopkins University (2,205 articles). At the country-level, the United States are the prime producers of research in the area, with Chinese institutions standing just behind their American counterparts. Besides these two countries, we can observe the presence of the University of Cambridge (1,699 articles) and of the University of Tokyo (1,816 articles). It is also worth to underline that the National Cancer Institute ranks 4th with 2,196 articles, which largely confirms our previous analyses on the importance of cancer research and biomedical issues in the field of epigenetics.

But this simple ranking is obviously insufficient to grasp the ecology of epigenetics research, especially as it does not render research networks apparent. Epigenetics is eminently international in its promises to treat cancer and other pathologies, thus necessitating to collect and analyze data for collaborations *between* scientific institutions and across national borders. Figure 3 maps out the main collaborations occurring in epigenetics research, as measured by the number of articles of our corpus to which two given institutions

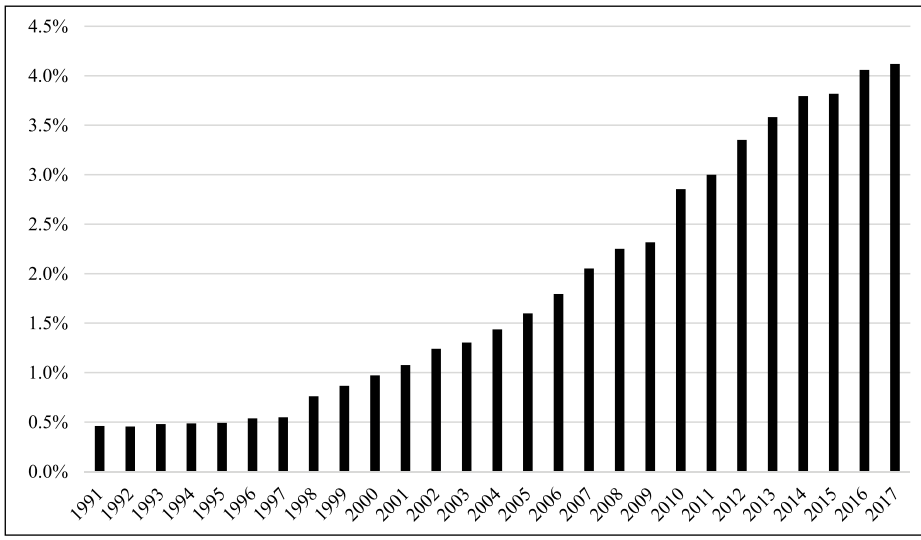

Figure 2. Evolution of the proportion of epigenetics articles in biomedical research, 1991–2017 (*n*=94676).

Table 2. Main institutions (1500 articles and more) contributing to epigenetics research.

Institution	Country	Articles
Harvard University	USA	4,559
Chinese Academy of Sciences	China	3,090
Johns Hopkins University	USA	2,205
National Cancer Institute	USA	2,196
Shanghai Jiao Tong University	China	2,193
University of Pennsylvania	USA	1,962
Nanjing Medical University	China	1,947
Fudan University	China	1,906
University of Texas	USA	1,882
University of California San Francisco	USA	1,846
Ohio State University	USA	1,838
University of Tokyo	Japan	1,816
University of Cambridge	UK	1,699
University of California Los Angeles	USA	1,675
Sun Yat-sen University	China	1,642
Stanford University	USA	1,630
University of Michigan	USA	1,556

contributed (through the individual authors' affiliations). To avoid superfluous nuance, we restricted our analyses to the central networks, which means that we only graphically represented the collaborations that were equal and superior to 30 co-written articles.

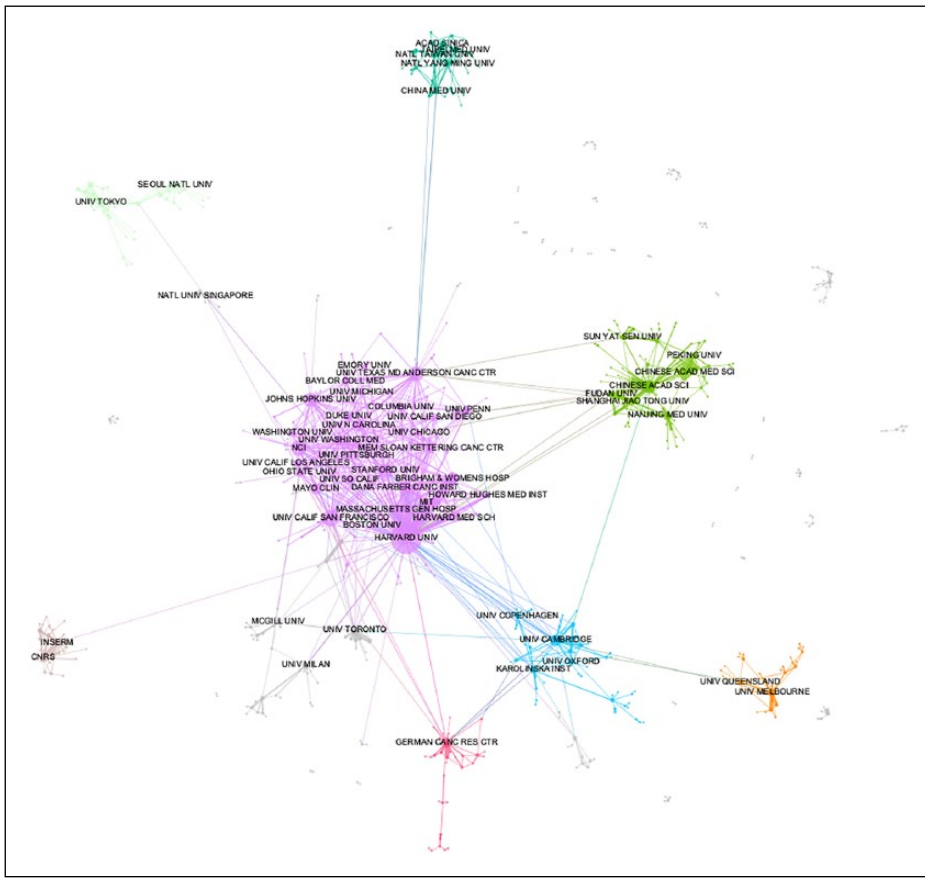

Figure 3. Collaborations between scientific institutions in epigenetics research (threshold of 30 co-authored articles).[1]

[1]This figure and the followings have been realized with Gephi's Force Atlas algorithm. In this case, the size of nodes is proportional to the number of collaborations with all of the other nodes (degree), while the length of the link between two given institutions is proportional to the number of articles that they published together (weight).

