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ALESSANDRA CAPUTO[1], DOMENICO SCALERA[2], EMANUELA SIRTORI[3]

[1] *Centre for Industrial Studies, Italy. caputo@csilmilano.com*
[2] *Corresponding author. Department of Law and Economics. University of Sannio, Italy. scalera@unisannio.it*
[3] *Centre for Industrial Studies, Italy. sirtori@csilmilano.com*

Patterns of development in the European biopharmaceutical industry. A network analysis of cross-sectoral linkages (2000-2016).

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Comments are welcome: caputo@csilmilano.com

PATTERNS OF DEVELOPMENT IN THE EUROPEAN BIOPHARMACEUTICAL INDUSTRY. A NETWORK ANALYSIS OF CROSS-SECTORAL LINKAGES (2000-2016).

Alessandra Caputo, Domenico Scalera, Emanuela Sirtori

Abstract

This paper aims at identifying geographical patterns of Biopharma transformation trends in the EU over the period 2000-2016 through an analysis of cross-regional and cross-sectoral linkages. To this purpose, information on co-patenting, mergers and acquisitions, and joint ventures and alliances is used to carry out a network analysis at region level. Results show an increasing involvement of European regions in cross-sectoral Biopharma operations. However, while the network displays a tendency to enlarge toward the East (Poland) and West (Spain), a significant reduction in the activity of peripheral nodes in the Southern and Northern borders of the network is observed. More recently, the overall interconnectedness of the network slightly decreases; the network becomes sparser, showing a propensity toward regionalisation of cross-sectoral linkages. Finally, by exploiting information on the location of companies and inventors involved in cross-sectoral operations, the investigation allows pinpointing regional communities and their evolution throughout the years.

Keywords: Biopharmaceutical industry, Cross-sectoral linkages, Emerging Industries, Network analysis

JEL Classification: R11, R12, L14, L65

1. Introduction

Cross-sectoral linkages (CSLs) can be defined as inter-firm relationships (e.g., alliances and collaborations, R&D joint activities, open innovation networks, supplier-client relationships) between two interacting companies belonging to different industrial and/or service sectors, typically as defined by an industry code (e.g. NACE, NAICS, SIC industry nomenclature). Taking place between firms operating in different industries, inter-sectoral ties are deemed to be crucial in economic development and industrial transformation even more than other forms of connectivity and networking thanks to the knowledge spillovers, innovation transfers, skill relocation, reconfiguration in industrial leadership patterns that they trigger.

The literature has widely recognised this role. In his path-breaking work, Hirschman (1958) was the first to acknowledge that the evolution of competitive industries typically takes place through linkages with other existing economic activities. Later on, the literature on multi-industry clusters (Henderson et al., 1995) recognised to the spillovers engendered by CSLs particular importance in favouring high-tech sectors, for which the pace of technological change is faster, and cross-fertilisation is crucial for breakthroughs in product and process innovations. In a similar vein, the economic geography literature developed the concept of “related variety” (Frenken et al., 2007 Hidalgo et al., 2018) as a key driver of economic growth by emphasising the beneficial effects of the interaction between firms operating in different industries, which offers valuable opportunities to interact, copy, modify and recombine ideas, practices and technologies across industries. In the same vein, CSLs have been recently identified by the European Cluster Observatory (2015) as a key feature of the so-called “emerging industries”, defined as high-growth and high-market-potential sectors that transform, evolve or merge to respond to new impulses by market demand. The presence of CSLs strongly characterises emerging industries (Monfardini et al., 2012) and is more generally associated with industrial environments with prominent technological levels, increasing productivity, and strong economic growth. Consequently, in terms of regional development, high numbers and large growth rates in CSLs are rightfully associated with the most dynamic and fast-growing territories (Balland and Boschma, 2019).

Many authors document how, in the last couple of decades, CSLs have remarkably increased, both domestically and at the international level (Criscuolo and Timmis, 2018). Others argue that CSLs matter in export take-offs and acceleration (Bahar et al., 2019); are crucial for successful innovation in the modern knowledge-based economy (Barber and Scherngell, 2011); heavily affect the international transmission of demand shocks through global value chains (Frohm and Gunnella, 2017). Concerning the relationship between the occurrence of CSLs and the degree of regional development, Mahnken and Moehrle (2018) maintain that cross-industry innovation primarily takes place in highly developed markets, where the saturation level of traditional products is high, and companies aim to differentiate their products employing additional functions. In particular, they analyse co-patenting in several industries (semiconductor devices, electric digital processing, chemicals, materials, medicine, and mobility technologies) to show that CSLs are a broad phenomenon strictly related to industry innovation and regional development.

This paper aims at investigating recent technological and industrial transformations in the biopharmaceutical industry (henceforth, Biopharma) at the scale of EU regions, over the period from 2000 to 2016, through an analysis of cross-sectoral linkages. The main reason for focusing on Biopharma is that it is one of the most important emerging industries in Europe.[1] Our analysis refers to a time span before the outburst of the Coronavirus pandemic, an event that probably will spur further important developments in this industry (Ayati et al., 2020; Deloitte, 2020). According to European Cluster Observatory (2015), Biopharma is massively involved in CSLs, with a number of other traditional and emerging industries. In particular, by using tools of the network analysis, we consider the European regional network where Biopharma cross-regional and cross-sectoral operations take place, to study the main features of the overall network and key nodes from a static and dynamic viewpoint, detect the local clusters (regional communities) and examine their recent dynamics. The analysis is carried out over three distinct time-periods, i.e. 2000-2004, 2005-2010 and 2011-2016, to capture the dynamic transformation in both the overall network and the different geographical areas, and draw a picture on reinforcement or weakening of regional agglomerations, the emergence of new regional patterns and so on.

To pursue our goal, we focus in particular on operations of co-patenting, mergers and acquisitions (M&As) and joint ventures and alliances (JV&As) conducted by Biopharma companies with firms operating in other industries. The choice of these three indicators as proxies of CSLs is due first to data availability (other kinds of CSLs often do not take the form of explicit agreements or contracts and then cannot be properly accounted for). Second, the joint analysis of these operations is suitable

[1] Monfardini et al. (2012) include Biopharma among the ten emerging industries in the EU, the other being: Advanced Packaging, Blue Growth Industries, Creative Industries, Digital Industries, Environmental Industries, Experience Industries, Logistical Services, Medical Devices, Mobility Technologies.

to give a picture of the transformations occurring along the entire Biopharma value chain: patents account for Research and Development (R&D) collaboration activities, typically regarding the upstream segment of the value chain, while M&A and JV&A operations are related to firms' strategic choices (for example, about vertical or horizontal integration) occurring in both the upstream and downstream segments of the value chain.

As concerns the methodology, the paper implements methods of network analysis. In particular, the spin-glass algorithm based on the Potts model, initially proposed by Reichardt and Bornholdt (2006), is employed to detect regional communities. While the network analysis represents a consolidated and widely used methodology, its application to investigate technological and industrial transformations connected to CSLs is much more recent and still little common. Its use in the analysis of emerging industries was introduced by the European Cluster Observatory (2015) and EOCIC (2019). A novel aspect of our investigation is the replication of the analysis for three different periods, suitable to obtain a dynamic perspective on the evolution of Biopharma in European regions. We employ a large dataset including 5,837 observations on Biopharma co-patenting (3,215), M&As (1,859), and JV&As (762) completed in Europe between 2000 and 2016. Data are drawn from PATSTAT (for co-patenting), Zephyr (for M&As), and SDC Platinum Thomson Reuters (as concerns JV&As).

The main findings of our analysis are the following. First, data indicate that companies and researchers operating in the EU Biopharma industry have been increasingly involved in CSLs, collaborating through cross-border operations and developing national and regional networks. Second, the network has displayed a tendency to enlarge toward the East (Poland) and West (Spain) while showing a significant reduction in the activity of peripheral nodes in the Southern and Northern borders of the network. Third, in the last period considered 2011-2016, the overall interconnectedness of the network as a whole has slightly decreased, i.e. the network has become sparser, showing a propensity toward regionalisation of CSLs.

