PERSPECTIVE AND HYPOTHESIS

Computing the Extended Synthesis: Mapping the Dynamics and Conceptual Structure of the Evolvability Research Front

JOURNAL OF EXPERIMENTAL ZOOLOGY PART B MOLECULAR AND DEVELOPMENTAL EVOLUTION

LAURA NUÑO DE LA ROSA*
IAS-Research Group, University of the Basque Country, San Sebastian, Spain

ABSTRACT

Since the late 1970s, the field of evolutionary biology has undergone empirical and theoretical developments that have threaten the pillars of evolutionary theory. Some evolutionary biologists have recently argued that evolutionary biology is not experiencing a paradigm shift, but an expansion of the modern synthesis. Philosophers of biology focusing on scientific practices seem to agree with this pluralistic interpretation and have argued that evolutionary theory should rather be seen as an organized network of multiple problem agendas with diverse disciplinary contributors. In this paper, I apply a computational analysis to study the dynamics and conceptual structure of one of the main emerging problem agendas in evolutionary biology: evolvability. I have used CiteSpace, an application for visualizing and analyzing trends and patterns in scientific literature that applies cocitation analysis to identify scientific specialities. I analyze the main clusters of the evolvability cocitation network with the aim to identify the main research lines and the interdisciplinary relationships that structure this research front. I then compare these results with the existing classifications of evolvability concepts, and identify four main conceptual tensions within the definitions of evolvability. Finally, I argue that there is a lot of usefulness in the inconsistency in which the term evolvability is used in biological research. I claim that evolvability research has set up "trading zones" in biology that make possible interdisciplinary exchanges. *J. Exp. Zool. (Mol. Dev. Evol.) 328B:395–411, 2017.* © 2017 Wiley Periodicals, Inc.

J. Exp. Zool. (Mol. Dev. Evol.) 328B:395–411, 2017

How to cite this article: Nuño de la Rosa L. 2017. Computing the extended synthesis: Mapping the dynamics and conceptual structure of the evolvability research front. J. Exp. Zool. (Mol. Dev. Evol.) 328B:395–411.

Since the late 1970s, the field of evolutionary biology has undergone empirical and theoretical developments that have put to the fore the need to integrate into evolutionary theory the role played by factors that were not included in the modern synthesis (MS), such as development, epigenetic inheritance, niche construction, or multilevel selection. Evolutionary biologists have held three main positions regarding the challenge these new developments pose to the MS framework, ranging from those arguing that nothing new has been added to the received view of evolution to those claiming that the challenges are so substantial that the MS needs to be replaced by a new theory (see Müller and Pigliucci, 2010 for references). A middle position holds that evolutionary biology is not experiencing a paradigm shift, but an expansion of the structure and content of the MS (Pigliucci, 2009).

Philosophers and historians of biology focusing on scientific practices seem to agree with this more pluralistic view of the recent historical development of evolutionary biology. Love (2010) and Brigandt (2010) have argued that philosophy of biology should shift the emphasis from theories to problems or epistemic goals in evolutionary biology, and particularly in

Grant sponsor: KLI Postdoctoral Fellowship (2013-2014); Grant sponsor: Juan de la Cierva Fellowship; Grant number: FJCI-2014-22685.

Additional Supporting Information may be found in the online version of this article.

*Corresponence to: Laura Nuño de la Rosa, Facultad de Filosofía y Ciencia de la Educación, Dpto Lógica y Filosofía de la Ciencia, Universidad del País Vasco, Avenida Tolosa, 70, 20018 San Sebastian, Spain.
E-mail address: lauranrg@gmail.com

Received 13 January 2017; Revised 11 March 2017; Accepted 24 March 2017
DOI: 10.1002/jez.b.22741
Published online 10 May 2017 in Wiley Online Library (wileyonlinelibrary.com).

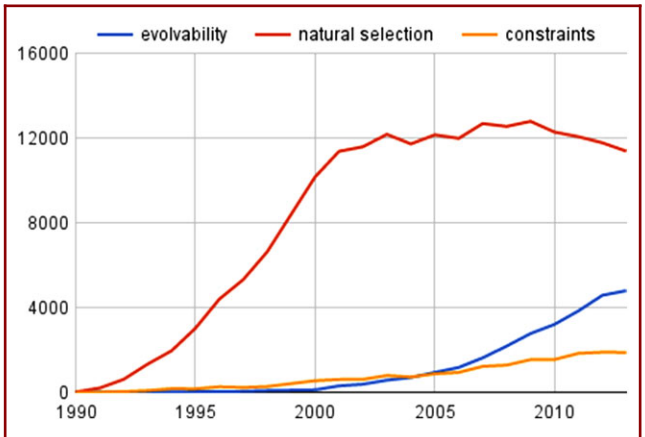

Figure 1. Evolution of the number of citations (according to the WoS) on natural selection, evolvability, and developmental constraints, from 1990 to 2014. Since 2000 evolvability has experienced a constant increase in the number of publications that contrasts with the stabilization of the number of citations related to natural selection and developmental constraints. [Color figure can be viewed at wileyonlinelibrary.com]

evolutionary developmental biology or evo-devo. In this view, evolutionary theory is seen as an organized network of multiple problem agendas with diverse disciplinary contributors. Thus, the identity of evo-devo as a discipline does not consist of being a theory, but derives from the pursuit of specific epistemic goals, such as the explanation of evolvability, evolutionary novelty, or homology. In a recent paper, Winther (2015) has argued that evo-devo can be understood as a trading zone, in which various scientific cultures (disciplines, styles, and paradigms) interact and negotiate theories, instruments, and concepts.

Nowadays, the identification of conceptual patterns and interdisciplinary interactions in the development of a discipline requires the analysis of a large amount of literature that can be done exhaustively only with the help of automatic analytical tools (Laubichler et al., 2013). In this context, the development of big data-based approaches and computational analytical methods promises to revolutionize the field of the history and philosophy of science.

In this paper, I combine these new approaches to the history and philosophy of science to study one of the main emerging concepts in evolutionary biology: evolvability (see Fig. 1). Evolvability is usually taken to be a cornerstone of evo-devo (von Dassow and Munro, '99) and, more generally, of the extended synthesis (Pigliucci, 2008; Pigliucci and Müller, 2010). In the last years, several efforts have been made to understand what evolvability is and what is the cause of the sudden interest in this concept (Pigliucci, 2008; Brookfield, 2009; Brown, 2014; Minelli, 2017). I aim to show how a computational analysis of evolvability can shed a new light into this debate.

The problem agenda of evolvability can be considered a "research front," a notion used in science studies to refer to the body of articles that scientists in a research field actively cite (Price, '65), defining the state of the art of a speciality (Small, '99). There is a variety of techniques to analyze research fronts from bibliometric data, and many software tools are currently available to map them. In this paper, I have used CiteSpace (Chen, 2006), a freely available Java application for visualizing and analyzing trends and patterns in scientific literature, which applies cocitation analysis (Small and Griffith, '74) to identify scientific specialities. CiteSpace has two main advantages that make it an ideal tool for mapping the dynamical and conceptual structure of changing interdisciplinary research fronts such as evolvability. First, cocitation networks (where nodes correspond to cited references and links to cocitation relationships) are extended to multiple slice network analysis, that is, a time series of networks, that permit to analyze the evolution of a research front. Second, CiteSpace includes a clustering function that allows to identify the main subtopics or research lines within a research front.

This paper is organized as follows. After describing the methods used to map the evolvability research front, I analyze the main clusters of the evolvability cocitation network with the aim to identify the main research lines and the interdisciplinary relationships that structure this research front. I then compare these results with the existing classifications of the concepts of evolvability, and identify four main conceptual tensions within the definitions of evolvability. Finally, I argue that, despite the irreducibility of some definitions of evolvability, there is a lot of usefulness in the inconsistency in which the term evolvability is used in biological research. In particular, I claim that evolvability research has set up "trading zones" in biology that make possible interdisciplinary exchanges.

METHODS

Bibliographic records were gathered from ISI's Web of Science[1] based on a topic search for articles and proceeding papers on "evolvability" or "evolutionary adaptability"[2] published in English between 1970 and 2014. The resultant data set contains

[1] The ISI covers less academic sources (e.g., conference and workshop proceedings) than other web search engines such as Google Scholar. However, the ISI databases are considered to be the best sources for bibliometric analysis due to their broad coverage and high-quality citation data (Boyack et al., 2005).

[2] One of the difficulties when exploring the history of a scientific concept is the change of the words used by scientists to refer to these concepts. In the case of evolvability, other terms (e.g., "variability," "versatility" or "evolutionary adaptability") were used before Dawkins stabilized the term "evolvability" in 1989. I constrained my topic search to "evolvability" and "evolutionary adaptability" because both "variability" and "versatility" are used in different scientific contexts than evolutionary biology and deliver too many nonrelated items.

a total of 1,415 records. Full record and cited references were saved. This data file was downloaded and manually cleaned before importing the data into the software package CiteSpace, version 3.9.R7. Duplicate records for books cited in different editions were merged, resulting in a final database containing 1,039 unique references. To improve cluster labeling, I removed ID generic terms (e.g., biology, perspective, information, discovery) and combined words with alternate spellings and hyphenated words with nonhyphenated synonyms.

The cleaned data file was used to build and visualize a single merged network (i.e., a network based on networks corresponding to consecutive years) in CiteScape. The time interval was sliced into 24 1-year segments (1990–2014). The first 10% most cited documents with more than five citations in each time slice were selected. Citation numbers do not reflect the total number of citations of the documents of a cocitation network. Rather, they refer to the number of citations of each paper within the cocitation network of evolvability. The layout of the network was produced by the Kamada and Kawai's algorithm.

Clusters were computed by the CiteSpace clustering function, and automatically labeled by a cross-mapping technique generated by Index terms. The modularity and the silhouette scores of clustered cocitation networks are two indicators of the general structural properties of a research front. The modularity value (*Q*), ranging from 0 to 1, measures the extent to which a network can be divided into independent modules: a low modularity suggests a network that cannot be divided into well-demarcated clusters, whereas a high modularity suggests a well-structured network. The silhouette value (S), ranging from −1 to 1, captures the conceptual homogeneity of a cluster.