Two main findings emerge from this analysis. First, contrarily to what we may have thought, epigenetics research remains eminently *national* in practice. The presently displayed collaborative networks are clearly defined by countries, even though this variable was not available to the spatialization algorithm. Far from being a mere coincidence, this spatial repartition is statistically robust, as the coefficient of modularity is quite high (0.764). Coefficients of modularity are comprised between 0 and 1. The more a given network's coefficient is close to 1, the more its constituent clusters are autonomous from each other. In our case, a coefficient of 0.764 indicates that the connections between the clusters are sparse. Far from being an idiosyncrasy of epigenetics research, the national dimension of scientific research is well-known among sociologists of science: countries

remain the first determinants of scientific activities despite the internationalization mantra (Maisonobe et al., 2016).

We can thus observe a central, densely populated network of prestigious American scientific institutions orbiting around Harvard University, and other peripheral networks from other countries which are linked to the first yet far enough to be depicted as semi-autonomous. Closest to the American network, we can mention the German network organized around the Germany Cancer Research Center; the Canadian network organized around McGill University, University of Toronto and University of British Columbia; the Italian network organized around the University of Milan; lastly, one Chinese network organized around the Chinese University of Hong-Kong. At mid-distance, and somewhat serving as a bridge between different communities, is the British network organized around two main institutions: University of Cambridge and University of Oxford. Lastly, farthest away from the American network, we find the French network organized around INSERM and CNRS; the Singaporean one organized around the National University of Singapore; the Australian one organized around the University of Melbourne.

A second finding is that the American ecology of epigenetics research can be further differentiated according to local geography. Confirming previous data, Harvard University is uncontestably the main institution in the field of epigenetics. Not only are Harvard University researchers the main publishers of articles, but they also closely collaborate with several other American institutions, especially in the Boston area: MIT, Broad Institute, Boston Children's Hospital, Dana-Farber Cancer Institute, Massachusetts General Hospital, Boston University, etc. And the importance of Harvard University is not merely local. French, British and Canadian institutions, among others, have all collaborated with the Ivy League University. Overall then, the Boston area serves as a hub for epigenetics research.

Still evolving: The many faces of epigenetics research

Until now, we have investigated the field of epigenetics through our corpus of articles mentioning keywords associated to epigenetics research. While the number of papers thus obtained was high and more than satisfactory (199,484), it remains possible that the importance of some subparts of epigenetics research were underestimated. Furthermore, our previous analyses predominantly relied on the number of articles published as a proxy for prominence within the field of epigenetics, which might lead to overestimate the importance of dominant, wealthy institutions. For instance, the undeniable fact that the Boston area in general, and Harvard University in particular, serve as an institutional hub for epigenetics research does not necessarily mean that every sub-area of epigenetics considers Bostonian research as *scientifically* important.

Hence, to complement and balance previous investigations, we performed bibliographic coupling analyses. While the previous sections predominantly investigated the institutional structure of epigenetics research, the first aim of bibliographic coupling is to investigate its intellectual structure by adopting a relational perspective. By contrast with co-citation analysis, which 'measure[s] the degree of relationship or association between papers as perceived by the population of citing authors' (Small, 1973: 265), bibliographic coupling 'links documents that reference the same set of cited documents' (Boyack & Klavans, 2010: 2391). Although co-citation analysis is usually considered as the methodological

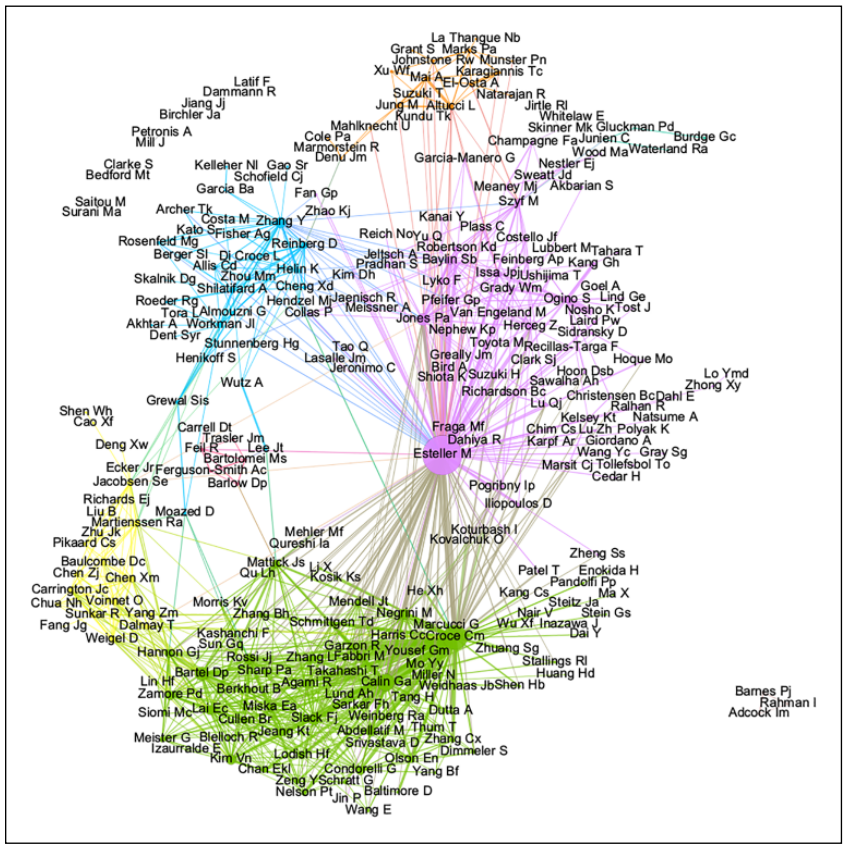

Figure 4. Network of bibliographic coupling extracted from the 199,484 epigenetics articles, 2006–2011 (threshold of 1,000 edges; first authors only).

standard in such endeavors, recent investigations suggest that bibliographic coupling is actually slightly more accurate in mapping out research specialties (Boyack & Klavans, 2010), which motivated our choice.