The paper is organised as follows. After this introduction, section 2 outlines the main features and recent evolution of Biopharma in Europe. Section 3 describes data and methodology, section 4 comments on results, and section 5 draws the main conclusions.

2. The Biopharma industry

European Cluster Observatory (2015) and EOCIC (2019) recognise the biopharmaceutical industry (Biopharma) as an emerging high-growth and strong market-potential industry. With respect to the global industry[2], European Biopharma occupies an important place in terms of market share, innovation capability and R&D expenditure. Between 2011 and 2016, the European top five producing countries (Germany, France, Italy, Spain and UK) launched 17.5% of all medicines and active ingredients newly marketed, against 64.7% of the USA and 7.3% of Japan (EFPIA, 2018). In Europe, employment amounts to about 2.4 million people, with top levels of labour productivity and average wages (about 50,800 Euros in 2016), and human capital estimated to be about 50% higher than other European emerging industries (EOCIC, 2019).

Over the period 2011-2016, the overall number of employees and enterprises in the European Biopharma industry has increased on average by 0.9% and 6.1% per year. In detail, Table 1 displays the yearly growth rates in the number of firms and employees in each European country, as well as the geographical distribution across the different countries in 2011 and 2016. Estonia, Latvia, Croatia, Hungary and Poland display the strongest development in Central and Eastern Europe, while Western countries consolidate a condition of high growth in both the number of employees and enterprises only in some cases (the United Kingdom, Spain and Netherlands), while in others the evolution is less favourable. In particular, a net decrease in both employees and enterprises is recorded for Ireland, while in France and Denmark, the number of firms rises and employees diminish. Italy stands out for its very high number of firms, connected to a relatively small average firm size; in that country, the number of employees remained stable between 2011 and 2016, while the number of firms dropped so that the share of companies with respect to total European units fell from 20.1% to 15.4%.

Table 1. Biopharma enterprises and employment in the EU (2011-2016)

Country	Number of firms Average yearly growth rate (%)	Number of employees Average yearly growth rate (%)	Firms' geographical distribution (%) 2011	Firms' geographical distribution (%) 2016
Austria	1.0	2.1	2.5	2.1
Belgium	0.6	6.8	2.4	1.9
Bulgaria	5.2	4.3	1.9	1.9
Croatia	2.2	18.7	0.9	0.8
Cyprus	3.0	-4.0	0.2	0.2
Czech Republic	n.a	n.a.	n.a.	0.2
Denmark	3.6	-11.8	1.5	1.4
Estonia	8.9	30.7	0.4	0.5
Finland	2.7	8.0	1.4	1.3
France	5.4	-6.8	9.9	10.2
Germany	4.6	2.0	0.0	0.0
Greece	21.1	-1.0	6.4	9.2
Hungary	2.4	6.0	5.6	5.0
Ireland	-5.8	-15.3	0.6	0.3
Italy	-0.8	0.2	20.1	15.4
Latvia	7.1	2.0	0.5	0.6
Lithuania	28.9	0.4	0.6	1.4
Luxembourg	3.0	2.0	0.2	0.2
Malta	n.a.	n.a.	n.a.	0.1
Netherlands	7.9	0.6	5.8	6.7
Poland	7.7	0.7	4.8	5.4
Portugal	0.8	0.5	3.0	2.5
Romania	2.2	-2.3	3.0	2.6
Slovenia	11.2	-0.5	1.0	1.2
Slovakia	5.1	0.8	1.7	1.7
Spain	9.0	3.6	8.8	10.8
Sweden	1.6	3.8	7.0	6.0
United Kingdom	5.8	14.0	9.8	10.3

Source: Authors' elaborations on Eurostat data

[2] For 2017, the global turnover of Biopharma industry was assessed to be between EUR 164 billion (Allied Market Research, 2018) and EUR 192 billion (Mordor Intelligence, 2018), with an estimated average growth rate for the period 2018–2023 ranging from 8% to 13%. While the distinction between "biotech" and "pharma" companies is today less meaningful than in the past, since every major pharmaceutical company continuously develops biotech-related drugs, Biopharma currently accounts for more than 25% of the total pharmaceutical market and represents its highest-growth area.

Biopharma is an evolution of the traditional pharmaceutical industry. Its core area includes products such as vaccines, blood components, hormones, antibodies, cell-based therapies, stem cells, gene therapy and enzymes. Like in other emerging industries, Biopharma companies are increasingly interconnected with firms belonging to other industrial and technological areas, favouring the rise of new industrial and technological trends. Sectors involved in CSLs with Biopharma tend to change over time in response to the evolution of the industry. For example, the traditional interactions between Biopharma and the basic materials chemistry sector have progressively declined the more the industry has moved its focus from traditional drugs to new products, such as nano-medicine and additive manufacturing of personalised medicines (EOCIC, 2019). Driven by the digital transformation of cell culture processes, the industry is currently moving towards Biopharma 4.0, for which not only superior data analytics methods but also higher flexibility, efficiency, and robustness of manufacturing processes are needed (Nargund et al., 2019).

The Biopharma industrial value chain is driven by lead firms, which are in most cases big pharmaceutical companies organising and governing large networks of university laboratories, biotechnology start-ups, and global and regional suppliers to push drugs into and through the clinical pipeline. Typical of science-based highly innovating industries, a great deal of uncertainty affects the relationships among the different actors within the value chain of Biopharma. Large uncertainty derives from the inability to know the full range of potential outcomes associated with the decision to invest in a certain technology. Uncertainty on the outcome of research and highly risky investments are likely to influence firms' decisions, often driving their choices toward safer and more profitable market targets (i.e. the development of drugs for chronic pathologies such as cancer, diabetes and hypertension), rather than investing on research into rare and infectious diseases. The latter point is emphasised by recent literature (Florio, 2020) as a major reason for the poor development of drugs able to prevent and fight coronavirus infections before SARS-COVID-19, despite the alarming concerns raised by the scientific community for almost 20 years.

As investment cycles span several decades and capital intensity is high, lead firms often carry out multiple partnerships or acquisitions of dedicated biotechnology firms, where novel technologies can be drawn out of university laboratories and go through the initial tests of technical and commercial viability. Innovation in Biopharma is often achieved through inter-firm alliances that allow companies to acquire new knowledge (Hagedoorn, 2002; Krätke, 2010). Moreover, the high riskiness involved in the uncertainty of the research outcome and the long and arduous clinical trials process require significant collaboration on various private and public actors and a supportive and stable institutional framework (Zucker and Darby, 1996). All this makes CSLs vital for innovation and the profitability of companies and pushes firms to locate in countries and regions that can offer a stable business environment. Accordingly, the Biopharma industry has mainly developed within regional clusters of advanced industrialised countries. More generally, the literature (George and Zaheer, 2004; Gutiérrez de Mesa and Munoz, 2007; Perugini et al., 2008) has pinpointed the main determinants of Biopharma localisation in market size, turnover growth, human capital availability, entrepreneurship, finance and intellectual property rights, but also labour costs and corporate taxes.

3. Data and methodology

The analysis is based on three main indicators of cross-sectoral linkages, namely: i) co-patenting, ii) mergers and acquisitions (M&As), and iii) joint ventures and alliances (JV&As). As stated in the introduction, this choice is based on the idea that these kinds of linkages between different industrial sectors are an essential feature of technological and industrial change. In particular, cross-sectoral co-patenting facilitates the diffusion of local technological knowledge across economic actors (Breschi and Lissoni, 2009; Jaffe et al., 1993; Maggioni et al., 2011), while the joint analysis of M&As and JV&As can describe transformations occurring at different stages of the entire Biopharma value chain. Inspection of data over such a long time period allows the identification of historical and current trends and the geographical evolution of the Biopharma industry over time.