CiteSpace's clustering of the evolvability network is a preliminary reasonable division of the evolvability research front into its main research lines, but needs to be manually corrected on the basis of a detailed analysis of the members of each cluster. From the 14 clusters identified by CiteSpace, I have only considered six clusters (see Table 1). Clusters ranging from Cluster # 6 to # 14 might be seen as artificial and not representative, since they are too small and their members have a low number of citations. I have, nonetheless, included Cluster # 8 because it captures a research line (Macroevolution), which is usually considered as an important approach in evolvability research (see section Macroevolution Approach: Cluster # 8).

RESEARCH LINES IN THE EVOLVABILITY RESEARCH FRONT

The merged cocitation network of evolvability generated by CiteSpace contains 967 nodes (cited references) and 17,466 cocitation links partitioned in 14 clusters (see Figs. 2 and 3). A first glance of the network allows to infer some general conclusions regarding the dynamical and conceptual structure of the evolvability research front.

Since the mid-1990s, "evolvability" has been the most commonly used word to refer to the ability of a biological system to evolve.

Table 1. Summary of the main properties of the clusters of the evolvability cocitation network

Cluster ID	Size	Silhouette	Mean (year)
0	174	0.577	1998
1	159	0.771	1993
2	156	0.623	1993
3	125	0.624	1994
4	106	0.7	1998
5	41	0.899	1990
8	27	0.919	1998

Cluster numbers correspond to cluster size, measured by the number of cocited documents in each cluster. The silhouette value is an indicator of the conceptual homogeneity of a cluster. The mean year refers to the average year in which the first cocitation links of each cluster were created.

Regarding the historical origins of this research agenda, cocitation network indicates that the evolvability research front was formed in the mid-late 1990s, when many of the documents of the network were published and cocited for the first time (see Fig. 2, links in light blue)[3]. The first paper specifically related to evolvability to show up in the network is (Dawkins '89), followed by (Conrad '90), (Kauffman '90), (Alberch '91), and (Altenberg

[3] This does not mean that evolvability research started in the 1990s (Brigandt, 2015), but that the *evolvability research front,* as a scientific speciality within evolutionary biology that can be tracked as a corpus of related articles that biologists actively cite, was formed after the publication of Dawkins' paper. Ideas on evolvability root back to the works of Schmalhausen, Waddington, and Ruper Riedl (see Wagner and Laubichler, 2004), and a search on "evolvability" in Google Scholar between 1920 and 1989 renders 252 results. Nonetheless, these results include those documents that are later cited by papers containing "evolvability" in their titles, and the vast majority of them relate to software design. According to Google Scholar, the term "evolvability" shows up for the first time in 1932, in a book written by the Scottish naturalist John Arthur Thomson, where he refers to evolvability as the ability of the individual organism to influence its own evolution by selecting stimuli, moving from one environment to the other, or "moulding itself by its efforts" (1932, p. 28). After Thomson's work, biological evolvability only appears again in the English translation of a book written in Spanish by the Catalan physiologist August Pi Suñer, where he refers to evolvability as "[v]ariability affording opportunity for adaptability" (1955, p. 220). In the 1960s, the term evolvability is mentioned in the context of the debate on the origins of life, and in a 1971 biology book, where it is related to the mechanism enabling an organism "to evolve more suitable structures and functions in the face of a changing environment" (Case and Stiers, '71, p. 111). However, all these previous references to evolvability are only anecdotal from the perspective of the evolvability research front. None of them (differently to Schmalhausen, Waddington, Riedl, or Conrad's work) was retrospectively recognized as part of the "prehistory" of the evolvability research.

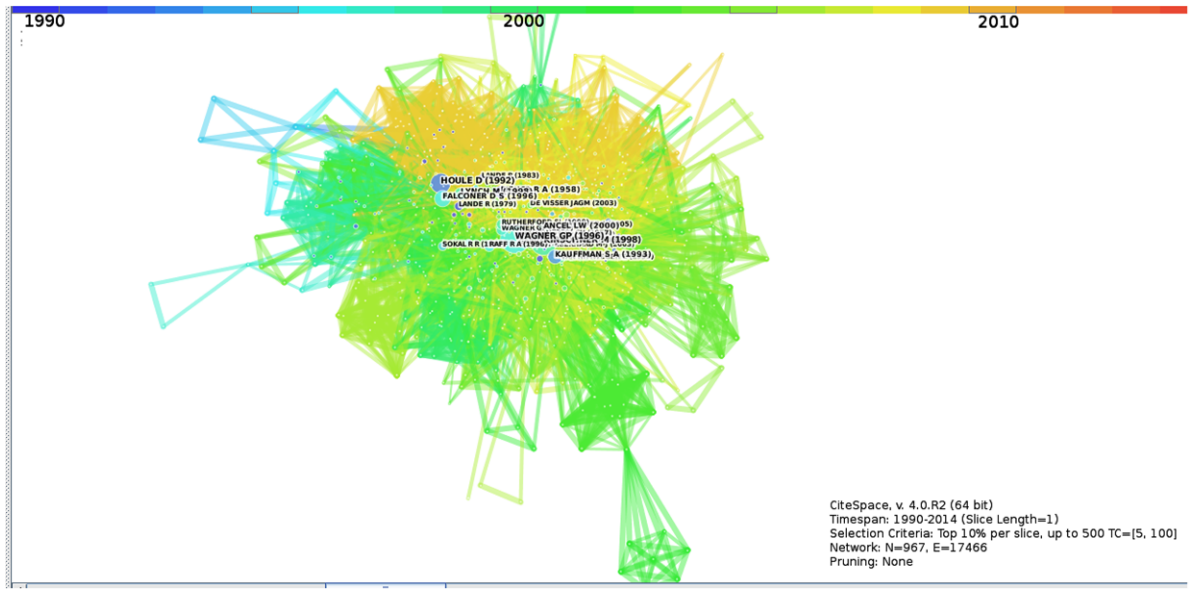

Figure 2. Cocitation network of evolvability. The merged cocitation network of evolvability generated by CiteSpace contains 967 cited references (N, nodes) and 17,466 cocitation links (E). The colors of the upper bar represent the years when citations and cocitations were made. The relative size of the nodes reflects the number of citations of each document (according to ISIS Citation Report) during the selected time interval. The width and the length of a link are proportional to the corresponding cocitation coefficient, and the colors of links show when a connection was made for the first time. [Color figure can be viewed at wileyonlinelibrary.com]

'94). However, only three later papers (Houle, '92; Wagner and Altenberg, '96; Kirschner and Gerhart, '98) succeeded in making of evolvability a true research front. Research on evolvability became an active area of research in the early 2000s, and since 2008, it has turned into a highly active research front (see the number of cocitation links in green in both the center and the periphery of the network, and the density of cocitation links in yellow and light orange in Fig. 2). The evolvability cocitation network also shows that evolvability research has turned into a differentiated research front, showing a significant increase in the number of well-developed clusters since its origin in the 1990s.

From a conceptual viewpoint, CiteSpace identifies 14 clusters within the cocitation network of evolvability. The modularity of the network is intermediate ($Q = 0.46$), and the mean silhouette summarizing the average conceptual homogeneity of the clusters is reasonably high ($S = 0.73$). These two indicators suggest that although the evolvability research front is reasonably structured in coherent and relatively independent research lines, there is also a strong collaboration between the different approaches to evolvability.

In what follows, I analyze the clusters of the evolvability cocitation network with the aim to identify the main research lines and the interdisciplinary relationships that structure this research agenda (see Table 1). I choose to discuss the clusters identified by CiteSpace in relation to six broad disciplinary approaches, namely the (1) evo-devo (Cluster # 2), (2) complex network (Cluster # 0), (3) molecular evolution (Clusters # 0 and # 4), (4) population genetics (Cluster # 3), (5) quantitative genetics (Clusters # 1 and # 5), and (6) macroevolution approach to evolvability (Cluster # 8).

Within each cluster, I distinguish those documents that play the role of the "intellectual base" of each research line from those documents specifically related to evolvability. Among the latest, I identify the main documents and the role they play within the evolvability research front by paying attention to two indicators. First, I consider the number of citations of the documents. I only analyze documents with more than five citations and pay special attention to highly cited articles (landmark nodes). Second, I take into account the topological properties of these documents, since the main works of a research front usually have topologically unique features that are independent of their number of citations. Two types of nodes can be distinguished in this respect (Chen, 2004): hub nodes are highly cocited by documents of the same cluster, while pivot nodes are highly connected to documents belonging to different clusters. Finally, I look at the

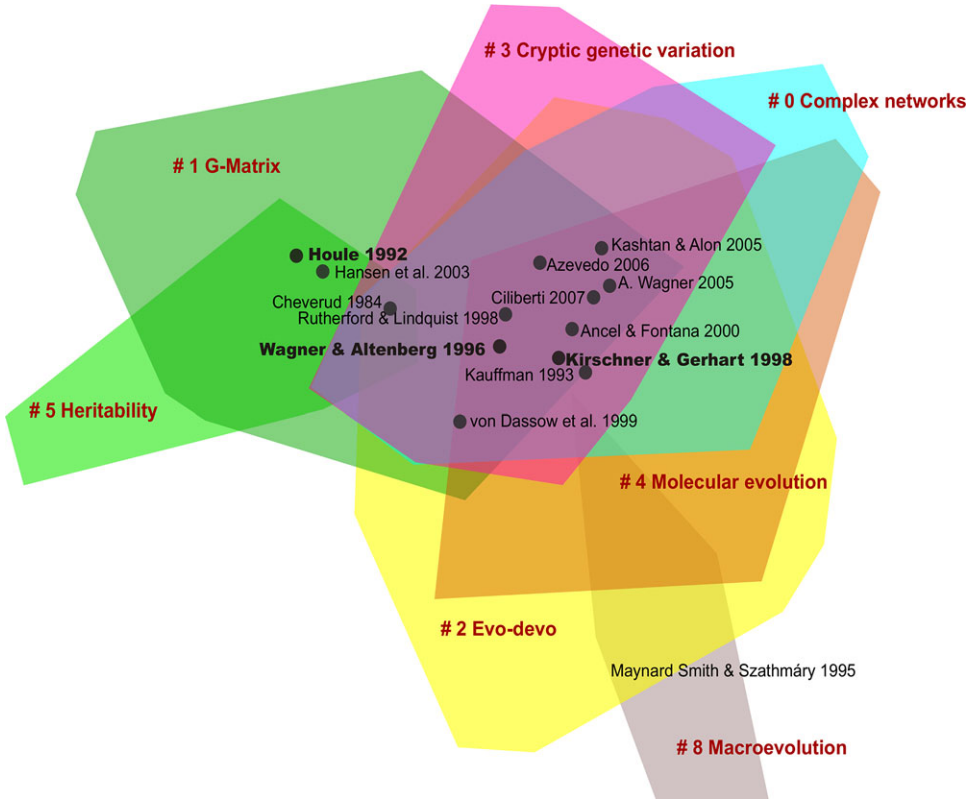

Figure 3. Cocitation network of evolvability partitioned in clusters. Cocitation links have been removed. Cluster numbers (#) represent the size of each cluster. The main documents of the network are shown. The three most cocited articles are highlighted in bold. [Color figure can be viewed at wileyonlinelibrary.com]

overlaps and interconnections between the clusters in order to investigate the interdisciplinary patterns structuring the evolvability research front.