To obtain a dynamic view of epigenetics research, we performed bibliographic coupling on two distinct periods: 2006–2011 (Figure 4) and 2012–2017 (Figure 5). Time is a major factor in the structuration of scientific fields (Bourdieu, 1991; Frickel & Gross, 2005), and we expect this approach to render the evolution of epigenetics across time visible. One of the main outcomes of these analyses is that the intellectual structure of epigenetics research is a little more homogenous than its institutional structure (Figure 3). Indeed, while the coefficient of modularity for the institutional networks was 0.764, the coefficients obtained for the authors' networks are lower (0.479 for 2006–2011, 0.633 for 2012–2017).[8]

To be sure, this is only a matter of degree and intellectual affinities, which are still clearly diversified. Although most of the sub-communities are linked together either directly or indirectly, the coefficients of modularity demonstrate that epigenetics

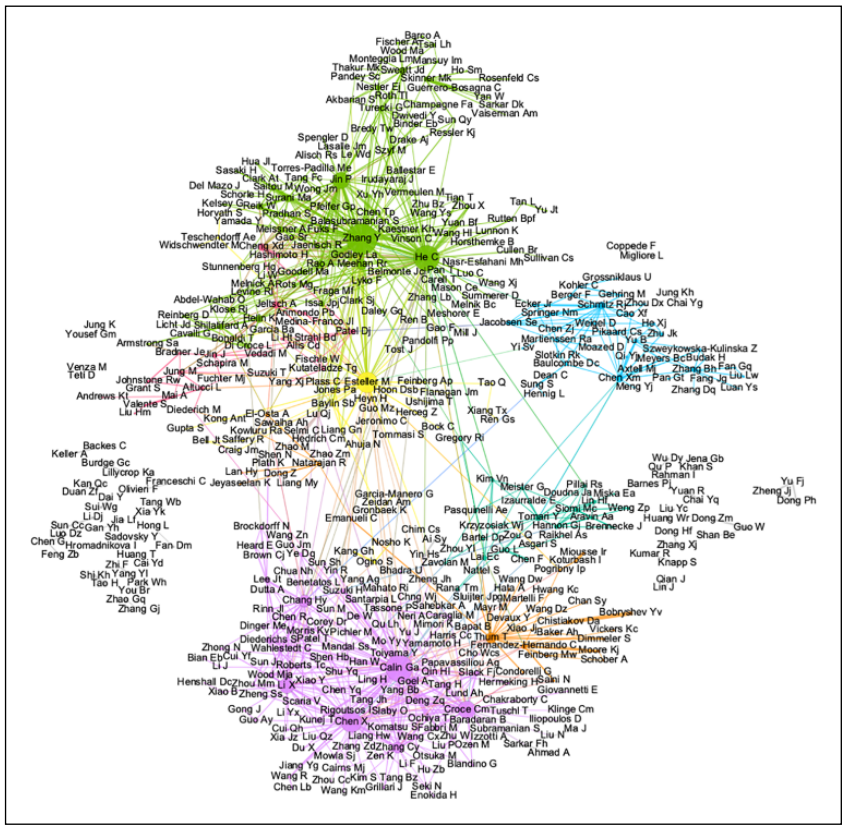

Figure 5. Network of bibliographic coupling extracted from the 199,484 epigenetics articles, 2012–2017 (threshold of 1000 edges; first authors only).

researchers still distinguish between different scientific approaches to the epigenome. Moreover, it is important to underline that the heterogeneity of epigenetics research has been increasing over time, with the 2012–2017 period displaying more nodes (authors) and communities of thought than the 2006–2011 period, which is clearly visible when one puts Figure 4 and Figure 5 side by side. The number of nodes thus almost doubled, from 260 to 474, while the number of communities almost tripled and went from 16 to 41. At the same time, the network's density went from 0.3 to 0.009. Overall then, if one considers that the number of newcomers is a reliable proxy for the structuration of a given scientific specialty (Raimbault et al., 2016), then the field of epigenetics is clearly not stabilized yet and is still welcoming outsiders' worthwhile scientific contributions.

This intellectual diversity partly mirrors a division of scientific labor, with each subgroup specializing on a specific aspect of epigenetics. To be clear, the different communities do share many overlapping research interests, as demonstrated by the fact that the networks of publishing journals is much more homogeneous than the institutional and intellectual ones.[9] Still, it is possible to identify clusters that correspond to certain elective topical concerns and/or to specific disciplines, although we also observe a growing

conceptual standardization over time (see next section), which means that the bibliographic clusters are probably first and foremost translating thematic interests. For instance, the 2006–2011 green network (Figure 4) is mostly interested in estimating the role of non-coding RNAs and microRNAs in diseases, including cancer, which can be illustrated by the type of research conducted by two of its main representatives, Carlo M. Croce and George A. Calin.[10] Comparatively, the purple network that is symbolized by the prominent figure of Manel Esteller, a researcher affiliated to the Bellvitge Biomedical Research Institute in Barcelona, Spain, also focuses on cancer but through the guise of histone acetylation and DNA methylation. This division is interesting because there exists a rather clear social hierarchy between DNA and RNA, with non-coding RNAs long considered scientifically uninteresting by molecular biologists and geneticists. Epigenetics is somewhat rehabilitating this molecule, or, to quote a widely read popularization epigenetics book, 're-defining rubbish' (Carey, 2012: 186). Yet, the focus on DNA remains predominant and seemingly unquestioned, which can explain why another widely-read guide to epigenetics would simply exclude microRNAs from its scope (Moore, 2015: 42).