3.1 Data

Our database is composed of 5,836 observations. It includes all cross-regional and cross-sectoral operations (3,215 co-patents, 1,859 M&As, and 762 JV&As) in which Biopharma European firms were involved between 2000 and 2016. Overall, the number of operations is significantly increasing between 2000-2004 and 2005-2010, while remaining fairly constant between 2005-2010 and 2011-2016.[3] However, as we will see later, important differences in the dynamics of each kind of operation emerge when considering single nodes (regions) and clusters (communities).

Data on the location of inventors and companies involved in cross-sectoral operations are available in the form of long address, city or postal code, so that the geographic dimension of cross-sectoral operations, i.e. the key information with which the network analysis is able to identify edges and regional communities, is easily derived. Following the European Commission NUTS 2016 geographical classification, each patent/deal is assigned to the correspondent regional NUTS 2 code based on the inventors/firms' postal code/city. The location of inventors is used for patents, which means that the location of firms, individuals or public organisations that have discovered a new product or created the invention is considered, instead of the entities filing the patent applications. The location of companies involved in the business operation is also considered for M&As and JV&As. This approach ensures that economic operators who have been engaged in cross-sectoral operations are singled out rather than their headquarters.

Data on co-patents are drawn from the PATSTAT database. PATSTAT contains bibliographical and legal status patent data from the main industrialised and developing countries. Data are extracted by selecting priority claims filed between 1 January 2000 and 31 December 2016 by inventors located in the EU28 Member States. To focus on cross-technological and cross-sectoral patents, priority claims are further filtered by selecting only applications for which inventors are located at least in two different regions, and the patent authority assigns at least two technological fields (one of which to the Biopharma sector).

Data on mergers and acquisitions are drawn from the comprehensive Zephyr database, which contains official and unofficial (rumours) information on M&As, IPOs, private equity and venture capital deals. Data are extracted by selecting acquisitions, mergers, and minority stakes completed between 1 January 2000 and 31 December 2016 by firms located in the EU28 Member States. To focus on cross-sectoral M&As in Biopharma, deals are further filtered by selecting only acquisitions, mergers, and minority stakes where either the acquirer or the target firm belongs to the Biopharma industry, as defined at NACE 4-digits codes, and the counterpart to another sector, and the two parties are located in different regions.

Data on joint ventures and alliances are drawn from the SDC Platinum database, which is part of Thomson Reuters. This database contains data on joint ventures and strategic alliances that occurred since 1988 and collected through the aggregation of several sources, including SEC filings, news feeds and so on. Data are extracted by selecting joint ventures and alliances completed between 1 January 2000 and 31 December 2016, where the interacting parties are located in at least two different EU regions. Data are further filtered by selecting only joint ventures and alliances where one company belongs to the Biopharma industry and the counterpart to another industrial sector.

[3] In detail, in the first period co-patenting operations rise from 876 to 1304 and then decrease to 1035 in 2011-2016. In the same years, mergers and acquisitions escalate from 242 to 698 and then still increase to 879. Joint Ventures and Alliances remain more or less constant, being 242 in 2000-2004, 271 in 2005-2010 and again 249 in 2011-2016.

Table 2 illustrates the overall geographical distribution of cross-regional cross-sectoral Biopharma co-patents, M&As, and JV&As among European countries from 2000 to 2016.[4] Data show that the highest occurrence of operations takes place in Germany, France and Spain for co-patenting; in the United Kingdom, Germany and Spain for M&As; in the United Kingdom[5], Germany and France for JV&As. In relative terms, i.e. considering the number of firms located in each country reported in Table 1, Netherlands and Finland also display a considerable number of cross-sectoral operations; on the other hand, in Italy and Greece co-patenting, M&A and JV&A are relatively little developed, despite the rather strong presence of Biopharma companies operating in those countries, probably because of firms' smaller average size and structural weakness.

Table 2. Cross-sectoral biopharmaceuticals patents, M&As, and JV&As in Europe (by country, 2000-2016)

Country	Co-patenting operations	M&A operations	JV&A operations
Austria	402	48	22
Belgium	350	147	56
Bulgaria	3	41	2
Croatia	36	4	5
Cyprus	6	5	3
Czech Republic	79	64	6
Denmark	83	75	43
Estonia	32	22	2
Germany	4227	472	256
Greece	28	40	15
Finland	559	147	52
France	2698	369	226
Hungary	139	28	6
Ireland	109	52	30
Italy	931	164	100
Latvia	106	37	0
Lithuania	9	8	2
Luxembourg	31	31	4
Malta	2	0	4
Netherlands	838	261	106
Poland	475	160	8
Portugal	14	11	8
Romania	60	42	1
Spain	1400	421	40
Sweden	245	228	76
Slovenia	146	13	1
Slovakia	11	14	0
United Kingdom	358	814	490

Source: Authors' elaborations based on PATSTAT, Zephyr, and SDC Platinum data

3.2 Methodology

The network analysis focuses on studying the relationships occurring across a set of entities referred to as nodes or vertices (Aldous & Wilson, 2007). Based on the graph theory (Scott, 2005), it has been extensively used in the analysis of complex systems by a long-standing strand of literature (Fortunato, 2010). In this paper, consistently with the network analysis approach, we aim at investigating technological and industrial transformations of the Biopharma industry that occurred through CSLs, by analysing the features of the overall network of cross-sectoral cross-regional co-patents, M&As and JV&As, the intensity of relationships between nodes (regions), the appearance of European regional communities (i.e. local clusters characterised by strong internal relationships and diversity from other clusters).[6]

While network analysis is an established method in many fields, its use in studying CSLs of emerging industries is novel since it was introduced by European Cluster Observatory (2015) and recently refined by EOCIC (2019). Nodes represent all the 282

[4] Note that a single operation (patent application, M&A, JV&A) is double-counted, reflecting the number of co-inventors signing the filing application.

[5] Notably, unlike the other countries, in the United Kingdom M&As and JV&As are much more numerous relative to co-patenting, probably in connection to the greater degree of financial development of that economy.

[6] We analyse the community structure of actors involved in Biopharma cross-sectoral operations, by using the spin-glass algorithm, which has been found to perform better than the other closely related module detection algorithms (West et al., 2013). Moreover, this algorithm has the advantage of depending on just one parameter, that can be tuned to optimise the trade-off between the number of inferred communities and their size (West et al., 2013; Yang et al., 2016).

regions (as defined by the NUTS 2 nomenclature published in 2016) in EU28.[7] Edges (cross-regional CSLs) are connections between pairs of nodes. The presence of an edge between two regions implies a cross-sectoral operation involving the two regions appearing as nodes. As an illustrative example, the acquisition of a Biopharma company located in Piedmont (Italy) by a company operating in the semiconductors sector and located in Centre-Val-de-Loire (France) is visualised in the network by an edge (line) between Piedmont and Centre-Val-de-Loire.

The analysis is carried out at three different levels (i.e. network, cluster, and node) over three time periods, i.e. i) 2000-2004; ii) 2005-2010, and iii) 2011-2016, to capture the dynamics of geographical transformation in Biopharma industry throughout those periods. Comparing the set of results obtained for each period allows drawing conclusions on existing regional agglomerations in each span of time and outlining the overtime evolution (e.g. reinforcement of connections, the emergence of new regional agglomeration, etc.). This approach is consistent with a broad literature that has acknowledged that the analysis of the dynamics of industrial clusters is essential to ascertain their existence and understand their nature, features and likely future evolution (Iammarino and McCann, 2006; Swann et al. 1998; TerWal and Boschma, 2011).