The Evo-Devo Approach: Cluster # 2

With 156 members, Cluster # 2 is the third biggest cluster of the evolvability network. With a relatively high conceptual homogeneity ($S = 0.623$), the cluster groups those documents with a developmental approach to evolvability and related concepts, the main topics being the definition of evolvability and the role of developmental modularity in evolution. Situated at right center of the network (Fig. 3), it partly overlaps with the clusters on molecular evolution (# 0, # 4), cryptic genetic variation (# 3), and quantitative genetics (# 1). From a dynamical perspective, it is an old cluster. Formed in 1993, most of the cocitation links were established in the late 1990s, and there are almost no new documents (see Supplementary Table S1, yellow rows).

The Definition of Evolvability. The main documents of Cluster # 2 deal with the definition of evolvability, and they include two of the three landmark papers of the evolvability research front, namely Wagner and Altenberg ('96) (hereafter W&A'96) and Kirschner and Gerhart ('98) (hereafter K&G'98) (Supplementary Table S1, refs. 1, 2, 75). All the following numbered references pertain to the Supplementary Table S1).

W&A'96 and K&G'98 are central nodes in the overall network of evolvability in many respects. First, they are landmark papers, since they are the two most cited papers of the network, with 90 and 76 citations (c.), respectively. Furthermore, they have been persistently cited since their publication. Third, they are hub nodes, since they both play an important integrative role within Cluster # 2. They are also pivot nodes, insofar as they play a significant role in connecting Cluster # 2 to the other clusters of the network. Before 1996, the developments on evolvability research had occurred with very little exchange among the different disciplines. W&A'96 and K&G'98 revolutionized the connectivity pattern of the evolvability research front, although they did so in different ways. Placed at the top center of Cluster # 2 (Fig. 3), K&G'98 plays a major role in connecting this cluster with that on molecular evolution (Cluster # 4), whereas W&A'96, located

at the bottom of Cluster # 2, connects this cluster to the clusters on population and quantitative genetics (Clusters # 1 and # 5).

All these properties show that W&A'96 and K&G'98 are the two main publications initiating the evolvability research front. But why did these papers and not earlier ones, such as Conrad ('90) (ref. 85), Alberch ('91), or Altenberg ('94) (ref. 85), manage to awake the interest of the community of evolutionary biologists on evolvability and initiate the disciplinary collaborations between different approaches to evolvability? Social "external" factors, such as the social validation of the authors of these papers or the journals where they were published (including the impact factor and the scientific audience of these journals), help to explain the success of W&A'96 and K&G'98 and the relative failure of earlier papers. However, the computational approach to the history of science taken in this paper offers new insights on the internal, conceptual reasons that help to explain the relative success of scientific publications. In particular, W&A'96 and K&G'98 contain several conceptual elements that became central in the evolvability research front. As we will see, some of these conceptual elements were already present in previous publications, but they were only perceived by biologists coming from different disciplines as key conceptual innovations in the shape they took in these two articles.

W&A'96 is the most cited publication of the evolvability network and contains several of the conceptual traits, which will become dominant in the evolvability research front. First, the genotype–phenotype map (hereafter, GP map) is introduced as the theoretical tool that articulates variation (i.e., the actually realized differences between individuals) and variability (i.e., the propensity to vary). Second, evolvability (defined as "the ability of random variations to sometimes produce improvement," p. 967) is defined as the notion connecting adaptation and variability. According to Günter P. Wagner and Lee Altenberg, evolvability is not only about whether or not variation can be produced, but about whether or not *adaptive* variation can be produced. Third, W&A'96 discusses the *evolution of evolvability*, which is understood as the possibility that the GP map, or the variability of traits itself, can evolve. Finally, *modularity* is discussed as one of the main variational properties that make GP maps evolvable.

W&A'96 was key in establishing disciplinary connections that will turn evolvability into a transdisciplinary research topic. In the 1990s, there were two disconnected clusters on evolvability, one on evolutionary computation and another one on quantitative genetics. The publication of W&A'96 was a fundamental intellectual turning point, insofar as it played a pivot role in connecting these two clusters. On the one hand, W&A'96 connected evolutionary biology and evolutionary computation through the problem of complex adaptations: in order to evolve, complex systems (computer programs or organisms) must be able to do so, that is, to possess the ability to generate random variations that sufficiently often produce improvement. On the other hand, W&A'96 argues for the need for describing the variability of traits and its evolution in population genetic terms. In this sense, W&A'96 emerges as the founding paper in introducing a developmental approach to evolvability into population genetics. The connectivity pattern of W&A'96 seems to confirm Hansen's suggestion that the renewed interest in incorporating more realistic representations of the GP map into population genetics may be motivated by advances in evo-devo and the interest in the evolution of evolvability (Hansen, 2006).

K&G'98 is the second most cited document of the evolvability cocitation network. The goal of this paper is to explore the properties of the gene regulatory processes that allowed metazoan diversification. Marc W. Kirschner and John Gerhart (see also ref. 118) identify five properties (namely, versatile protein elements, weak linkage, compartmentalization, redundancy, and exploratory behavior) that confer robustness and flexibility on developmental processes. They argue that these properties also confer evolvability on the organism by reducing constraints and allowing the accumulation of nonlethal variation.

Attending to the theoretical context in which K&G'98 is cited by later documents, we can identify two main conceptual reasons that explain its success. First, despite its focus on animal development and evolvability, the definition of evolvability as "the capacity to generate heritable, selectable phenotypic variation" (p. 8420) is general enough to be adopted by biologists working at different levels of organization. Second, Kirschner and Gerhart's view of evolvable systems as robust, flexible systems will be inherited by other research lines in the evolvability research front. Robustness is broadly defined as the buffering of a phenotype against the environmental or genetic perturbations that affect its expression. Since, by definition, robustness reduces variation and evolution requires phenotypic variation, genetic robustness seems to be an obstacle for evolvability. However, in the last years a lot of work has been devoted to show that mutational robustness actually promotes evolvability. Many of the documents working at different levels of biological organization refer to this tension between robustness and evolvability, on which we find several highly cited reviews in our network (Kitano 2004; de Visser et al., 2003; Lenski et al., 2006).

Besides W&A'96 and K&G'98, the evolvability network includes other earlier papers on the definition of evolvability that did not manage to make of evolvability a research front, namely Dawkins ('89), Conrad ('90), Alberch ('91), and Altenberg ('94). Only two of them (Conrad, '90; Altenberg, '94) have more than five citations within the network[4].

[4] Alberch ('91) can be considered as the founder of a developmental view of evolvability and contains some of the conceptual elements that will be later inherited by the core documents of the evolvability research front. In particular, Alberch introduced the G-P map as the main concept underlying evolvability, defined as a property of developmental systems that makes them "better at evolving" (p. 9). However, the relative failure of the developmental approach to evolvability might explain that it has been poorly cited since its publication.

Michael Conrad was probably the first to truly pursue the idea of evolvability. In a 1985 article he already used the word "evolvability" (Conrad, '85), and his 1990 paper has many of the conceptual elements we find in W&A'96 and K&G'98. First, evolvability (referred to as the "amenability to evolve" or "evolutionary adaptability") is introduced as a bridge concept connecting the structuralist and the adaptationist approaches to evolution. Second, Conrad develops the notion of evolvability within the theoretical framework of the debate on complex systems. Third, he talks about the evolution of evolvability ("self-facilitation of evolution" or "bootstrapping"). Fourth, the relationship between evolvability and programmability is explored. Finally, Conrad identifies the apparent conflict between evolvability and stability/robustness and suggests compartimentalization (modularity), component redundancy, and weak interactions as properties of biological systems that might solve this conflict.

Altenberg's ('94) is a low-medium cocited document (10 c.) included by CiteSpace in a nonrepresentative cluster (# 6). In this paper, Altenberg develops the concept of "evolvability" as a performance measure for genetic algorithms. In this context, evolvability is defined as "the ability of the genetic operator/representation scheme to produce offspring that are fitter than their parents." It is argued that this ability can evolve, since selection can act on the variational properties of programs, that is, how changes in the representation map to changes in behavior of the code. Altenberg suggests that this might be produced by the proliferation of blocks of code that have a higher chance of increasing fitness when added to programs.

Both Conrad ('90) and Altenberg ('94) contain several of the conceptual elements that spread in the development of the evolvability research front. However, none of them was able to introduce these conceptual elements in the community of evolutionary biology. Altenberg (personal communication) attributes the neglect of his work by biologists to a lack of matching of conceptual frameworks. Our cocitation network confirms this view, which also applies to Conrad ('90). In particular, although both papers are well connected to documents on evolutionary computation, they were not integrated into the theoretical framework of quantitative genetics.

Modularity. Following the papers on the definition of evolvability, we find a group of medium-cited books and classic papers on development and evolution that conform the intellectual base of Cluster # 2 (refs. 73, 110, 132). Most of them are cited in the theoretical context of the role of *developmental modularity* in evolution (refs. 9, 48, 82, 91, 95, 102, 134, 193). In the disciplinary context of developmental genetics, the modularity concept is applied both to genes and gene regulatory networks, and linked to the notion of cooption: modules, understood as sets of coregulated genes with specific functions, may be recycled in different contexts. Several documents hypothesize that "promoters may be more 'evolvable' than coding regions" (Wray et al., 2003), and this evolvability is partly explained by their modularity (Gerhart and Kirschner, '97; Wilkins, 2002). The most cited paper connecting modularity and evolvability is of von Dassow and Munro ('99). George von Dassow and Edwin Munro claim that evolvability is the central problem of evo-devo and argue that modularity and dissociability are the key architectural properties that make developmental systems evolvable. Finally, developmental plasticity also appears as a subtopic connected to modularity (refs. 22, 25, 156, 194).