How did the subcommunities evolve between 2006–2011 and 2012–2017? One important advantage of bibliographic coupling is that it maps out the intellectual *distance* between researchers and communities alike. Indeed, not only are edges representative of affinities between two nodes, but their length is directly proportional to the number of times that they were associated with each other. Comparing the two networks can thus be a way to evaluate the evolution of the relative intellectual affinities between different subcommunities of epigenetics research. One interesting case in this regard is Manel Esteller, whom we mentioned earlier. Trained in medicine and molecular genetics, Esteller is mainly known for his epigenetic approach to cancer and his focus on histone acetylation and DNA methylation (see for instance Esteller, 2008; Esteller et al., 2001). While Esteller was by far the most central node in 2006–2011 with a degree of 144,[11] he became relatively less important in the 2012–2017 period, ranking 4th with a degree of 53. This loss of centrality is quite clear when one compares Figure 4 with Figure 5. As singular as it is, the case of Esteller might pinpoint a larger evolution, namely the relative regression of the centrality of cancer research in the field of epigenetics between 2006–2011 and 2012–2017. To be sure, cancer does remain one of the main dimensions and *raison d'être* of epigenetics. Still, it would appear that its importance has been diluted across the last few years with the growing arrival and development of other branches. Hence, besides Esteller, other academics who are well known for their research on cancer have lost some centrality in the networks, including Carlo M. Croce from Ohio State University and Peter A. Jones from the Van Andel Research Institute.

While cancer researchers were losing some of their relative centrality, other researchers and networks were gaining visibility. The most impressive progress can be credited to the genetics and developmental biology network that is mainly represented by Yi Zhang from Harvard Medical School, Chuan He from University of Chicago's Department of Chemistry and Peng Jin from Emory University's Department of Human Genetics (green network, Figure 5). This network became the main community in the 2012–2017 period with a total of 123 nodes, thus overcoming the purple network of cancer/RNA researchers (113 nodes). This achievement was partly rendered possible by absorbing previously semi-independent communities. In particular, it is worthwhile to underline that the green network from Figure 5 became closely associated with epigenetics researchers interested

in cognitive functions, including well-known rodent specialists Frances A. Champagne, Michael J. Meaney and Eric J. Nestler (Malberg et al., 2000; Weaver et al., 2004).

The growing conceptual standardization of epigenetics research

In the previous developments, we demonstrated that epigenetics research was not disciplined but rather took the form of an archipelago where we could identify several semi-autonomous institutional and intellectual clusters. This last section is aimed at complementing these findings by shedding light on the conceptual standardization of epigenetics research between 1991 and 2017. A superficial analysis of the research interests put forth by prominent epigenetics laboratories reveals that despite the different objects investigated by researchers, the conceptual vocabulary is in fact rather homogenous (Box 1). For instance, while the Jones Lab, the Sweatt Lab and the Jacobsen Lab clearly focus on distinct biological objects (cancer, cognitive functions and plants respectively), they also share a common interest for one single biological mechanism, namely DNA methylation.

Box 1. Illustrations of the different facets of epigenetics research.

DNA methylation and the epigenetics of cancer
Jones Lab, Van Andel Research Institute: 'Our laboratory is focused on the mechanisms by which epigenetic processes become mis-regulated in cancer and contribute to the disease phenotype. We focus on the role of DNA methylation in controlling the expression of genes during normal development and in cancer. Our work has shifted to a holistic approach in which we are interested in the interactions between processes such as DNA methylation, histone modification and nucleosomal positioning to structure the epigenome and we want to determine how mutations in the genes which modify the epigenome contribute to the cancer phenotype. We have had a longstanding interest in the mechanism of action of DNA methylation inhibitors both in the lab and in the clinic. In the clinic, we are working with several major institutions to bring epigenetic therapies to the forefront of cancer medicine.'[1]

Non-coding RNAs and the epigenetics of cancer
Calin Laboratory, University of Texas: 'We showed that UCRs are frequently located at fragile sites and genomic regions involved in cancers, and that profiling genome-wide UCRs reveals distinct signatures in human cancers. These findings argue that non-coding genes are involved in tumorigenesis to a greater extent than previously thought and offer the perspective of identification of signatures associated with diagnosis, prognosis and response to treatment composed by various categories of non-coding RNA genes.
During the last few years, we pioneered the idea that small non-coding RNAs – microRNA genes (miRNAs) – are involved in human tumorigenesis (Calin et al., Proc Natl Acad Sci USA, 2002). We also proved that another family of ncRNAs named ultraconserved genes (UCGs) are involved in human cancers and directly interact with miRNAs (Calin et al., Cancer Cell, 2007). Finally, we focused on how to quickly translate these discoveries to better diagnosis and treat cancer patients (Fabbri et al., JAMA, 2011).'[2]

(Continued)

BOX 1. (Continued)

Epigenetics of cognitive functions
Sweatt Lab, Vanderbilt University: 'An ongoing focus of the Sweatt Lab is to elucidate the function of basic epigenetic mechanisms (including DNA methylation and hydroxymethylation, histone modifications, histone variant exchange, and proteins that modify the epigenome) within the brain, especially within the context of learning and memory. Our ultimate goal is to understand how these mechanisms contribute to cognition and how changes in these mechanisms may lead to cognitive impairments in a range of memory-related disorders.'[3]

Epigenetics of plants
Jacobsen Lab, UCLA: 'We study DNA methylation in the model plant Arabidopsis thaliana because of its facile genetics, small size, and trim genome. Furthermore, unlike other organisms like mouse, where DNA methylation mutants are inviable, Arabidopsis can tolerate mutations that virtually eliminate methylation, allowing for further study. Arabidopsis methylation mutants display developmental abnormalities because of defects in the methylation of several key genes that regulate development.'[4]

Epigenetics at the molecular level
Zhang Lab, Harvard University: 'Built upon our strength in protein biochemistry, the lab has expanded its capability to use a variety of state-of-the-art techniques, including single-cell live imaging, single cell transcriptomics and epigenomics, cell lineage tracing, somatic cell nuclear transfer, CRISPR/Cas9-based genomic and epigenomic editing, and intravenous self-administration to understand the molecular events at the beginning of mammalian life, somatic cell nuclear transfer reprogramming, and the development of drug addiction.'[5]

[1]https://joneslab.vai.org (accessed 6 February 2019).
[2]https://www.mdanderson.org/research/departments-labs-institutes/labs/calin-laboratory.html (accessed 19 March 2019).
[3]https://my.vanderbilt.edu/sweattlab/team/ (accessed 6 February 2019).
[4]https://www.mcdb.ucla.edu/Research/Jacobsen/LabWebSite/P_Index.php (accessed 6 February 2019).
[5]https://www.zhanglab.tch.harvard.edu (accessed 6 February 2019).