Identifying the large European cluster (a giant component of the network) and its communities draws on the database created by combining the information provided by the three data sets (co-patenting, M&As and JV&As) described above. The analysis is conducted using specific software[8] that detects regions where cross-sectoral linkages are concentrated and identifies larger cross-border or international communities that are the closest linked according to the selected indicators. Edges connect regions where either patent co-inventors' residences or firms' locations have been identified: the edge (A, B) frequency corresponds to the sum of co-patents, M&As, and JV&As involving the two regions A and B. Thus, the results provide insights into European regional communities leading technological and industrial transformations in the Biopharma industry, without focussing only on R&D activities or strategic co-operation activities.

Finally, the intensity of the cross-sectoral activities of each node (region) included in the giant component is estimated and classified. The assessment on intensity builds on the frequency counts so that regions are classified according to the number of cross-sectoral linkages they are involved in. Notably, regions where the number of cross-sectoral operations is below the average, are not taken into account because, even if they have connections within the giant component, the intensity of their activities is deemed not to be significant enough. By focusing on areas whose cross-sectoral activity is above average, only more active regions are analysed. The latter are classified as regions at high, medium or low intensity if the percentile of the frequency distribution they fall in is respectively above 85%, between 60% and 85%, below 60%.

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[7] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02003R1059-20180118&from=EN

[8] The software used for our investigation is R-Studio (version 1.1.447, open source, available at https://www.rstudio.com/products/RStudio/). We used the packages "matrix" (Bates and Mächler, 2014) for the network estimation, "CINNA" (Ashtiani et al., 2019) for the giant component detection, and "igraph" (Csardi and Nepusz, 2006) for the community detection through the spin-glass algorithm. As mentioned above, the adopted algorithm builds on the assumption that edges connect nodes belonging to the same community, whereas nodes belonging to different communities should not be connected (Yang et al., 2016). Hence, each region is assigned to one community only.

4. Results and discussion

As customary in network analysis, the results presented in this section are related to the analysis carried out at network, cluster and node levels. For each time interval (i.e. 2000-2004, 2005-2010 and 2011-2016), the main descriptive statistics of nodes and networks are displayed in Tables 3 and 4, respectively. This information allows assessing features, centrality and evolution of key nodes and evaluating network size, density and degree of interconnection over time.

Table 3 describes basic descriptive statistics of nodes to evaluate the importance of the different regions in Biopharma cross-regional CSLs and assess the evolution in the years under consideration. The indexes employed are the node degree, weighted degree, betweenness centrality and eigencentrality. The node degree corresponds to the number of regions with which a region is connected through CSLs, while the node weighted degree is the number of CSLs that firms operating in a region hold with firms operating in any other region. Both these indicators show that throughout the period 2000-2016, the key nodes remain the regions of Central Western Europe, i.e. Ile-the-France and Rhône in France, Oberbayern, Darmstadt and Köln in Germany, Lombardy in Italy and Cataluña and Madrid in Spain.[9] This indication is strongly corroborated by the calculation of the betweenness centrality and eigencentrality indexes.[10] For both these indicators, Ile-the-France, Oberbayern, Darmstadt, Köln, Inner London, Lombardy and Cataluña can be considered the key nodes of Biopharma CSLs network.

[9] Looking in detail at the main connections of key nodes, it is interesting to underscore that the Ile de France has strengthened its linkages within its national borders, particularly with Rhône-Alpes, and to a smaller extent with Austrian, Belgian, German, and Dutch regions, while slightly loosening its connections with Italian and British regions. Similarly, Oberbayern has retained the majority of its cross-sectoral operations within the national borders.

[10] Betweenness centrality of a node measures how often that node appears on a geodesic path (the shortest path connecting two points in a surface) between other nodes in the network, thus assuming a role as intermediary. Eigenvector centrality (eigencentrality) is a measure of the centrality of a node based on its own centrality as well as the centrality of the nodes it is connected with. Regions with a high value of eigenvector centrality are characterised by the fact that they are strongly connected to other regions which in turn have strong connections with others.