The relationship between modularity and evolvability in the framework of pleiotropy, the phenomenon of a single gene affecting multiple traits, was established in W&A'96. The problem of the "cost of complexity" (ref. 184) was raised by Ronald Fisher in a landmark document in our network (ref. 3). Fisher argued that the increase in phenotypic complexity (i.e., an increase in the number of characters) entails a reduction in the rate of adaptation. W&A'96 suggested that this complexity constraint could be solved through the modularity of the GP map. If the GP map was divided into modules with more pleiotropic gene effects within than between modules, then each module would be able to evolve independently. Several documents of the evolvability network test the hypothesis that modular pleiotropy reduces the cost of complexity. Welch and Waxman (2003) conclude that although modularity does mitigate this cost, the increase in the number of characters still imposes a constraint on adaptation. Baatz and Wagner ('97) use a model to conclude that hidden pleiotropic effects, which cancel out across genes and therefore do not contribute to genetic correlation, nevertheless, lead to adaptive inertia.

The centrality of modularity confirms that, in the evo-devo literature, the main aspect of developmental systems that has been considered relevant to evolvability is their modularity (Hansen, 2016; Minelli, 2017). However, our results seem to contradict the extended view that evolvability is mainly an evo-devo research topic (Hendrikse et al., 2007; Minelli, 2017). Our cocitation network shows that the evo-devo approach was key in initiating and connecting the different research lines within the research front of evolvability, and retains an important role in the theoretical debates on the definition of evolvability. However, the age of the links connecting the nodes of Cluster # 2 (Fig. 2) and the average low number of cocitations (see Supplementary Table S1, rows in yellow) indicates that developmental biology does not play a main role in the evolvability research front, and that evo-devo has not such a major role in the most active areas of evolvability.

Probably the reason is that it was only focused on the developmental approach to evolvability and did not make any connection to other disciplinary approaches in evolutionary biology.

Complex Networks Approach: Cluster # 0

Established in 1998, Cluster # 0 represents an active research area, as indicated by the number of recently published papers (Supplementary Table S1, blue rows). With 174 members, it is the biggest but also the least homogeneous ($S = 0.58$) cluster of the evolvability network. This low conceptual homogeneity derives from the fact that the cluster contains different but linked research lines: one focused on Boolean networks, scale-free networks, and modularity, a group of documents on the relationship between innovation and robustness in gene networks (see also ref. 125), and a cluster of articles on innovation and robustness in RNA networks. Finally, connected to Cluster # 0, there is a group of documents dealing with the application of computer science tools such as genetic algorithms to the understanding of the evolution of biological networks (refs. 24, 33, 90, 145). Nonetheless, all these research lines share a common theoretical approach: the shift from a biology focused on assigning functions to individual molecules, to a biology addressed to understand the organizational principles of complex networks of molecular interactions. It is a highly interdisciplinary cluster, since it overlaps with most of the other clusters of the network.

Boolean Networks, Scale-Free Networks, and Modularity. The complex systems approach to evolvability goes back to Stuart Kauffman's work, which is highly represented in Cluster # 0. Kauffman was one of the first authors to define evolvability (the ability to "successively accumulate useful variations," p. 135), wondering about "the construction requirements" of a system that confer an ability to evolve, and whether selection can achieve such a system (Kauffman, '90). Kauffman ('90) contains many of the conceptual elements present in W&A'96 and K&G'98, such as the analogy between evolution and computation, and the identification of key properties of evolvable systems, including the constraints imposed by integration and the role of redundancy as a mechanism enabling gradual evolution. However, this paper has a very low number of citations in the network (4 c.) and Kauffman is not usually acknowledged as one of the founding authors of evolvability research. Nonetheless, Kauffman's work does show a lot of recognition in our network (refs. 6, 115, 140). Most of the documents citing Kauffman refer to his book *The Origins of order* (Kauffman, '93), a landmark document (40 c.) in our network (ref. 5). Similarly to K&G'98, Kauffman proposed that biological systems need to be stable but sensitive enough to perturbations to be able to evolve. According to Kauffman, biological systems might behave as Boolean networks "at the edge of chaos," a regime that permits both robustness and flexibility against perturbations.

The network approach to evolvability is mainly represented by a group of medium-low cited papers (6–11 c.) on the organizing principles that govern the evolution of complex networks (ref. 68), particularly of scale-free networks, that is networks composed of few highly connected and many less connected nodes (ref. 84). Most of them investigate the topological properties of scale-free networks such as metabolic networks (ref. 63), signaling pathways, and regulatory transcription networks. In particular, several documents explore the relationship between the scale-free topology of biological networks and their robustness (refs. 104, 152). Oikonomou and Cluzel (2006) show that scale-free networks evolve rapidly and continuously and are more robust to variations of their connectivity than homogeneous random networks.

Modularity emerges as an important subtopic in Cluster # 0 as well. Some papers explore the relationship between topological and functional modules in metabolic and gene transcription networks (refs. 79, 92, 101). Hartwell et al. ('99) argue that the survival of organisms implies that the critical parameters of functional modules are simultaneously robust and evolvable, insofar as they are insensitive to many environmental and genetic perturbations and sensitive to others. Barabási and Oltvai (2004) also mention the role of the evolvability of modules in the evolution of robustness, arguing that modules involved in key cellular functions might be less robust to uncommon errors. The largest group of documents on modularity and evolvability investigate, by means of computer simulations, the relationship between network modularity and environmental modularity (ref. 144). Most of them suggest that highly variable environments (Lipson et al., 2002) and particularly the modular structure of changing environments (Kashtan and Alon, 2005) lead to the evolution of modularity and that this modularity speeds up evolution (Kashtan et al., 2007). Gardner and Zuidema (2003) challenge Lipson and co-workers' model, arguing that modularity cannot confer enhanced evolvability.

Robustness and Innovation in Gene Networks. In this subcluster, gene networks are mostly analyzed as neutral networks, genotypes being equated to gene networks and phenotypes to gene expression profiles. In two highly cited papers, Ciliberti and co-workers explore the dynamics of the GP map in transcriptional regulatory networks. They show that different network topologies can have the same gene expression pattern, and that some of them are much more robust than others to mutations and gene expression noise. It is shown that genetic robustness can evolve through gradual and neutral evolution (Ciliberti et al., 2007b), and that this robustness is required for the emergence of innovations in gene expression patterns (Ciliberti et al., 2007a). Landry et al. (2007) investigate the genetic properties that influence the evolvability of gene expression, understood as the sensitivity of gene expression to mutations. Aldana and co-workers (2007) address the dilemma of the robustness and evolvability of gene regulatory networks and show the role of duplication in innovation. Gene duplication followed by genetic divergence is well represented in our network as an important mechanism of evolvability, insofar as it allows duplicated genes to evolve new functions (refs. 34, 119). The network also includes some

papers on genetic redundancy as a mechanism explaining genetic robustness (refs. 117, 119).

The main case study connecting robustness, modularity, and innovation in the evolvability network is the segment polarity network of insects analyzed by von Dassow et al. (2000). Although the authors do not explicitly refer to evolvability, the relationship between robustness and modularity explored in this paper is recurrently referred to as a mechanism of evolvability.

Molecular Evolution Approach: Clusters # 0 and # 4

The molecular evolution approach (see ref. 136) studies the evolvability of molecular structures, particularly of RNA secondary structures and protein structures (Supplementary Table S1, brown rows). Both the RNA folding map, understood as the relationship between sequences and secondary structures, and the sequence-protein structure map, offer a model of the GP map that permits understanding the *relationship between neutrality* (ref. 27), *robustness*, and *evolvability*. The molecular evolution approach is well represented in the evolvability network, including the set of most cited papers of the network. Cluster # 4, with 106 members, is a big and highly homogeneous cluster ($S = 0.7$). Situated at the top-left of the network (Fig. 3), it overlaps with the clusters on complex systems (# 0), cryptic genetic variation (# 3), and evo-devo (# 2). Cluster # 4 is highly connected to a group of documents of Cluster # 0 focused on innovation and robustness in RNA networks.

In the molecular evolution approach, the relationship between robustness and evolvability is mainly explained in the theoretical framework of "neutral networks." Neutral networks of RNA and protein molecules are sets of genotypes with the same phenotype/fitness that are interconnected by neutral mutations. The documents on neutral networks are mainly authored by a group of collaborating theoretical biologists related to the University of Vienna and the Santa Fe Institute. Several of these articles deal with the characterization of neutral networks (refs. 40, 43, 86, 165, 169), and most of them explore the role of neutrality (ref. 28, 164) on the evolution of robustness and adaptation (Huynen et al., '96; van Nimwegen et al., '99; van Nimwegen and Crutchfield, 2000; Stadler et al., 2001). In this view, genetic robustness is defined as the probability that a genotype remains on the neutral network after a mutation, whereas evolvability is conceived as "the ability of a population on one neutral network to discover another network of higher fitness" (Masel and Trotter, 2010). Burch and Chao (2000) examine the role of mutational neighborhood (i.e., the accessibility of advantageous genotypes within the mutational neighborhood) on evolvability. They show that neutral mutations cause populations to occupy an increasingly lager region of the genotypic space, thus increasing evolvability. In a highly cocited paper (36 c., see ref. 8), Ancel and Fontana (2000) explore the relationship between plasticity, robustness, modularity, and evolvability in RNA evolution. They conclude that genetic robustness evolves as a side effect of the evolution of environmental robustness, and that the evolution of genetic robustness leads to the evolution of modularity.

Andreas Wagner's papers are the most cited works using RNA secondary structure as a study system of the relation between robustness and evolvability. Wagner introduces two related conceptual distinctions that will be inherited by several research lines in the evolvability research front (Wagner, 2005a,b). First, instead of defining evolvability as the capacity of a biological system to produce heritable genetic variation, Wagner links evolvability with innovation. He defines evolvability as the ability of a biological system to "acquire novel functions through genetic change, functions that help the organism survive and reproduce" (p. 1772). Second, Wagner proposes two solutions to the seemingly paradoxical relationship between robustness and evolvability. Wagner (2005) argues that if neutrality is defined as restricted to one aspect of a system, change neutral with respect to one aspect of function could lead to innovation in other aspects. In another paper, he introduces the distinction between individual genotypic robustness and phenotypic robustness, defined as "the average genetic robustness of all genotypes encoding a phenotype" (Wagner, 2008). If evolvability is defined as the probability of finding novel functions in the immediate mutational neighborhood, genotypic robustness does hamper evolvability. In contrast, phenotypic robustness would promote evolvability because it is associated with a larger region of the genotypic space, therefore having access to a larger neighborhood with a single mutational step, thus increasing evolvability of a population.