It is thus crucial to distinguish between epigenetics researchers' thematic interests and conceptual apparatus. One way to gauge conceptual standardization is to analyze the keywords referenced in epigenetics articles over time. We thus compared three periods: 1991–2000 (Figure 6), 2001–2010 (Figure 7) and 2011–2017 (Figure 8). The main finding is that the keywords used in epigenetics articles have become more and more homogenous over time, which clearly demonstrates that thematic diversity is not synonymous with conceptual fuzziness. Such standardization is visible both graphically, as the three networks are more and more revolving around a small, tight-knit set of keywords over time, and statistically, as the coefficients of modularity for the three networks are getting smaller over time (0.547 for the 1991-2000 period, 0.404 for the 2001–2010 period and 0.339 for the 2011–2017 period).

In the 1990s, the number of keywords clusters was high and the conceptual network little structured, although overarching interests went to DNA methylation and chromatin (Figure 6). Furthermore, while histone was already present in the main keywords used in epigenetics articles, other concepts were still largely absent from the literature, most

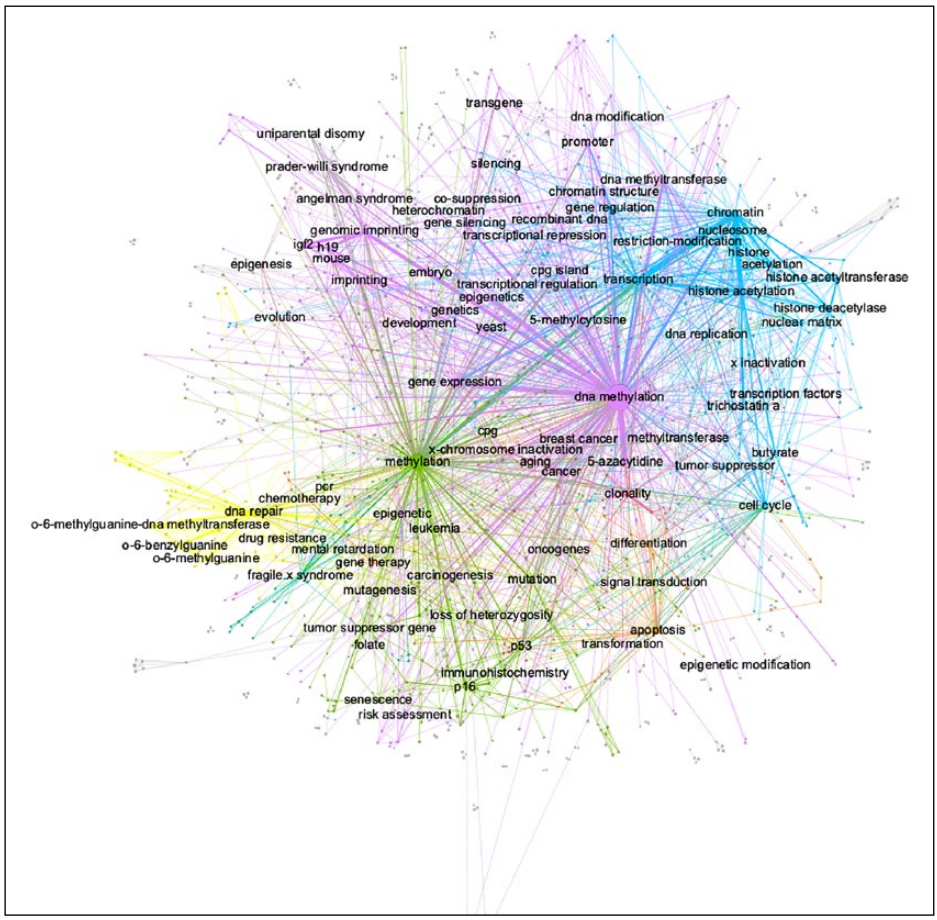

Figure 6. Network of keywords extracted from the 199,484 epigenetics articles, 1991–2000 (threshold of 2 edges).

prominently RNAs. Another interesting finding is that the keyword 'epigenetics' itself is not only as central as other terms but is also related to a subset of the keywords only, meaning that a number of epigenetics research conducted in the 1990s was not labeled as such.

The 2001–2010 conceptual map is comparatively more homogenous and denser (Figure 7), which explains the smaller coefficient of modularity that the network exhibits (0.404). Overall, three main clusters emerge: a green one concerned by methylation in relation to cancer and metastasis; a purple one, closely associated to the epigenetics label, which revolved around DNA methylation and gene expression; a blue one focusing on chromatin and histone methylation. Although we can also witness the apparition of microRNA-related keywords, (orange network), this interest is limited and still peripheral compared to the importance it took in the most recent years.