Table 3. Descriptive statistics of nodes in the three periods

NUTS 2 code	NUTS 2 Label	Degree			Weighted Degree			Betweenness centrality			Eigencentrality		
		Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016
AT11	Burgenland	6	5	4	50	36	17	3.0	5.3	0.0	0.10	0.07	0.04
AT12	Niederösterreich	10	12	8	95	78	80	84.5	89.2	48.0	0.17	0.22	0.06
AT13	Wien	13	18	23	165	152	109	149.6	533.3	1109.2	0.23	0.33	0.36
AT21	Kärnten	2	5	3	2	19	3	0.0	5.2	8.2	0.06	0.04	0.05
AT22	Steiermark	6	9	3	23	25	19	65.3	58.5	84.8	0.10	0.10	0.04
AT31	Oberösterreich	1	3	6	1	14	9	0.0	0.0	30.6	0.01	0.02	0.07
AT32	Salzburg	3	10	3	12	44	3	0.0	48.4	234.5	0.03	0.18	0.05
AT33	Tirol	1	14	3	2	60	4	0.0	405.9	8.5	0.03	0.21	0.08
AT34	Vorarlberg	n.a.	4	1	n.a.	6	8	n.a.	13.1	0.0	n.a.	0.07	0.02
BE10	Région de Bruxelles-Capitale	28	14	14	172	42	57	838.2	441.6	464.9	0.48	0.22	0.16
BE21	Prov. Antwerpen	16	13	14	73	14	36	127.8	149.4	544.9	0.34	0.28	0.25
BE22	Prov. Limburg	5	4	1	27	13	6	1.1	4.1	0.0	0.10	0.07	0.01
BE23	Prov. Oost-Vlaanderen	23	15	9	80	17	20	643.5	414.3	61.0	0.44	0.26	0.13
BE24	Prov. Vlaams-Brabant	21	9	20	124	24	73	425.9	56.5	633.1	0.40	0.14	0.30
BE25	Prov. West-Vlaanderen	4	7	12	8	7	21	0.3	214.2	83.5	0.14	0.13	0.20
BE31	Prov. Brabant Wallon	9	8	7	29	23	15	39.0	85.1	56.2	0.18	0.14	0.10
BE32	Prov. Hainaut	7	2	5	32	4	15	20.4	0.0	240.1	0.15	0.02	0.05
BE33	Prov. Liège	6	6	8	20	37	58	14.8	47.1	190.5	0.08	0.08	0.14
BE34	Prov. Luxembourg	5	2	1	15	24	1	2.1	0.0	0.0	0.07	0.02	0.00
BE35	Prov. Namur	6	3	2	29	4	3	3.8	0.9	0.0	0.10	0.07	0.03
BG31	Severozapaden	1	n.a.	2	2	n.a.	2	0.0	n.a.	12.7	0.00	n.a.	0.01
BG32	Severen tsentralen	n.a.	n.a.	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.00
BG33	Severoiztochen	n.a.	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.00	n.a.
BG34	Yugoiztochen	n.a.	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.00	n.a.
BG41	Yugozapaden	1	5	3	2	5	3	0.0	473.1	259.1	0.00	0.04	0.02
CY00	Cyprus	1	3	2	1	3	2	0.0	8.3	87.1	0.00	0.05	0.03
CZ01	Praha	8	5	15	46	10	69	95.6	91.5	450.1	0.13	0.04	0.17
CZ02	Střední Čechy	2	4	11	8	7	44	0.0	0.0	137.2	0.06	0.03	0.09
CZ03	Jihozápad	5	5	8	27	8	47	0.0	25.1	23.0	0.06	0.03	0.08
CZ04	Severozápad	1	n.a.	4	1	n.a.	4	0.0	n.a.	15.9	0.02	n.a.	0.03
CZ05	Severovýchod	1	4	12	1	11	27	0.0	0.0	275.9	0.00	0.03	0.15
CZ06	Jihovýchod	6	8	9	21	18	38	15.5	250.2	180.6	0.09	0.09	0.08
CZ07	Střední Morava	5	5	7	37	16	20	0.0	179.7	26.9	0.06	0.02	0.05
CZ08	Moravskoslezsko	5	3	4	30	4	7	0.0	19.3	0.7	0.06	0.02	0.03
DE11	Stuttgart	14	8	19	36	22	49	77.1	10.8	290.8	0.35	0.24	0.40
DE12	Karlsruhe	33	39	23	323	329	146	1559.4	1283.1	272.8	0.66	0.75	0.45
DE13	Freiburg	11	20	17	50	187	94	32.2	281.1	133.9	0.27	0.41	0.37
DE14	Tübingen	21	21	16	132	95	58	581.2	272.1	181.4	0.46	0.49	0.34
DE21	Oberbayern	41	60	55	153	458	277	1664.9	3007.8	3534.8	0.76	1.00	0.94
DE22	Niederbayern	n.a.	1	5	n.a.	1	8	n.a.	0.0	6.9	n.a.	0.01	0.11
DE23	Oberpfalz	6	5	9	32	16	35	12.4	225.7	54.9	0.11	0.11	0.17
DE24	Oberfranken	3	5	n.a.	14	13	n.a.	1.2	3.0	n.a.	0.10	0.10	n.a.
DE25	Mittelfranken	12	17	13	30	26	42	148.3	201.3	372.3	0.25	0.35	0.24
DE26	Unterfranken	11	16	12	56	77	25	37.6	84.5	20.0	0.28	0.33	0.28
DE27	Schwaben	3	5	5	6	30	12	1.1	3.5	8.5	0.09	0.13	0.09
DE30	Berlin	38	28	24	202	727	172	1535.1	371.3	561.3	0.68	0.55	0.46
DE40	Brandenburg	11	15	7	76	335	74	30.2	36.7	26.1	0.27	0.34	0.15
DE50	Bremen	8	9	6	23	57	9	5.5	23.2	9.5	0.21	0.21	0.13
DE60	Hamburg	19	27	27	65	147	109	323.9	712.1	550.7	0.43	0.60	0.54
DE71	Darmstadt	33	45	34	203	430	255	826.8	1181.1	984.9	0.66	0.82	0.61
DE72	Gießen	8	12	7	54	37	29	34.6	509.1	14.9	0.23	0.23	0.20
DE73	Kassel	4	8	11	8	9	35	2.9	9.0	98.3	0.10	0.19	0.18
DE80	Mecklenburg-Vorpommern	6	7	7	13	19	18	7.2	14.5	21.3	0.11	0.17	0.14
DE91	Braunschweig	10	20	11	75	94	55	51.6	146.5	46.8	0.17	0.44	0.19
DE92	Hannover	13	19	17	33	85	121	102.1	117.8	322.2	0.27	0.42	0.25
DE93	Lüneburg	7	8	7	15	26	13	10.5	62.0	19.5	0.17	0.20	0.14
DE94	Weser-Ems	2	6	4	3	12	7	0.0	2.0	5.6	0.08	0.14	0.05
DEA1	Düsseldorf	29	34	26	136	282	136	598.2	1352.5	772.6	0.64	0.62	0.50
DEA2	Köln	25	34	33	119	259	173	356.9	753.9	836.8	0.50	0.67	0.57
DEA3	Münster	4	10	13	4	32	39	10.5	35.5	70.2	0.10	0.21	0.22
DEA4	Detmold	5	9	14	12	20	21	4.1	19.9	188.8	0.13	0.19	0.24
DEA5	Arnsberg	12	13	15	24	59	87	40.3	25.7	97.2	0.31	0.28	0.30
DEB1	Koblenz	1	3	5	1	5	9	0.0	4.5	18.1	0.03	0.09	0.13
DEB2	Trier	1	n.a.	4	1	n.a.	8	0.0	n.a.	0.0	0.04	n.a.	0.15
DEB3	Rheinhessen-Pfalz	29	32	24	119	216	149	768.0	1249.6	285.6	0.53	0.59	0.42
DEC0	Saarland	4	7	8	23	20	38	0.0	30.3	17.5	0.13	0.23	0.19
DED2	Dresden	5	7	5	8	40	21	1.0	129.9	8.1	0.16	0.12	0.08
DED4	Chemnitz	n.a.	1	n.a.	n.a.	2	n.a.	n.a.	0.0	n.a.	n.a.	0.01	n.a.
DED5	Leipzig	4	8	9	24	40	22	0.0	243.7	45.5	0.12	0.19	0.19
DEE0	Sachsen-Anhalt	7	8	10	30	13	24	192.3	41.9	44.8	0.17	0.22	0.21
DEF0	Schleswig-Holstein	11	13	13	37	43	69	185.2	100.0	87.5	0.24	0.30	0.23
DEG0	Thüringen	8	13	18	45	201	64	10.1	44.5	694.3	0.21	0.31	0.34