The documents on protein evolvability deal with several aspects related to the evolvability of protein structures, such as the GP map (ref. 108), the stability or mutational robustness of protein structures (refs. 155, 168, 192), the relationship between neutrality and innovation, functional promiscuity (ref. 116), and mutation rates. Again, the two most cited documents deal with the relationship between robustness and evolvability in protein evolution. Bloom et al. (2006) show that evolvability is enhanced by mutational robustness. Aharoni et al. (2005) argue that evolvability depends on favoring robustness of protein native functions while promoting the plasticity of promiscuous functions.

Finally, Cluster # 4 also includes some documents on the relationship between robustness and evolvability in genotypes. Wilke and co-workers (2001) show in an experiment with digital organisms that selection favors genotypes with high mutation rates that occupy lower, but flatter (more robust) fitness peaks than those with a low mutation rate. Wilke (2001) shows that in populations in which mutations are either neutral or deleterious, adaptation takes place as neutral regions are discovered.

Population Genetic Approach: Cluster # 3

Cluster # 3 is a big cluster (125 members). It was formed in 1994, although most of the cocitation links were established in the early 2000s. Situated at the center of the network (Fig. 3), it is a

highly interdisciplinary cluster that overlaps with all the clusters of the network. Its Silouhette score is intermediate ($S = 0.62$), a value that might be attributed to the fact that most of the documents (Supplementary Table S1, pink rows) deal with the same topic (robustness), but from different theoretical approaches.

The link between *robustness and evolvability* is the main theme of Cluster # 3. Most of the documents of the cluster focus on genetic robustness, and in particular on mutational robustness, that is, the buffering of the phenotype against mutations. In population genetics, the concept of genetic robustness is referred to as *canalization* (refs. 31, 74, 78, 122, 135, 190). Canalization (and its relationship with evolvability) is generally related to the notion of hidden, unexpressed or cryptic genetic variation. Wild-type genotypes are considered to have evolved genetic robustness, and this robustness is believed to represent a potential for evolvability, since it can be broken and release phenotypic variance in populations in the face of a major mutation or stressful environments.

This approach to genetic robustness and its relationship to evolvability goes back to Schmalhausen's (ref. 188) and particularly to Waddington's views of canalization, two highly cited works in Cluster # 3 (refs. 15, 51, 124). Departing from Waddington's ideas, a lot of work has been devoted to solve the question of how genetic systems can accomplish the storing and release of variation. This work is represented in our network as a highly homogeneous subcluster that aggregates articles on *cryptic genetic variation and the molecular mechanisms which may regulate it*, particularly the heat-shock protein Hsp90 (Rutherford and Lindquist, '98; Rutherford, 2000; Queitsch et al., 2002), but also prions (Partridge and Barton, 2000; True and Lindquist, 2000; Masel and Bergman 2003) and chromatin-inheritance genes (Rutherford and Henikoff, 2003). In this research line, these molecular mechanisms are simultaneously seen as mechanisms of robustness and evolvability (Masel and Trotter, 2010). As robustness mechanisms, they provide buffering of the wild population against environmental stress. As evolvability mechanisms, they are "capacitors" of phenotypic variation, since the breakdown of these mechanisms (due to an environmental change or a major mutation) leads to a release of potentially adaptive variation. Masel (2005) studies the invasion dynamics of evolutionary capacitors.

In contrast, many papers of Cluster # 3 challenge the hypothesis of molecular mechanisms of evolvability. Wagner et al. ('99) discuss two questions raised by the hypothesis of HsP90 as a mechanism of evolvability. First, under what conditions can Hsp90 be an enhancer of evolvability if we consider the deleterious side effects of mutations? Second, which are the selective forces that originated the Hsp90 system? Several authors have challenged the very notion of buffering mechanisms or evolutionary capacitors. In this view, the accumulation and release of genetic variance after an environmental or genetic change is seen as a generic property of developmental systems. This approach is also well represented in our network (Siegal and Bergman, 2002; Bergman and Siegal, 2003). A group of highly cited papers interpret *robustness and evolvability as a consequence of epistatic effects*. Epistasis occurs when the effect of a gene depends on the genetic background, and can explain both canalization and the release of hidden variation. Canalization is interpreted in terms of evolution of reduced gene effects through epistatic interactions with an evolving genetic background (refs. 10, 47), whereas the release of hidden variation results from the evolutionary dynamics of epistatic interactions (Hermisson et al., 2003; Hermisson and Wagner, 2004). Pepper (2003) investigates the relationship between modularity and evolvability by exploring the influence of linkage patterns (i.e., the ordering of genes on chromosomes) on evolvability. The author claims that linkage patterns are subject to lineage-level selection for evolvability and discusses mechanisms that may enhance evolvability under epistatic clustering.

Cluster # 3 also includes various articles on canalization and the evolution of gene networks (refs. 107, 186). Finally, there is a group of documents on mutation rates and the evolutionary forces that shape them (refs. 96, 149, 163, 187). Earl and Deem (2004) argue that evolvability (equated to mutation rates) is a selectable property, particularly under varying environments.

Quantitative Genetics Approach: Clusters # 1 and # 5

The quantitative genetics approach to evolvability is represented by two clusters centered on heritability (# 5), the G-Matrix (# 1), and the relationship between modularity, pleiotropy, and evolvability (# 5) (Supplementary Table S1, green rows).

Cluster # 5: Heritability. With 41 members, Cluster # 5 is a small-medium size cluster (Table 1). It is the oldest cluster of the evolvability network. Formed in 1990, most connexions were established in the 1990s. Conceptually, Cluster # 5 is a highly homogeneous cluster ($S = 0.89$). Highly cited books and articles on population genetics, quantitative genetics, and biometry constitute the intellectual base of the cluster (refs. 12, 99, 112, 158), but the main topic is *heritability*. The cluster includes various papers on the heritability of morphological and life-history traits mainly published in the 1980s and early 1990s (refs. 42, 76, 94, 109, 151, 166, 180), as well as a group of documents from the 1990s on phenotypic plasticity and reaction norms in Drosophila (refs. 62, 99, 114, 130, 182).

The document that specifically relates heritability to evolvability is Houle ('92) (hereafter H'92), the main node of Cluster # 5 (ref. 4). In this classic paper, Houle argues that evolvability, defined as "the ability of a population to respond to natural or artificial selection" (p. 195), should be calculated on the basis of additive genetic coefficients of variation (i.e., the additive genetic variance relative to the mean), rather than of heritabilities (i.e., the proportion of the phenotypic variance accounted for by additive genetic effects).

All the reviews on evolvability identify H'92 as the founder article of one of the main concepts of evolvability. The number of citations and the topological features of this node confirm this view. H'92 is a landmark paper, being the third node in number of citations (59 c.) H'92 is also a pivot node, insofar as it plays a major integrative role within Cluster # 5. It is also a hub node, but it has less global connecting strength than W&A'96 and K&G'98. Our cocitation network shows that Houle's distinction between heritability and evolvability has been reasonably successful in quantitative genetics, as shown by the number of cited papers published after H'92, where heritabilities and evolvabilities (as defined by Houle) are compared (refs. 139, 170, 189), and different measures of evolvability are proposed (Hansen et al., 2003). Moreover, independently of the method developed to calculate evolvability, Houle's definition of evolvability as "the ability of populations to respond to natural selection" is the main reference to the concept of evolvability among those papers endorsing a population approach to evolvability. However, although it is the main connecting node of all the clusters of the quantitative genetics approach to evolvability, H'92 is loosely connected to the other clusters of the network. Therefore, it does not play a major integrative role within the evolvability research front. The reason might be the fact that it does not integrate any concept alien to the field of quantitative genetics, and in particular those concepts that have awoken more interest in the other approaches to evolvability, namely, robustness, neutrality, innovation, and modularity (see section Evolvability Concepts and Trading Zones).

Cluster # 1: G-Matrix. With 100 publications, Cluster # 1 is the second biggest cluster of the network (Table 1). From a dynamical viewpoint, it was formed in 1993, and, as reflected by the orange color of most of its cocitation links (Fig. 2), is an active research area. The conceptual homogeneity of Cluster # 1 is high ($S = 0.77$). It includes many classic papers and books on evolutionary biology (refs. 5, 3, 61, 67, 98) and quantitative genetics (refs. 6, 23, 72, 131, 141), but the main topic is the genetic variance–covariance matrix (G-matrix), the central concept used in quantitative genetics to explain the inheritance of multiple traits. The G-matrix "summarizes the additive genetic contribution to the variances and covariances (arising from pleiotropy and linkage disequilibrium) between phenotypic traits" (Steppan et al., 2002, p. 7). Since it quantifies the role of the genetic system in evolution, it is not surprising that the influence of the G-matrix on the evolvability of populations has become one of the main topics in the quantitative genetic approach to evolvability. Two of the most salient nodes in Cluster # 1 are Lande and Arnold's classic papers, where they set up the methods for predicting the response to selection as the product of an additive genetic variance matrix and a directional selection gradient (refs. 13, 20). The cluster includes earlier papers on covariances (ref. 185) and later papers on selection gradients (refs. 49, 89, 128, 150) and the G-matrix (refs. 113, 172). The more recent papers in quantitative genetics deal with the stability and evolution of the G-matrix (refs. 174, 175) and on the comparison of G-matrices (ref. 121).

A second research subline within Cluster # 1 includes papers on *evolvability and modularity*, mainly authored by Thomas Hansen. Challenging the thesis that modularity promotes evolvability, Hansen (2003) argues that genetic architectures with an intermediate level of integration among characters might be more evolvable. Hansen and co-workers propose to study the evolvability of characters, and define "conditional evolvability" as "the ability of a population to respond to directional selection in the presence of stabilizing selection on other trait combinations" (Hansen et al., 2003, p. 1201). Hansen and Houle (2008) develop measures of evolvability based on the G-matrix, and derive measures of character modularity and integration that can be used to interpret and compare G-matrices.