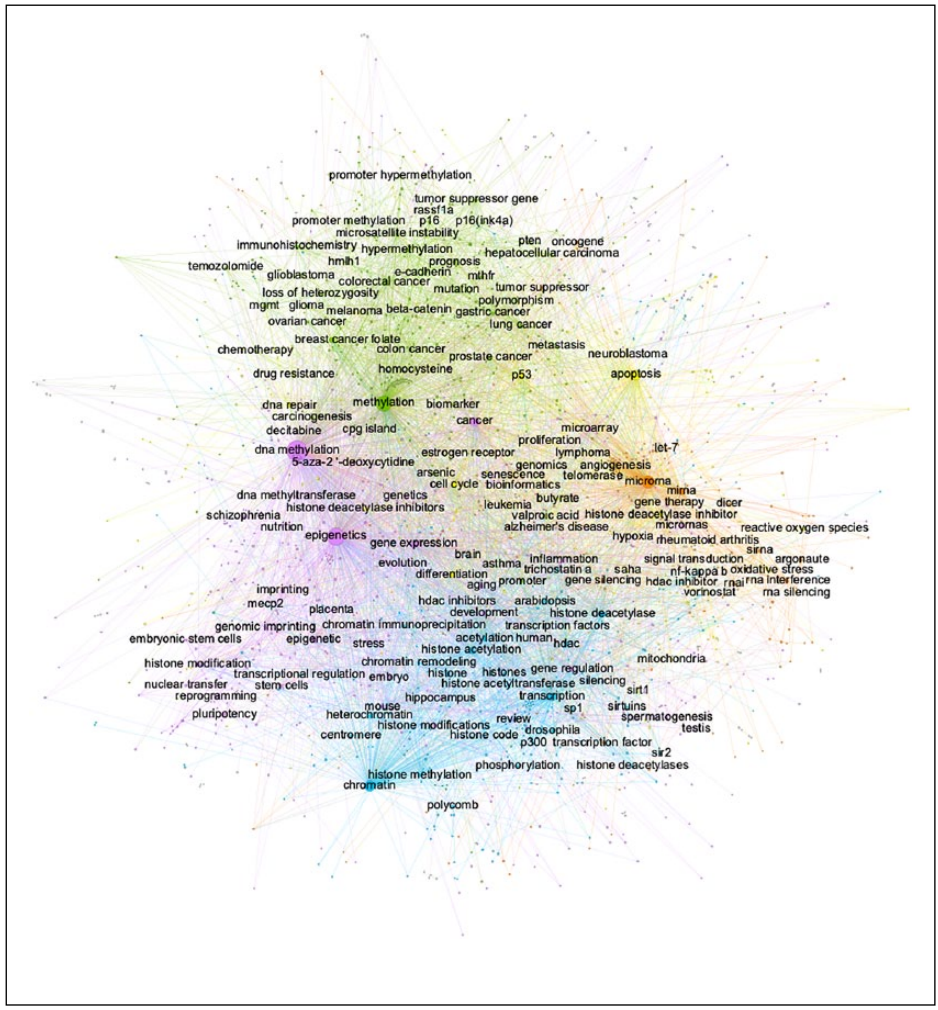

Figure 7. Network of keywords extracted from the 199,484 epigenetics articles, 2001–2010 (threshold of 4 edges).

The 2011–2017 period is uncontestably the last touch to the growing conceptual standardization of epigenetics research (Figure 8). The network of keywords is even more dense than the previous ones, which is visible in the coefficient of modularity (0.339). Most importantly, the network is now densely organized around a small set of prominent concepts, with two clusters making up the bulk of the literature. The green cluster is primarily concerned with RNAs (microRNAs, non-coding RNAs, etc.), especially in relation with cancer. The centrality of RNAs in epigenetics literature is thus a very recent phenomenon, as this concept was still peripheral in the early 2000s and largely absent in the 1990s. The purple cluster is mainly interested in DNA methylation

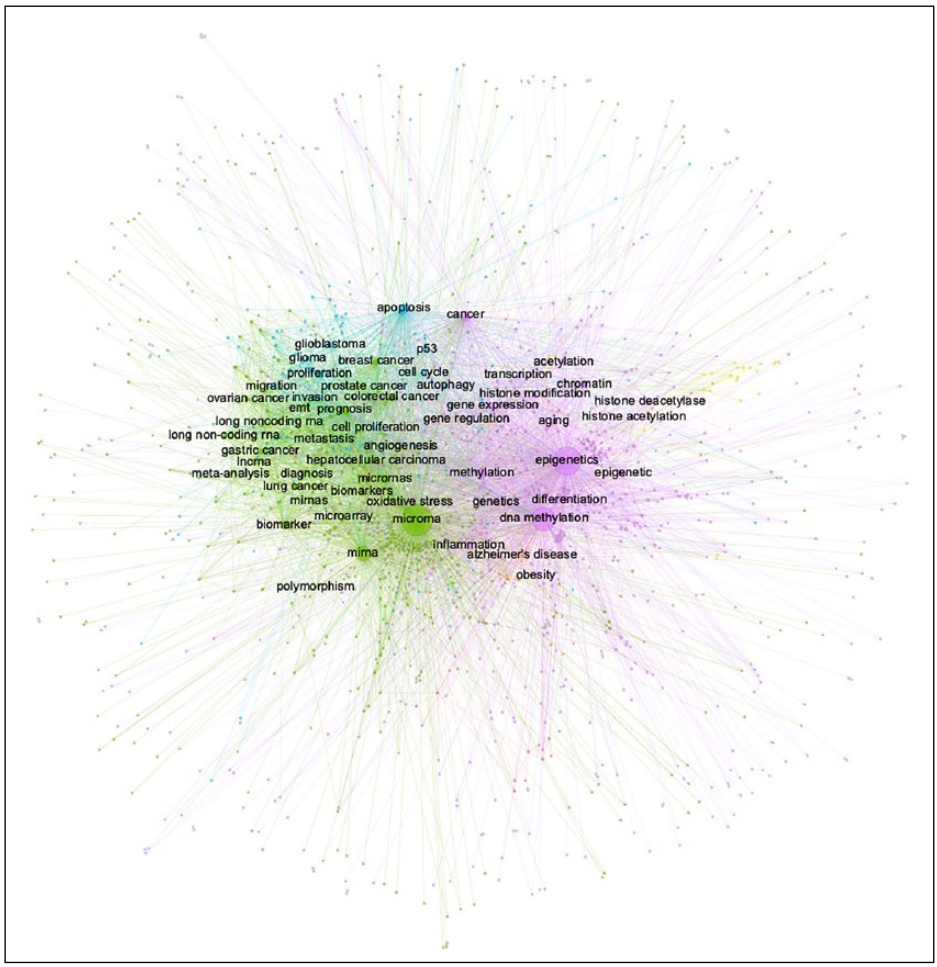

Figure 8. Network of keywords extracted from the 199,484 epigenetics articles, 2011–2017 (threshold of 9 edges).

and histone acetylation. Interestingly, the main keyword of this cluster is 'epigenetics' itself, which further accentuates the trend already observed in the 1990s that the epigenetics label is predominantly associated with DNA methylation. To be clear, the fact that the network of keywords became more homogenous over time does not signify that epigenetics research has become less diverse. In fact, as the number of epigenetics articles increased, the number of keywords and concepts related to the field also augmented. But this augmentation had the paradoxical effect of cementing epigenetics research, which now relies on a limited number of identifiable concepts.