NUTS 2 code	NUTS 2 Label	Degree			Weighted Degree			Betweenness centrality			Eigencentrality		
		Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016
DK01	Hovedstaden	24	21	25	42	49	54	702.1	559.2	629.4	0.43	0.38	0.46
DK02	Sjælland	1	2	5	1	2	14	0.0	2.5	11.7	0.02	0.02	0.06
DK03	Syddanmark	1	3	6	3	10	16	0.0	0.4	31.6	0.00	0.08	0.05
DK04	Midtjylland	3	2	6	3	2	9	8.9	0.0	20.1	0.07	0.05	0.09
DK05	Nordjylland	n.a.	7	7	n.a.	7	11	n.a.	22.6	36.4	n.a.	0.15	0.11
EE00	Eesti	2	3	3	2	3	7	0.0	27.5	85.4	0.06	0.06	0.03
EL30	Attica	n.a.	12	8	n.a.	21	17	n.a.	844.3	701.6	n.a.	0.22	0.14
EL43	Crete	n.a.	n.a.	3	n.a.	n.a.	6	n.a.	n.a.	0.0	n.a.	n.a.	0.01
EL51	Eastern Macedonia and Thrace	n.a.	1	3	n.a.	1	8	n.a.	0.0	0.0	n.a.	0.00	0.01
EL52	Central Macedonia	n.a.	2	n.a.	n.a.	3	n.a.	n.a.	225.0	n.a.	n.a.	0.01	n.a.
EL61	Thessaly	n.a.	n.a.	3	n.a.	n.a.	12	n.a.	n.a.	0.0	n.a.	n.a.	0.01
ES11	Galicia	2	6	3	4	57	5	0.0	197.1	4.2	0.03	0.13	0.04
ES12	Principado de Asturias	n.a.	n.a.	2	n.a.	n.a.	4	n.a.	n.a.	0.0	n.a.	n.a.	0.03
ES13	Cantabria	n.a.	n.a.	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.00
ES21	País Vasco	n.a.	5	7	n.a.	10	48	n.a.	33.4	59.4	n.a.	0.08	0.16
ES22	Comunidad Foral de Navarra	n.a.	2	1	n.a.	2	1	n.a.	30.6	0.0	n.a.	0.03	0.02
ES23	La Rioja	n.a.	n.a.	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.00
ES24	Aragón	1	2	4	1	2	26	0.0	1.3	12.4	0.02	0.04	0.05
ES30	Comunidad de Madrid	14	15	21	65	164	231	480.9	423.0	649.3	0.22	0.23	0.27
ES41	Castilla y León	n.a.	1	8	n.a.	21	26	n.a.	0.0	69.5	n.a.	0.01	0.10
ES42	Castilla-La Mancha	n.a.	n.a.	4	n.a.	n.a.	4	n.a.	n.a.	17.1	n.a.	n.a.	0.06
ES43	Extremadura	n.a.	n.a.	4	n.a.	n.a.	20	n.a.	n.a.	9.3	n.a.	n.a.	0.06
ES51	Cataluña	16	35	31	75	216	213	245.4	1675.4	1731.6	0.34	0.50	0.40
ES52	Comunidad Valenciana	3	6	5	10	7	25	0.0	27.5	15.9	0.11	0.09	0.08
ES53	Illes Balears	1	n.a.	3	2	n.a.	23	0.0	n.a.	1.6	0.02	n.a.	0.04
ES61	Andalucía	n.a.	10	7	n.a.	145	99	n.a.	176.0	112.5	n.a.	0.22	0.14
ES62	Región de Murcia	n.a.	2	n.a.	n.a.	2	n.a.	n.a.	0.7	n.a.	n.a.	0.01	n.a.
ES70	Canarias	n.a.	1	2	n.a.	1	6	n.a.	0.0	0.0	n.a.	0.03	0.04
FI19	Länsi-Suomi	3	5	3	20	110	8	0.0	22.7	1.8	0.03	0.05	0.05
FI1B	Helsinki-Uusimaa	11	20	16	142	180	79	172.7	991.7	504.8	0.20	0.27	0.26
FI1C	Etelä-Suomi	11	5	5	104	100	55	479.0	19.4	18.7	0.18	0.06	0.07
FI1D	Pohjois- ja Itä-Suomi	8	6	7	94	42	16	50.9	240.0	43.2	0.12	0.06	0.08
FR10	Ile-de-France	67	72	66	465	788	1034	5197.9	5569.2	4615.2	1.00	1.00	1.00
FRB0	Centre — Val de Loire	3	5	7	5	26	34	8.1	9.4	38.6	0.05	0.11	0.14
FRC1	Bourgogne	2	7	9	2	13	16	0.0	24.9	82.3	0.08	0.09	0.15
FRC2	Franche-Comté	3	3	6	3	63	11	0.0	1.3	1.3	0.10	0.09	0.14
FRD1	Basse-Normandie	3	5	9	4	41	67	0.0	67.4	8.0	0.13	0.12	0.19
FRD2	Haute-Normandie	2	11	4	15	48	56	0.0	39.1	3.4	0.07	0.24	0.10
FRE1	Nord-Pas de Calais	5	12	19	16	60	66	37.2	42.5	187.3	0.15	0.22	0.32
FRE2	Picardie	2	2	10	4	7	89	0.0	0.0	8.3	0.07	0.06	0.19
FRF1	Alsace	10	12	15	62	112	98	36.1	75.0	109.9	0.28	0.20	0.26
FRF2	Champagne-Ardenne	1	5	n.a.	1	6	n.a.	0.0	3.9	n.a.	0.01	0.13	n.a.
FRF3	Lorraine	5	8	11	36	29	27	2.9	14.1	267.5	0.15	0.19	0.14
FRG0	Pays de la Loire	6	13	19	23	34	154	9.8	62.4	134.2	0.15	0.26	0.31
FRH0	Bretagne	8	16	10	25	174	136	21.3	151.8	31.2	0.21	0.30	0.17
FRI1	Aquitaine	3	5	9	7	13	50	1.4	12.3	41.9	0.07	0.12	0.18
FRI2	Limousin	4	3	n.a.	7	9	n.a.	2.3	6.7	n.a.	0.12	0.06	n.a.
FRI3	Poitou-Charentes	5	3	5	7	3	9	20.8	0.0	4.1	0.14	0.08	0.13
FRJ1	Languedoc-Roussillon	6	9	12	31	121	187	3.2	25.2	65.5	0.17	0.19	0.23
FRJ2	Midi-Pyrénées	5	9	14	67	27	78	2.9	23.1	321.4	0.13	0.23	0.26
FRK1	Auvergne	2	2	8	3	13	24	0.0	0.0	22.2	0.08	0.05	0.15
FRK2	Rhône-Alpes	20	32	31	97	317	248	251.6	1072.3	939.1	0.41	0.50	0.54
FRL0	Provence-Alpes-Côte d'Azur	16	12	20	73	39	158	293.7	140.3	443.7	0.31	0.21	0.36
FRM0	Corse	n.a.	1	3	n.a.	6	3	n.a.	0.0	0.0	n.a.	0.05	0.08
HR03	Jadranska Hrvatska	n.a.	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.05	n.a.
HR04	Kontinentalna Hrvatska	1	4	n.a.	1	23	n.a.	0.0	26.5	n.a.	0.01	0.02	n.a.
HU11	Budapest	3	12	12	7	67	133	14.1	893.9	966.0	0.06	0.19	0.14
HU12	Pest	2	n.a.	4	4	n.a.	47	0.0	n.a.	10.2	0.06	n.a.	0.03
HU21	Közép-Dunántúl	n.a.	n.a.	3	n.a.	n.a.	21	n.a.	n.a.	0.0	n.a.	n.a.	0.01
HU23	Dél-Dunántúl	2	2	n.a.	7	24	n.a.	0.0	0.0	n.a.	0.01	0.06	n.a.
HU31	Észak-Magyarország	1	3	3	1	15	9	0.0	225.0	0.0	0.00	0.01	0.01
HU32	Észak-Alföld	n.a.	n.a.	1	n.a.	n.a.	2	n.a.	n.a.	0.0	n.a.	n.a.	0.01
HU33	Dél-Alföld	2	2	6	27	26	38	0.0	0.0	69.7	0.01	0.01	0.03
IE04	Northern and Western	3	2	1	3	2	1	4.3	3.8	0.0	0.05	0.02	0.03
IE05	Southern	2	3	6	2	18	9	3.1	3.1	42.0	0.04	0.05	0.09
IE06	Eastern and Midland	8	26	25	9	63	45	75.5	1601.0	1031.3	0.14	0.35	0.45
ITC1	Piemonte	5	13	7	20	67	17	25.5	147.7	19.1	0.06	0.27	0.12
ITC3	Liguria	3	2	5	10	3	21	1.3	0.0	10.3	0.04	0.03	0.07
ITC4	Lombardia	25	38	31	102	258	134	1745.5	1744.8	1792.1	0.33	0.54	0.50
ITF1	Abruzzo	2	4	1	4	23	29	0.0	8.2	0.0	0.02	0.09	0.03
ITF3	Campania	2	9	4	12	38	9	0.0	74.3	2.3	0.02	0.16	0.13
ITF4	Puglia	1	6	9	1	46	21	0.0	11.6	97.9	0.01	0.10	0.17
ITF6	Calabria	n.a.	3	1	n.a.	4	1	n.a.	0.0	0.0	n.a.	0.04	0.01
ITG1	Sicilia	2	2	6	9	12	15	0.0	0.0	104.5	0.03	0.02	0.07