Hansen (2006) has argued that since evolvability is a disposition and is thus related to variability rather than variation, the measures of evolvability at the population level should be seen as a measure, rather than as a definition, of evolvability. Nonetheless, in quantitative genetics, the distinction between variation and variability has been related to the difference between the G-matrix and the mutational M-matrix. The M-matrix appears as the main emerging concept in the quantitative genetics approach to evolvability. Although the G-matrix "describes the standing additive genetic variances and covariances for a suite of traits," the M-matrix "describes the effects of new mutations on genetic variances and covariances" (Jones et al., 2007, p. 727). Thus, whereas the G-matrix governs a population's immediate response to selection, the M-matrix captures the ability of mutations to produce adaptive variants in the long term. Jones and collaborators (2007) use analytical theory and simulations to examine the evolution of mutational correlation and show that it evolves in response to selection.

Modularity, Pleiotropy, and Evolvability. Finally, Cluster # 1 includes a group of papers having the relationship between modularity, pleiotropy, and evolvability as the main research topic (Table 1). The intellectual base of this cluster roots to Everett C. Olson and Robert C. Miller pioneer work on morphological integration (ref. 58), where they pointed out how the patterns of correlations among phenotypic traits seem to relate to developmental and functional relationships. The main group of publications is formed by papers written in the 1980s and the mid-1990s by James M. Cheverud. Following Olson and Miller's approach, Cheverud explores the correspondence between morphological variation and morphological integration (refs. 37, 38, 103, 163), and between phenotypic and genetic correlations (ref. 53, 133). In particular, Cheverud investigates the relationship between morphological variation (ref. 160) and pleiotropy (ref. 39, 160, see also 191). It is shown that morphological modularity is

derived from modular pleiotropy, with pleiotropic effects often being restricted to subsets of functionally and developmentally related traits.

Macroevolution Approach: Cluster # 8

Cluster # 8 is a small (27 members), loosely connected, and highly homogeneous cluster (S = 0.92) mainly composed of lowly cited publications on levels of organization and major transitions in evolution (Table 1, Supplementary Table S1, gray rows). From a dynamical perspective, Cluster # 8 was formed in 1998, and most of the connections among the documents were formed in the early 2000s.

In this view, evolvability is related to major innovations at a macroevolutionary scale, and changes in evolvability are seen as the result of major changes in the development or structure of the organism. The only document of the cluster with more than five citations in the cocitation network is Maynard Smith and Szathmáry ('97) (hereafter M&S'97, ref. 66). In their classic book, John Maynard Smith and Eörs Szathmáry interpreted the major transitions in evolution as major changes in how the organism transmits genetic information. In this context, evolvability is connected to innovation: some evolutionary events such as the evolution of multicellularity or sex and recombination are seen as key innovations insofar as they change what is possible to evolve. Nonetheless, M&S'97 is not highly cocited and is not referenced as a definition of evolvability by other documents of the network (see Supplementary Table S1, fourth column).

EVOLVABILITY CONCEPTS AND TRADING ZONES

In a highly cited review, Pigliucci (2008) has distinguished three concepts of evolvability on the basis of the biological entities and the corresponding time scales they apply to. Evolvability sensu Houle depends on the standing pool of genetic variation and covariation and determines the short-term response of populations to natural selection. Evolvability sensu Wagner and Altenberg depends on the genetic architecture of species and affects mid-term adaptation. Finally, evolvability sensu Maynard Smith and Szathmáry consists of breaking the developmental constraints that restrict clade variation, opening new areas of phenotypic space (novelties) for further evolution. In this view, evolvability refers to different phenomena and hence these three definitions are seen as irreducible. The three conceptual approaches to evolvability distinguished by Pigliucci are well captured by some of the approaches to evolvability identified in our cocitation network, namely the quantitative genetics, the evo-devo, and the macroevolutionary approaches. However, the theoretical contexts delimited by our clusters show important differences with regard to Pigliucci's classification[5]. First, I have identified more approaches to evolvability than those distinguished by Pigliucci. The complex network, the molecular evolution, and the population genetics approach are important research lines in our network that are not captured by Pigliucci's classification. Second, in our network, the definitions of evolvability used in each research line (see Supplementary Table S1, column 5) are not so much related to the biological entities that exhibit evolvability, and therefore are not only dependent on the irreducible epistemological goals of different biological disciplines. Rather, the definitions of evolvability handled in the documents of the evolvability network contain four main conceptual tensions that transcend disciplinary boundaries.

One of these conceptual tensions has to do with the relationship between the capacity to generate heritable variation and the capacity to generate *adaptive* heritable variation. Many of the documents of the molecular evolution approach, those within the population genetics approach which equate evolvability to mutation rates, as well as those exploring the topological properties of complex networks, define evolvability as the capacity of biological systems to vary. However, most of the documents of the evolvability network define evolvability as the capacity to vary in an adaptive way, excluding the capacity of a system for producing deleterious mutations as a part of the ability to evolve.

Another controversial issue in the definition of evolvability concerns the relationship between evolvability and innovation. Although some authors equate evolvability with the capacity to vary, other authors identify evolvability with the ability to innovate[6]. According to Pigliucci (2008), the notion of evolvability as innovation applies to clades and affects long-term evolutionary processes. However, in the evolvability research front, the link between evolvability and novelty is a main concern in other disciplinary contexts than macroevolution. In particular, many documents in the complex networks approach refer to Andreas Wagner's definition of evolvability (and not to M&S'97) as the ability to produce evolutionary innovations (Supplementary Table S1, blue rows, fourth column).

A third conceptual tension among the existing definitions of evolvability is related to the difference between variation and variability. Although the quantitative genetics approach relates evolvability to differences in variation, in the remaining

[5] The discordances between my results and other existing classifications of the evolvability concepts partly derive from the fact that my approach and the conceptual analysis of the formal definitions of evolvability pursue different epistemic goals. The conceptual landscape revealed by co-citation patterns in evolvability research does not necessarily reflect the existing meanings of evolvability, but rather the shared meanings that define the different research lines in the evolvability research front. However, individual reviews of research topics are often biased by the disciplinary trajectories of the authors of those reviews. Computational analysis of research agendas are free of such constraints and can identify some research areas and definitional debates that are often neglected in classical reviews or philosophical analysis of scientific research.

[6] A few authors (e.g., Hansen, 2006) also include in the definition of evolvability the ability of genetic systems to maintain potentially adaptive variation.

clusters evolvability is defined as the ability of biological systems to vary. It might be argued that since variability depends on the GP map and is conceptually independent of population parameters such as allele frequencies or variances (Hansen, 2006), the difference between variation and variability captures an essential tension between the irreducible research goals of population biology and more systemic approaches to evolution. Nonetheless, this basic conceptual tension cannot be strictly related to disciplinary demarcations either. Population biology does not seem to be doomed to ignore dispositions, since, as we saw in section Quantitative Genetics Approach: Clusters # 1 and # 5, the problem of variability has been incorporated into quantitative genetics through the concept of the M-matrix.

Finally, one the most striking differences among the existing definitions of evolvability concerns the very subject of evolvability. This seems to be the main criteria chosen by Pigliucci to distinguish his three meanings of evolvability. In his view, evolvability sensu Houle applies to populations, evolvability sensu W&A to species, and evolvability sensu M&S to clades. Reading of the main documents of the evolvability research front shows that the entities evolvability applies to are, in fact, much more diverse. Some works study the structural attributes of GP maps (e.g., modularity, robustness) that are suggested to enhance evolvability *of populations*. Other works investigate how these properties arise in evolution, focusing on the evolvability of the structure *of the GP map*. In this sense, evolvability does not only apply to different taxonomical levels, but also to different levels of organization, such as macromolecules, gene networks, metabolic networks, and whole organisms. Evolvability is seen as a property of the GP map, whose meaning depends on the level of organization one focuses on. Genotypes may correspond to amino acid sequences, gene regulatory circuits, or metabolic networks, whereas phenotypes may refer to the spatial conformation of macromolecules or gene expression patterns.

These four conceptual tensions show that, although we can distinguish a plurality of well-defined disciplinary approaches to evolvability, the existing definitions of evolvability are not fully reducible to disciplinary demarcations. In any case, this plurality of approaches to evolvability in biological practice does confirm the view that the existing notions of evolvability are multiple and seem to be irreducible to a single general definition. Some authors have claimed that we should stop using the same word with such different meanings if we want to make any progress in the debates on evolvability (Brookfield, 2009). The different notions of evolvability should be conserved, but they should do so "under different, or differently qualified names" (Minelli, 2017; see also Pigliucci, 2008). However, the dynamical and structural properties of the evolvability research front show that rather than being an obstacle, the vagueness of evolvability (and related concepts) has played a key role in the origination and development of evolvability research. Although the evolvability research front is reasonably structured in coherent research lines in which evolvability is specifically defined, an "inconsistent" notion of evolvability plays a unifying role in communicating different approaches to evolvability.

The notion of evolvability can be seen as a "nomadic concept," which, as many other biological concepts (Surman et al., 2014), has travelled from one discipline to the other, including evolutionary computation, molecular evolution, evo-devo, systems biology, population and quantitative genetics, and software design. I argue that, in this conceptual trip, evolvability, generally defined, has set up "trading zones" (Galison, '99) in evolutionary biology that make possible interdisciplinary exchanges.

The science historian Peter Galison ('99) has argued that scientific disciplines are neither unified nor fragmented into isolated subcultures separated by microrevolutions. Taking physics as a case study, he claims that the history of physics is rather intercalated, because the different traditions of instrumentation, experiment, and theory coordinate with one another without losing their separate identities. Galison uses the anthropological metaphor of unlike cultures that interact by trade to illustrate this view. Despite vast global differences, two groups coming from different cultures can collaborate in the local context of the "trading zone," agreeing on rules of exchange even if they ascribe a different meaning to the objects being exchanged. Cultures in interaction even establish contact languages such as pidgins or creoles to support the activities they are involved in. In the same way, experimentalists, theorists, and instrumentalists develop hybrid languages and simplify their practices for presentation to the other subcultures.