One interesting, although saddening, fact for the social scientists is the absence of environment-related keywords in the main concepts mobilized by epigenetics

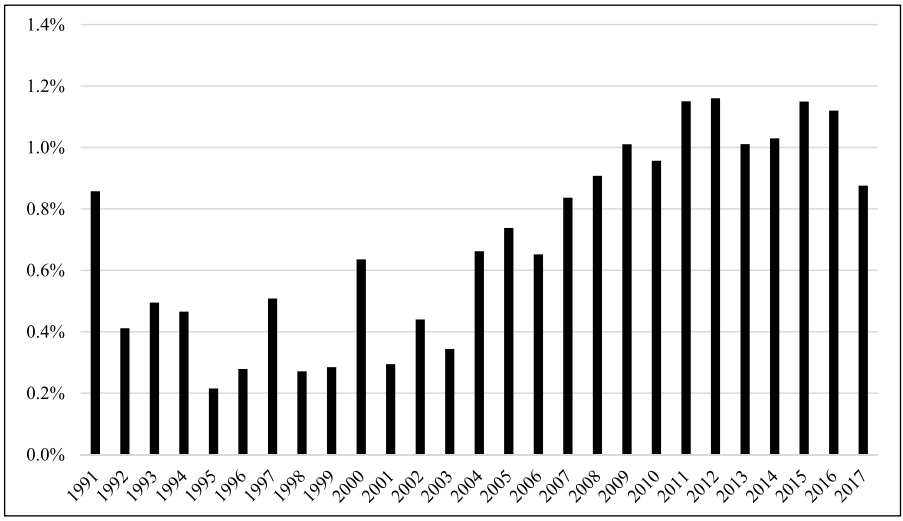

Figure 9. Evolution of the proportion of epigenetics articles mentioning the prefix 'environ' in their title, 1991–2017 (*n*=1893).

researchers, whether in the 1990s or in the most recent period. The potential for a social biology might well be real, but the concrete, empirical developments of epigenetics are not primarily devoted to understanding the embodiment of social variables. Since the network analyses were limited to core concepts, we performed additional investigations. Hence, Figure 9 presents the evolution of the proportion of epigenetics articles mentioning the prefix 'environ' in their title between 1991 and 2017. The results largely confirm our skepticism, as approximately 1% of epigenetics articles published every year mention environment-related keywords in their title. It is nonetheless the case that we observe a growing, albeit still relative, interest in this matter from the mid-2000s. But this upsurge has been rather stagnant in the most recent years and the environmental thematic remains a drop in the entire epigenetics bucket. While quantitative and qualitative importance are not necessarily correlated, it is telling that most social scientists' interest in epigenetics has been concentrated on this 1%.

Discussion and conclusion

In a remarked article entitled 'Scrutinizing the epigenetics revolution,' Maurizio Meloni and Giuseppe Testa (2014: 432) put forth the expression of 'epistemology of the imprecise' (borrowed from Rheinberger, 2003) to characterize the field of epigenetics. According to them, 'epigenetics seems to flourish in the remarkable ambiguity of its defining term, with its apparent ability to accommodate – and productively align – a rather diverse range of biological questions and epistemic stances,' thus rendering attempts at '[providing] a full disambiguation of epigenetics [. . .] largely futile and indeed counterproductive' (Meloni & Testa, 2014: 432–433). Though our own process of

disambiguation remained arduous and indeed uncomplete, we believe that it does provide readers, both epigeneticists and analysts and critics of epigenetics alike, with a set of coordinates to locate (even approximately) epigenetics on the map of science. For the conceptual ambiguities of epigenetics can be temporarily side-stepped, to be then better confronted, by focusing on the full-fledged agents of this 'passive revolution' (Meloni & Testa, 2014: 450): scientists, journals, universities, etc. Such circumvention brings a certain number of valuable insights regarding epigenetics research.

First, it teaches us the inconvenient fact that despite the high hopes that we social scientists may have placed since a few years in the passive revolution of epigenetics, the scientists, journals and institutions that drive most of the research in the field are overall little concerned with social dimensions of gene expression. Furthermore, environment-related keywords are noticeably absent from the main concepts mobilized in epigenetics research, whether in the 1990s or in the last years. Even if one considers that the study of cognitive functions among rodents that can be illustrated by the works of Frances A. Champagne, Michael J. Meaney or Eric J. Nestler is eminently related to human behaviors (which is contested among specialists), this research interest remains peripherical at the macro-level and much less visible than, say, molecular or cancer epigenetics. To be sure, this does not mean that social scientists should not try to develop research relations with those who do share similar interests, but maybe we should not place too much hope in the hype surrounding epigenetics, especially when a large array of questions remain debated and unanswered as of today (Dubois et al., 2018: 86–88).

Another finding, that largely confirms previous qualitative investigations of the field (Dubois et al., 2018; Meloni & Testa, 2014; Pickersgill et al., 2013), is that epigenetics is indeed constituted by diverse networks of scholars, institutions and research specialties that enjoy relative autonomy from each other and put forth different conceptions of epigenetics research. Regarding the institutional structure of epigenetics research, we found that geography was a crucial variable in scientific collaborations (as measured by articles' authorship), with two countries standing at the forefront of the field, namely the United States and China. Interestingly, epigenetics research in the United States was further subdivided, with the Boston area serving as a hub concentrating closely collaborating institutions, including Harvard University, MIT, Boston University, Broad Institute, Boston Children's Hospital, Dana-Farber Cancer Institute or the Massachusetts General Hospital. Interestingly, the intellectual structure of epigenetics, as objectified through bibliographic coupling analyses, revealed that thematic differentiations were a bit less important than institutional networks in accounting for the internal boundaries of epigenetics research (Figure 1). Indeed, while the coefficient of modularity for the institutional networks was relatively high (0.764), the coefficients obtained for the authors' networks were slightly lower.