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ITG2	Sardegna	n.a.	2	1	n.a.	21	1	n.a.	0.0	0.0	n.a.	0.03	0.01
ITH1	Provincia Autonoma di Bolzano	2	n.a.	1	6	n.a.	1	0.0	n.a.	0.0	0.02	n.a.	0.00
ITH2	Provincia Autonoma di Trento	n.a.	n.a.	3	n.a.	n.a.	6	n.a.	n.a.	0.0	n.a.	n.a.	0.02
ITH3	Veneto	7	6	13	17	13	20	332.1	11.7	203.2	0.12	0.12	0.18
ITH4	Friuli-Venezia Giulia	n.a.	2	7	n.a.	2	16	n.a.	0.0	34.4	n.a.	0.04	0.11
ITH5	Emilia-Romagna	4	10	14	8	45	32	17.7	120.2	370.7	0.06	0.13	0.24
ITI1	Toscana	2	12	5	16	100	8	1.0	158.9	25.4	0.02	0.18	0.11
ITI2	Umbria	4	4	3	16	5	6	14.4	1.9	3.2	0.04	0.05	0.05
ITI3	Marche	n.a.	3	4	n.a.	10	17	n.a.	0.0	4.7	n.a.	0.05	0.07
ITI4	Lazio	13	12	17	28	97	41	362.5	116.5	928.3	0.27	0.21	0.24
LT01	Sostinės regionas	3	2	1	3	10	1	379.0	0.0	0.0	0.06	0.07	0.00
LT02	Vidurio ir vakarų Lietuvos regionas	1	1	1	1	1	1	0.0	0.0	0.0	0.00	0.01	0.00
LU00	Luxembourg	5	20	17	5	29	26	22.2	245.2	661.0	0.14	0.41	0.28
LV00	Latvia	1	3	4	1	3	9	0.0	0.5	237.8	0.04	0.02	0.05
MT00	Malta	1	n.a.	1	1	n.a.	3	0.0	n.a.	0.0	0.02	n.a.	0.02
NL11	Groningen	7	3	6	26	5	30	7.4	3.0	39.0	0.11	0.04	0.07
NL12	Friesland	6	1	n.a.	9	1	n.a.	8.7	0.0	n.a.	0.11	0.01	n.a.
NL13	Drenthe	4	5	1	13	7	1	0.0	0.7	0.0	0.06	0.07	0.01
NL21	Overijssel	5	9	6	9	13	8	0.6	44.5	37.1	0.12	0.15	0.15
NL22	Gelderland	13	18	13	100	104	108	45.2	307.8	414.7	0.22	0.34	0.16
NL23	Flevoland	7	9	6	21	25	17	16.2	38.3	12.6	0.16	0.20	0.07
NL31	Utrecht	17	12	11	124	70	72	185.4	92.3	263.6	0.32	0.23	0.18
NL32	Noord-Holland	31	26	24	151	75	95	757.4	1092.5	1242.2	0.64	0.43	0.40
NL33	Zuid-Holland	25	27	28	152	102	85	567.7	924.8	866.3	0.52	0.52	0.49
NL34	Zeeland	3	4	4	4	4	5	0.0	14.1	24.0	0.10	0.06	0.06
NL41	Noord-Brabant	18	25	17	43	71	100	253.0	437.7	433.7	0.41	0.43	0.30
NL42	Limburg	9	18	15	29	48	32	20.4	214.9	347.1	0.24	0.35	0.29
PL21	Małopolskie	4	6	11	7	16	60	110.8	452.5	296.6	0.09	0.08	0.05
PL22	Śląskie	1	6	8	1	12	35	0.0	246.2	64.2	0.00	0.05	0.03
PL41	Wielkopolskie	3	1	5	5	1	41	6.5	0.0	29.0	0.03	0.02	0.02
PL42	Zachodniopomorskie	n.a.	n.a.	7	n.a.	n.a.	25	n.a.	n.a.	8.5	n.a.	n.a.	0.03
PL43	Lubuskie	n.a.	n.a.	5	n.a.	n.a.	9	n.a.	n.a.	186.7	n.a.	n.a.	0.03
PL51	Dolnośląskie	n.a.	5	12	n.a.	5	62	n.a.	147.9	272.4	n.a.	0.07	0.05
PL52	Opolskie	n.a.	1	3	n.a.	1	6	n.a.	0.0	0.0	n.a.	0.00	0.01
PL61	Kujawsko-pomorskie	n.a.	2	4	n.a.	4	17	n.a.	225.0	7.0	n.a.	0.01	0.01
PL62	Warmińsko-Mazurskie	n.a.	n.a.	5	n.a.	n.a.	30	n.a.	n.a.	0.0	n.a.	n.a.	0.03
PL63	Pomorskie	1	1	9	1	1	45	0.0	0.0	474.7	0.00	0.00	0.10
PL71	Łódzkie	n.a.	4	11	n.a.	10	58	n.a.	225.0	178.6	n.a.	0.01	0.04
PL72	Świętokrzyskie	n.a.	3	2	n.a.	9	5	n.a.	0.0	0.0	n.a.	0.01	0.01
PL81	Lubelskie	1	1	5	1	1	18	0.0	0.0	215.4	0.00	0.00	0.07
PL82	Podkarpackie	n.a.	2	3	n.a.	2	18	n.a.	0.0	27.9	n.a.	0.01	0.03
PL84	Podlaskie	n.a.	1	2	n.a.	2	3	n.a.	0.0	0.0	n.a.	0.00	0.01
PL91	Warszawski stołeczny	5	8	20	6	19	105	569.2	687.6	1234.9	0.04	0.07	0.13
PL92	Mazowiecki regionalny	n.a.	4	7	n.a.	14	20	n.a.	278.2	122.7	n.a.	0.03	0.04
PT11	Norte	1	3	2	1	4	2	0.0	11.0	0.6	0.02	0.04	0.04
PT16	Centro	n.a.	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.00	n.a.
PT17	Área Metropolitana de Lisboa	2	4	2	2	20	8	1.7	19.3	0.0	0.05	0.04	0.07
PT18	Alentejo	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.01	n.a.	n.a.
RO11	Nord-Vest	1	1	3	1	1	5	0.0	0.0	1368.0	0.00	0.00	0.02
RO12	Centru	n.a.	n.a.	3	n.a.	n.a.	3	n.a.	n.a.	1151.0	n.a.	n.a.	0.00
RO21	Nord-Est	n.a.	n.a.	2	n.a.	n.a.	14	n.a.	n.a.	0.0	n.a.	n.a.	0.00
RO22	Sud-Est	n.a.	1	2	n.a.	1	40	n.a.	0.0	0.0	n.a.	0.00	0.00
RO31	Sud-Muntenia	n.a.	1	2	n.a.	1	2	n.a.	0.0	233.0	n.a.	0.01	0.00
RO32	Bucuresti-Ilfov	3	4	3	3	4	35	566.0	15.8	464.0	0.06	0.10	0.00
RO41	Sud-Vest Oltenia	2	1	1	2	1	1	190.0	0.0	0.0	0.00	0.00	0.00
RO42	Vest	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.00	n.a.	n.a.
SE11	Stockholm	20	24	22	50	131	49	940.8	683.4	2409.7	0.39	0.38	0.30
SE12	Östra Mellansverige	2	14	11	13	31	28	0.0	238.4	94.0	0.05	0.21	0.21
SE21	Småland med öarna	2	4	3	2	5	4	190.0	0.0	2.2	0.02	0.04	0.05
SE22	Sydsverige	7	10	18	13	35	30	15.6	131.8	432.6	0.15	0.16	0.36
SE23	Västsverige	7	11	12	54	49	15	87.5	98.5	271.4	0.14	0.14	0.20
SE31	Norra Mellansverige	n.a.	5	2	n.a.	7	3	n.a.	1.2	15.2	n.a.	0.05	0.02
SE32	Mellersta Norrland	1	2	1	1	2	2	0.0	0.0	0.0	0.00	0.03	0.02
SE33	Övre Norrland	2	1	1	2	1	1	2.0	0.0	0.0	0.03	0.00	0.01
SI03	Vzhodna Slovenija	n.a.	4	2	n.a.	79	14	n.a.	183.2	2.0	n.a.	0.06	0.01
SI04	Zahodna Slovenija	n.a.	4	7	n.a.	68	30	n.a.	69.4	181.5	n.a.	0.07	0.07
SK01	Bratislavský kraj	n.a.	4	3	n.a.	21	8	n.a.	84.7	16.3	n.a.	0.01	0.03
SK02	Západné Slovensko	n.a.	2	2	n.a.	5	3	n.a.	0.0	0.0	n.a.	0.00	0.03
SK03	Stredné Slovensko	1	3	1	1	4	1	0.0	20.3	0.0	0.02	0.04	0.00
SK04	Východné Slovensko	n.a.	n.a.	5	n.a.	n.a.	11	n.a.	n.a.	0.0	n.a.	n.a.	0.03
UKC1	Tees Valley and Durham	n.a.	3	2	n.a.	4	2	n.a.	1.9	0.0	n.a.	0.04	0.04
UKC2	Northumberland and Tyne and Wear	2	6	3	2	13	3	0.0	54.0	3.9	0.03	0.07	0.03
UKD3	Greater Manchester	13	20	14	24	46	15	380.4	477.1	182.5	0.24	0.30	0.17
UKD4	Lancashire	2	8	8	2	9	9	2.0	151.7	106.0	0.02	0.09	0.08