The notion of trading zone has awoken a recent interest among both biologists and philosophers of biology working on evolvability and evo-devo. In his lab Website, the theoretical biologist Walter Fontana (http://fontana.med.harvard.edu) uses the notion of trading zone to define their research. The philosopher of science Rasmus G. Winther has recently argued that evo-devo can be understood as a trading zone (Winther, 2015; see also Winther, 2012). Winther elaborates on Galison's concept, and describes a trading zone as "a richly overlapping domain" in which scientific cultures (disciplines, styles, and paradigms) interact at distinct levels of abstraction. Evo-devo is defined as a trading zone, in which these various cultures interact and negotiate theories, instruments, and concepts.

The computational approach to research agendas as cocitation networks makes possible to quantify the notion of trading zone. The study of research questions associated with different disciplines is useful for illuminating interdisciplinary interactions (Love, 2010), and the application of bibliometric analysis to the understanding of research networks is a powerful tool to identify in a quantitative way the overlapping areas where scientific trading of concepts and methodologies takes place. In cocitation networks, trading zones are captured by those areas where clusters overlap and authors coming from different disciplines collaborate (Fig. 3). Pivot nodes, through which documents belonging

to different clusters are linked, permit an identification of the main works that are perceived by different disciplinary communities as setting a common ground for evolvability research. As we have seen in section Research lines in the Evolvability Research Front, some research lines such as the macroevolution approach have remained relatively disconnected from other studies in evolvability and have failed to establish strong disciplinary collaborations, whereas other approaches (e.g., Clusters # 0 and # 3) strongly overlap with most of the research lines in the evolvability research front. Clusters on quantitative genetics (# 1 and # 5) are largely independent, but some authors such as Thomas Hansen, James Cheverud, and Günter Wagner have played a major role in connecting the population and quantitative genetic approaches to other approaches (molecular, evo-devo, complex networks) to evolvability.

The clustering of the evolvability research front in different research lines seems to depend on a mixture of factors, including methodologies, disciplinary demarcations, and conceptual relationships. Our clustered cocitation network shows that disciplinary demarcations have been the main factors in the generation of research lines within evolvability research. I have identified six major disciplinary approaches interacting in evolvability research, namely evo-devo, complex networks, molecular evolution, population genetics, quantitative genetics, and macroevolution. However, these relatively separate disciplinary approaches to evolvability have methodological and conceptual relationships that blur disciplinary boundaries.

First, evolvability research has adopted a variety of methodological styles, including conceptual analysis, mathematical modeling, computer simulations, mechanistic explanations, and historical studies of phylogenetic patterns[7]. Alan Love has identified three compatible but distinct approaches (computational, theoretical, and empirical) to evolvability (Love, 2003). These three investigative approaches are combined in all clusters of our cocitation network, although in an unequal manner. The mathematical modeling approach to evolvability is predominant in computational science and systems biology, whereas the mechanistic and the mathematical modeling style are combined in evo-devo, molecular evolution, and population genetics approaches to evolvability. In general, evolvability research is mostly based on computational and theoretical studies rather than on empirical analysis of data.

Second, evolvability research has contributed to establish interdisciplinary zones of collaboration by developing hybrid languages spoken by members of different disciplinary communities. Despite having a radically different significance for the different disciplines working on it, by means of simplification, evolvability and related concepts acquire a decontextualized meaning in these trading zones. In fact, the majority of the most successful documents in the evolvability network are precisely those that lack technical content and are addressed to a broad audience. The analysis of our clustered cocitation network allows to identify the main conceptual items exchanged in the trading zones of the evolvability research front. "Robustness," "modularity," and "innovation" appear as the main simplified concepts that allow authors coming from different scientific cultures to collaborate in evolvability research. As we have seen, all these concepts have very specific meanings when defined in different theoretical contexts. Thus, despite the notions of robustness and evolvability are differently defined by developmental, molecular, population, and systems biologists, the conflict between robustness and evolvability, broadly defined as the need of biological systems to resist and allow change, serves as a conceptual bridge connecting distinct disciplinary approaches. Similarly, modularity is differently defined in terms of topological connections (complex networks approach), developmental interactions (evo-devo approach), and constrained pleiotropic effects (quantitative genetics). However, the influence of modularity (broadly defined) in the ability of biological systems to evolve is a common theoretical assumption in all approaches to evolvability.

Evolvability research shows that the revolution undergone by evolutionary biology along the last three decades is not characterized by a replacement of paradigms consisting of a progressive subordination of different disciplines to a unique theoretical framework, but by a multiplication of interacting cultures on new research topics. Therefore, my results seem to confirm the pluralistic interpretations of the changes undergone by evolutionary biology in the past decades. As argued by Müller and Pigliucci (2010), the new theoretical framework that is being built in evolutionary biology is best characterized as an expansion of the MS rather than as a paradigm shift. However, the notion of trading zone complicates the picture of evolutionary biology as a continuously expanding conceptual tree (Gould, 2002; Pigliucci, 2008), being the growth of new branches of biological research permeated by methodological transfers and conceptual hybridization.

CONCLUSIONS AND FUTURE DIRECTIONS

A computational approach to problem agendas is a powerful tool for identifying research lines and interdisciplinary collaborations, and characterizing the historical development of research fronts. On the one hand, the application of bibliometric analysis to research fronts reveals conceptual and dynamical patterns of scientific research that traditional historical and philosophical approaches to scientific theories are unable to tackle. In turn, the analysis of the results of computational analysis under the light of new concepts in the history and philosophy of science, such as research agendas, nomadic concepts, and trading zones, provides theoretical insights into the conceptual structure and

[7] Winther talks of scientific styles, a broader notion than methods. Styles "provide overarching theoretical and experimental ways of doing science, and of viewing objects and processes in nature" (2005, p. 492).

dynamics of scientific research that are usually absent in the descriptive accounts common in bibliometrics.

This first exploration of the evolvability research front sets us in a good position to address further questions. First, our identification of the trading zones of the evolvability research front would require a detailed analysis of how concepts are exchanged among the different disciplinary approaches working on evolvability. Moreover, it would be necessary to explore the relation between the spread of theoretical knowledge and methodological advancements, such as the introduction of molecular techniques to track and manipulate genotypes in the early 1990s, the development of computational modeling of genetic regulatory networks and macromolecules, and the introduction of novel mathematical approaches in population genetics since the mid-1990s (de Visser et al., 2003)[8]. Second, this evolvability cocitation network may be compared with other networks mapping different aspects of the evolvability research front, such as the social structure (coauthorship networks), interdisciplinarity (journal co-citation networks), or the conceptual structure (co-word analysis) of the evolvability research front.

ACKNOWLEDGMENTS

This work was funded by the KLI Institute under a postdoctoral grant (2013-2014) and a Juan de la Cierva fellowship (FJCI-2014-22685) from the Spanish Ministry of Economy, Industry and Competitiveness, at the University of the Basque Country. Research toward this paper was conducted within the framework of two projects funded by the Spanish Government (numbers FFI2013-47849-P and FFI2014-57064-P). I thank the participants at the seminar given at Science Studies Colloquium Series, at the University of Oslo, for their comments, as well as the audiences at the 2014 Euro Evo Devo conference and the 5th SESBE Meeting for reactions to related material. The author also acknowledges the help received from the 1st Writing Week for Women Researchers, an event organized by the University of the Basque Country, in July 2015, at San Sebastian. I thank Erick Peirson for introducing me to some of the new techniques applied in the field of computational history of science. I am deeply thankful to Gunter Wagner and Lee Altenberg who encouraged me to write this paper. Together with Thomas Hansen, Mihaela Pavlicev, Ingo Brigandt, and an anonymous reviewer, they also made many insightful comments on early drafts of this manuscript that have greatly contributed to its improvement.

LITERATURE CITED

Aharoni A, Gaidukov L, Khersonsky O, et al. 2005. The "evolvability" of promiscuous protein functions. Nat Genet 37:73–76.

Alberch P. 1991. From genes to phenotype: dynamical systems and evolvability. Genetica 84:5–11.

Aldana M, Balleza E, Kauffman S, Resendiz O. 2007. Robustness and evolvability in genetic regulatory networks. J Theor Biol 245:433–448.

Altenberg L. 1994. The evolution of evolvability in genetic programming. AIGP 3:47–74.

Ancel LW, Fontana W. 2000. Plasticity, evolvability, and modularity in RNA. J Exp Zool 288:242–283.

Baatz M, Wagner G. 1997. Adaptive inertia caused by hidden pleiotropic effects. Theor Popul Biol 51:49–66.

Barabási AL, Oltvai ZN. 2004. Network biology: understanding the cell's functional organization. Nat Rev Genet 5:101–113.

Bergman A, Siegal ML. 2003. Evolutionary capacitance as a general feature of complex gene networks. Nature 424:549–552.

Bloom JD, Labthavikul ST, Otey C, Arnold F. 2006. Protein stability promotes evolvability. Proc Natl Acad Sci USA 103:5869–5874.

Boyack KW, Klavans R, Börner K. 2005. Mapping the backbone of science. Scientometrics 64:351–374.

Brigandt I. 2010. Beyond reduction and pluralism: toward an epistemology of explanatory integration in biology. Erkenntnis 73:295–311.

Brigandt I. 2015. From developmental constraint to evolvability: how concepts figure in explanation and disciplinary identity. In: Love AC, editor. Conceptual change in biology: scientific and philosophical perspectives on evolution and development. Dordrecht: Springer. p 305–325.

Brookfield J. 2009. Evolution and evolvability: celebrating Darwin 200. Biol Lett 5:44–46.

Brown RL 2014. What evolvability really is. Br J Philos Sci 65:549–572.

Burch CL, Chao L. 2000. Evolvability of an RNA virus is determined by its mutational neighbourhood. Nature 406:625–628.

Case JF, Stiers VE. 1971. Biology, observation and concept. New York: Macmillan Co.

Chen C. 2004. Searching for intellectual turning points: progressive knowledge domain visualization. Proc Natl Acad Sci USA 101:5303–5310.

Chen C. 2006. CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. J Am Soc Inf Sci Technol 57:359–377.

Ciliberti S, Martin OC, Wagner A. 2007a. Innovation and robustness in complex regulatory gene networks. Proc Natl Acad Sci USA 104: 13591–13596.

Ciliberti S, Martin OC, Wagner A. 2007b. Robustness can evolve gradually in complex regulatory gene networks with varying topology. PLoS Comput Biol 3:e15.

Conrad M. 1985. The mutation buffering concept of biomolecular structure. Proc Int Symp Biomol Struct Interactions Suppl J Biosci 8:669–679.