It is however important to underline that the results obtained from the bibliographic coupling showed that this intellectual structure became *more heterogenous* over time, as the coefficient of modularity went from 0.479 for the 2006–2011 period to 0.633 for 2012–2017. This demonstrates that the field of epigenetics is not stabilized yet, as its development over the last few years has had the counter-intuitive effect of producing still further differentiation. A possible explanation is that we are currently witnessing the

constitution of a scientific archipelago (Panofsky, 2014: 33), with disciplinary islands becoming more and more independent from each other as time goes by. Hence, completing our macro-level findings, we were able to relate the different communities populating the bibliographic coupling network to archetypical conceptions of epigenetics research. Cognitive-oriented scholars could thus be distinguished from plant specialists and molecular biologists, while cancer researchers could themselves be further sorted out depending on whether they were primarily interested in DNA methylation or non-coding RNAs. At the same time, this division of labor did not prevent epigenetics researchers to gather around a small set of clearly identifiable keywords that serve as a uniting conceptual apparatus. And while bibliographic networks got more heterogenous over time, concepts underwent a growing standardization between 1991 and 2017.

To conclude, we would like to acknowledge some limitations and suggest possible research avenues. The main limitation, which is at the same time the very contribution of this research, is the large scale of analysis that we chose to apply. By adopting a quantitative, macro-level approach to epigenetics research, we might here and there lack some analytical depth and nuance. Yet, we believe that this somewhat ungrateful labor had to be performed in order to complement more fine-grained understanding of the field. Although we touched upon the qualitative, micro-level translations of our macro-level quantitative findings by showing how differently situated scholars pursued different approaches to epigenetics, this question would deserve much more detailed and documented analyses. Hence, we hope that future researchers will piggy-back on our results and combine them with in-depth investigations of epigenetics research, for instance by conducting interviews with scholars belonging to, and content analyses of the scientific literature pertaining to, the main thematic and disciplinary networks that we were able to identify through bibliographic coupling and keywords analyses.

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Notes

1. http://www.roadmapepigenomics.org/overview
2. In his founding article, Gieryn (1983) defined boundary-work as the ‘attribution of selected characteristics to the institution of science (i.e., to its practitioners, methods, stock of knowledge, values and work organization) for purposes of constructing a social boundary that distinguishes some intellectual activities as ‘non-science’’.
3. As Meloni and Testa (2014: 437) underlined, ‘epigenetics offers no shortage of controversies, especially around the following themes: (i) the relevance of intergenerational inheritance of

epigenetic traits especially in higher organisms; (ii) the reappraisal of the concept of gene, and of the assessment of its functional significance, in the light of the unforeseen extent of several *epi*-layers of regulation (as most vividly captured in the heated controversies over the universe of non-coding RNAs unearthed by the ENCODE Project (Doolittle, 2013; Graur et al, 2013)); (iii) the tension between the Modern Evolutionary Synthesis as a settled canon and the renewed interest, much more vocal than in the past, in epigenetic, neo-Lamarckian mechanisms of inheritance (Jablonka & Lamb, 2005); and (iv) the epigenetic underpinnings of human behaviors.'

4. By gene-centric views, we refer to the theoretical perspectives postulating that genes are the prime movers of evolution and thus the most important units of inquiry for biologists, as they not only drive human inheritance but also the internal functioning of organisms. This gene-centric view has been questioned well before the advent of contemporary epigenetics (Barnes & Dupré, 2008).
5. The growing role that cultural factors are now thought to be playing in the neo-Darwinian evolutionary framework is yet another illustration of this trend (Boyd, 2017; Laland, 2017).
6. Similarly, see the report published by *ScienceWatch* in 2009: http://archive.sciencewatch.com/ana/st/epigen/ (accessed 11 May 2019).
7. A lot of the research surrounding epigenetics that was conducted during the second part of the 20th century was published in the *Doklady Akademii Nauk USSR*, that is in the *Proceedings of the USSR Academy of Sciences*. Hence, between 1955 and 1997, 69 articles touching to epigenetics were published in the journal. Though it would be very tempting to link this finding to Meloni's investigation of the status of Lamarckism and eugenics in the USSR during Cold War (2016), a quick analysis of the articles' titles reveals that the prefix 'epigen' was in fact predominantly used in its geological sense of epigenesis (and its associated adjective, epigenetic) and thus concerned rock formation rather than human or animal biology. For instance, a paper published in 1956 analyzed 'The late diagenesis (epigenesis) of Donetz carboniferous rocks'; another one, published in 1964, investigated the 'Formation of glacial horizons in epigenetic frozen strata'; yet another one, published in 1979, touched on the 'Galvanic effect in stratified magnetite ores and its influence upon the course of epigenetic processes.' While this fact might be regarded as irrelevant to our purpose, it serves to remind us that epigenetics is a polysemic term whose meaning has evolved over time.
8. Importantly, the findings displayed in Figures 4 and 5 are very similar to the results that we had originally obtained with a smaller dataset that was limited to articles explicitly mentioning the prefix 'epigen*' (77,289 articles). Not only does this demonstrates the pertinence of our corpus, but it also serves to underline that many scientists practice epigenetics research without revendicating the label. We shall come back to this latter point in the last section devoted to conceptual standardization.
9. Hence, the coefficient of modularity for the 1000 first edges of the 2006–2011 period is quite low (0.146), although it is possible to roughly distinguish between three subareas: generalist journals (*PNAS, PLOS One*, etc.), cancer journals (*Cancer Research, Oncogene*, etc.), genetics and molecular biology journals (*Nature Review Genetics, Genes & Development, Epigenetics*, etc.).
10. George A. Calin thus presents his main research interests as follow: '1) the involvement of non-coding RNAs in human diseases in general and of microRNAs in human cancers in particular, 2) the study of familial predisposition to human cancers, 3) the identification of ncRNA biomarkers in body fluids, and 4) the development of new RNA-based therapeutic options for cancer patients.' See: https://faculty.mdanderson.org/profiles/george_calin.html (accessed 19 March 2019).
11. The second one, Carlo M. Croce, had a degree of 87.

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