[8] Since the main topic connecting the population and the systemic approaches to evolvability is the relationship between robustness and evolvability, the reasons for the current interest in evolvability should be related to those explaining the increasing interest that research on robustness has experienced since the 1990s (de Visser et al., 2003).

Conrad M. 1990. The geometry of evolution. Biosystems 24:61–81.
Dawkins R. 1989. The evolution of evolvability. In: Langton C, editor. Artificial life 6, SFI studies in the sciences of complexity. Redwood City, California. Addison-Wesley Publishing Company. p 201–220.
De Visser, JAGM, Hermisson J, Wagner GP, et al. 2003. Perspective: evolution and detection of genetic robustness. Evolution 57:1959–1972.
Earl DJ, Deem M. 2004. Evolvability is a selectable trait. Proc Natl Acad Sci USA 101:11531–11536.
Galison P. 1999. Trading zone: coordinating action and belief. In: Biagoli M, editor. The science studies reader. New York and London: Routledge. p 137–160.
Gardner A, Zuidema W. 2003. Is evolvability involved in the origin of modular variation? Evolution 57:1448–1450.
Gerhart J, Kirschner M. 1997. Cells, embryos, and evolution: toward a cellular and developmental understanding of phenotypic variation and evolutionary adaptability. Malden: Blackwell Science.
Gould SJ. 2002. The structure of evolutionary theory. Cambridge, MA, and London: Harvard University Press.
Hansen TF, Houle D. 2008. Measuring and comparing evolvability and constraint in multivariate characters. J Evol Biol 21:1201–1219.
Hansen TF, Carlson ML, Armbruster WS, Pélabon C. 2003. Evolvability and genetic constraint in Dalechampia blossoms: genetic correlations and conditional evolvability. J Exp Zool B Mol Dev Evol 296:23–39.
Hansen TF. 2003. Is modularity necessary for evolvability? Remarks on the relationship between pleiotropy and evolvability. Biosystems 69:83–94.
Hansen TF. 2006. The evolution of genetic architecture. Annu Rev Ecol Evol Syst 37:123–157.
Hansen TF. 2016. Evolvability, Quantitative Genetics. In: Kliman RM, editor. Encyclopedia of evolutionary biology. Oxford: Academic Press. p 83–89
Hartwell LH, Hopfield JJ, Leibler S, Murray AW. 1999. From molecular to modular cell biology. Nature 402:C47–C52.
Hendrikse JL, Parsons TE, Hallgrímsson B. 2007. Evolvability as the proper focus of evolutionary developmental biology. Evol Dev 9:393–401.
Hermisson J, Wagner GP. 2004. The population genetic theory of hidden variation and genetic robustness. Genetics 168: 2271–2284.
Hermisson J, Hansen TF, Wagner GP. 2003. Epistasis in polygenic traits and the evolution of genetic architecture under stabilizing selection. Amer Nat 161:708–734.
Houle D. 1992. Comparing evolvability and variability of quantitative traits. Genetics 130:195–204.
Huynen MA, Stadler PF, Fontana W. 1996. Smoothness within ruggedness: the role of neutrality in adaptation. Proc Natl Acad Sci USA 93:397–401.
Jones AG, Arnold SJ, Bürger R. 2007. The mutation matrix and the evolution of evolvability. Evolution 61:727–745.
Kashtan N, Alon U. 2005. Spontaneous evolution of modularity and network motifs. Proc Natl Acad Sci USA 102:13773–13778.
Kashtan N, Noor E, Alon U. 2007. Varying environments can speed up evolution. Proc Natl Acad Sci USA 104:13711–13716.
Kauffman SA. 1990. Requirements for evolvability in complex systems: orderly dynamics and frozen components. Physica D 42:135–152.
Kauffman SA. 1993. The origins of order: self organization and selection in evolution. New York: OUP.
Kirschner M, Gerhart J. 1998. Evolvability. Proc Natl Acad Sci USA 95:8420–8427.
Kitano H. 2004. Biological robustness. Nat Rev Genet 5:826–837.
Landry CR, Lemos B, Rifkin SA, Dickinson WJ, Hartl DL. 2007. Genetic properties influencing the evolvability of gene expression. Science 317:118–121.
Laubichler MD, Maienschein J, Renn J. 2013. Computational perspectives in the history of science: to the memory of Peter Damerow. Isis 104:119–130.
Lenski RE, Barrick JE, Ofria C. 2006. Balancing robustness and evolvability. PLoS Bio 4:2190–2192.
Lipson H, Pollack JB, Suh NP. 2002. On the origin of modular variation. Evolution 56:1549–1556.
Love AC. 2003. Evolvability, dispositions, and intrinsicality. Philos Sci 70:1015–1027.
Love AC. 2010. Idealization in evolutionary developmental investigation: a tension between phenotypic plasticity and normal stages. Philos Trans R Soc Lond B Biol Sci 365:679–690.
Masel J. 2005. Evolutionary capacitance may be favored by natural selection. Genetics 170:1359–1371.
Masel J, Bergman A. 2003. The evolution of the evolvability properties of the yeast prion [PSI+]. Evolution 57:1498–1512.
Masel J, Trotter MV. 2010. Robustness and Evolvability. TIG 26:406–414.
Maynard Smith J, Szathmary E. 1997. The major transitions in evolution. Oxford: OUP.
Minelli A. 2017. Evolvability and its evolvability. In: Huneman P, Walsh D, editors. Challenging the modern synthesis. New-York: OUP. p. 231–260.
Müller GB, Pigliucci M. 2010. Extended synthesis: theory expansion or alternative. Biol Theor 5:117–123.
Oikonomou P, Cluzel P. 2006. Effects of topology on network evolution. Nat Phys 2:532–536.
Partridge L, Barton NH. 2000. Natural selection: evolving evolvability. Nature 407:457–458.
Pepper JWJ. 2003. The evolution of evolvability in genetic linkage patterns. BioSystems 69:115–126.
Pi Suñer A. 1995. Classics of biology. New York: Philosophical Library.
Pigliucci M. 2008. Is evolvability evolvable? Nat Rev Genet 9:75–82.
Pigliucci, M. 2009. An extended synthesis for evolutionary biology. Ann N Y Acad Sci 1168:218–228.
Pigliucci M, Müller GB, editors. 2010. Evolution—the extended synthesis. Cambridge, MA: MIT Press.
Price D. 1965. Networks of scientific papers. Science 149:510–515.

Queitsch C, Sangster TA, Lindquist S. 2002. Hsp90 as a capacitor of phenotypic variation. Nature 417:618–624.

Rutherford SL. 2000. From genotype to phenotype: buffering mechanisms and the storage of genetic information. BioEssays 22:1095–1105.

Rutherford SL, Henikoff S. 2003. Quantitative epigenetics. Nat Genet 33:6–8.

Rutherford SL, Lindquist S. 1998. Hsp90 as a capacitor for morphological evolution. Nature 396:336–342.

Siegal ML, Bergman A. 2002. Waddington's canalization revisited: developmental stability and evolution. Proc Natl Acad Sci USA 99:10528–10532.

Small H. 1999. Visualizing science by citation mapping. J Assoc Inf Sci 50:799–813.

Small H, Griffith BC. 1974. The structure of scientific literatures I: identifying and graphing specialties. Sci Stud 4:17–40.

Stadler BM, Stadler PF, Wagner GP, Fontana W. 2001. The topology of the possible: formal spaces underlying patterns of evolutionary change. J Theor Biol 213:241–274.

Steppan SJ, Phillips PC, Houle D. 2002. Comparative quantitative genetics: evolution of the G matrix. Trends Ecol Evol 17: 320–327.

Surman J, Stráner K, Haslinger P. 2014. Nomadic concepts in the history of biology. Stud Hist Philos Biol Biomed Sci 48:127–129.

Thomson, JA. 1932. Scientific riddles. London: Williams & Norgate Ldt.

True HL, Lindquist SL. 2000. A yeast prion provides a mechanism for genetic variation and phenotypic diversity. Nature 407: 477–483.

van Nimwegen E, Crutchfield JP. 2000. Metastable evolutionary dynamics: crossing fitness barriers or escaping via neutral paths? Bull Math Biol 62:799–848.

van Nimwegen E, Crutchfield JP, Huynen M. 1999. Neutral evolution of mutational robustness. Proc Natl Acad Sci USA 96:9716–9720.

von Dassow G, Munro E. 1999. Modularity in animal development and evolution: elements of a conceptual framework for EvoDevo. J Exp Zool 285:307–325.

von Dassow G, Meir E, Munro EM, Odell GM. 2000. The segment polarity network is a robust developmental module. Nature 406:188–192.

Wagner A. 2005a. Robustness and evolvability in living systems. Princeton and Oxford: PUP.

Wagner A. 2005b. Robustness, evolvability, and neutrality. FEBS Lett 579:1772–1778.

Wagner A. 2008. Robustness and evolvability: a paradox resolved. Proc R Soc Lond B Biol Sci 275:91–100.

Wagner GP, Altenberg L. 1996. Perspective: complex adaptations and the evolution of evolvability. Evolution 50:967–976.

Wagner GP, Laubichler MD. 2004. Rupert Riedl and the re-synthesis of evolutionary and developmental biology: body plans and evolvability. J Exp Zool (Mol Dev Evol) 302:92–102.

Wagner GP, Chiu CH, Hansen T F. 1999. Is Hsp90 a regulator of evolvability? J Exp Zool 285:116–118.

Welch JJ, Waxman D. 2003. Modularity and the cost of complexity. Evolution 57:1723–1734.

Wilke CO. 2001. Adaptive evolution on neutral networks. Bull Math Biol 63:715–730.

Wilke CO, Wang JL, Ofria C, Lenski RE, Adami C. 2001. Evolution of digital organisms at high mutation rates leads to survival of the flattest. Nature 412:331–333.

Wilkins AS. 2002. The evolution of developmental pathways. Sunderland, Massachusetts: Sinauer Associates.

Winther RG. 2012. Interweaving categories: styles, paradigms, and models. Stud Hist Philos Sci Part A 43:628–639.

Winther RG. 2015. Evo-devo as a trading zone. In: Love A, editor. Conceptual change in biology. Boston studies in the philosophy and history of science, vol. 307. Netherlands: Springer. p 459–482.

Wray GA, Hahn MW, Abouheif E, et al. 2003. The evolution of transcriptional regulation in eukaryotes. Mol Biol Evol 20:1377–1419.