NUTS 2 code	NUTS 2 Label	Degree			Weighted Degree			Betweenness centrality			Eigencentrality		
		Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016	Period 2000-2004	Period 2005-2010	Period 2010-2016
UKD6	Cheshire	6	5	14	8	6	18	14.7	29.2	215.6	0.11	0.10	0.23
UKD7	Merseyside	2	4	6	2	4	6	20.4	8.0	47.0	0.04	0.08	0.08
UKE1	East Yorkshire and Northern Lincolnshire	1	3	3	1	3	8	0.0	9.3	8.1	0.00	0.03	0.02
UKE2	North Yorkshire	5	3	5	5	3	8	70.7	6.1	23.2	0.13	0.05	0.10
UKE3	South Yorkshire	6	5	6	8	5	6	208.7	7.8	37.0	0.06	0.10	0.07
UKE4	West Yorkshire	3	7	9	3	7	11	22.8	68.4	97.4	0.05	0.09	0.12
UKF1	Derbyshire and Nottinghamshire	4	12	12	8	15	15	38.5	179.5	334.1	0.07	0.18	0.18
UKF2	Leicestershire, Rutland and Northamptonshire	3	5	5	6	6	5	0.0	41.9	96.4	0.07	0.06	0.08
UKF3	Lincolnshire	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.00	n.a.	n.a.
UKG1	Herefordshire, Worcestershire and Warwickshire	4	4	7	4	4	16	25.5	17.7	32.7	0.03	0.07	0.12
UKG2	Shropshire and Staffordshire	5	1	4	5	1	4	39.2	0.0	8.5	0.07	0.01	0.07
UKG3	West Midlands	5	10	3	5	14	7	212.0	293.0	0.0	0.04	0.12	0.10
UKH1	East Anglia	22	27	22	102	171	29	414.6	839.1	432.3	0.40	0.45	0.39
UKH2	Bedfordshire and Hertfordshire	8	13	15	40	81	24	266.7	270.2	473.0	0.18	0.25	0.28
UKH3	Essex	5	8	13	41	55	20	4.7	30.0	224.6	0.13	0.12	0.20
UKI3	Inner London — West	11	21	29	19	27	82	320.3	387.5	993.8	0.22	0.27	0.42
UKI4	Inner London — East	39	35	29	99	96	64	1869.9	1190.4	1083.6	0.69	0.51	0.52
UKI5	Outer London — East and North East	n.a.	2	2	n.a.	2	2	n.a.	0.6	0.5	n.a.	0.02	0.03
UKI6	Outer London — South	16	10	9	28	20	15	630.6	51.9	35.0	0.26	0.21	0.21
UKI7	Outer London — West and North West	5	6	12	6	6	16	7.3	20.3	166.9	0.13	0.10	0.21
UKJ1	Berkshire, Buckinghamshire and Oxfordshire	24	23	23	86	63	46	747.2	654.8	616.2	0.42	0.45	0.43
UKJ2	Surrey, East and West Sussex	7	9	10	9	10	14	30.7	49.1	165.8	0.11	0.20	0.18
UKJ3	Hampshire and Isle of Wight	7	10	7	17	10	8	24.5	525.2	15.1	0.12	0.15	0.12
UKJ4	Kent	10	4	4	38	4	4	34.9	17.5	23.8	0.26	0.04	0.05
UKK1	Gloucestershire, Wiltshire and Bristol/Bath area	11	10	10	19	17	14	57.2	173.7	137.1	0.28	0.18	0.19
UKK2	Dorset and Somerset	1	1	1	3	1	1	0.0	0.0	0.0	0.00	0.02	0.03
UKK3	Cornwall and Isles of Scilly	n.a.	1	n.a.	n.a.	1	n.a.	n.a.	0.0	n.a.	n.a.	0.02	n.a.
UKK4	Devon	1	1	n.a.	1	1	n.a.	0.0	0.0	n.a.	0.02	0.01	n.a.
UKL1	West Wales and The Valleys	3	1	3	3	2	3	3.0	0.0	4.3	0.09	0.02	0.03
UKL2	East Wales	5	7	9	7	22	11	89.0	47.9	53.3	0.13	0.09	0.07
UKM5	North Eastern Scotland	2	2	4	2	5	4	0.0	1.3	12.1	0.06	0.04	0.08
UKM6	Highlands and Islands	1	n.a.	2	1	n.a.	2	0.0	n.a.	0.7	0.02	n.a.	0.04
UKM7	Eastern Scotland	7	9	8	7	10	10	30.8	97.6	95.6	0.08	0.15	0.11
UKM8	West Central Scotland	5	4	11	5	4	19	16.9	9.3	125.8	0.11	0.04	0.16
UKM9	Southern Scotland	n.a.	1	2	n.a.	1	2	n.a.	0.0	0.0	n.a.	0.01	0.05
UKN0	Northern Ireland	2	1	5	2	5	5	3.0	0.0	9.2	0.04	0.02	0.07
UKZZ	Extra-Regio NUTS 2	n.a.	4	1	n.a.	4	1	n.a.	1.0	0.0	n.a.	0.09	0.03

Source: Authors' elaborations based on PATSTAT, Zephyr, and SDC Platinum data

Nevertheless, for the years 2011-2016, almost all the recalled key nodes (except the Spanish ones) exhibit a decrease in both the number of CSLs and regions to which they are connected. On the other hand, other regions come up showing livelier dynamics. This is the case of many regions of Poland (Pomorskie, increasing CSLs from 1 to 45, Wielkopolskie, Dolnośląskie, Łódzkie, and Warszawski stołeczny), Aragón in Spain, Bucuresti-Ilfov in Romania, Picardie in France, Friuli Venetia Giulia in Italy, Niederbayern in Germany, Praha in Czech Republic and Groningen in the Netherlands. Conversely, some other regions show decreasing dynamics in CSLs and a reduction in connections. This happens in many Central and Southern Italian (particularly Sardinia, Tuscany, and Campania), and Austrian (Tirol, Salzburg, and Kärnten) regions, as well as in Ireland and Luxembourg. Also, a few German (Bremen, Brandeburg, and Berlin), Scandinavian (Länsi-Suomi, Västsverige, and Stockholm) and the central-eastern UK regions (East Anglia, Bedfordshire, and Hertfordshire) display a negative evolution in CSLs.

The observed dynamics of the graph nodes and edges indicate a tendency of the network to enlarge toward the East (Poland) and West (Spain), while highlighting a reduced activity of peripheral nodes in the Southern and Northern borders of the network. This evidence is confirmed by the following analysis focusing on the whole network.

Table 4 summarises some descriptive statistics of the network regarding each of the three periods we studied. As shown in the first two rows of Table 4, the number of nodes in the network has progressively increased over time, with a sustained rise in the number of European regions involved in Biopharma cross-regional CSLs operations. In particular, while between 2000 and 2004, cross-sectoral cross-regional Biopharma operations occurred in 198 regions (a share around 70% of 282 EU regions), between 2005 and 2010, the number of regions increased to 220 (78%), and between 2011 and 2016 to 239 regions (85%). This means that 41 additional regions got involved in Biopharma cross-regional CSLs, increasing by 20.7% the number of the network nodes. Consistent with indications of Tables 1 and 2, the growth of cross-regional CSLs took place especially in Spain (10 additional regions) and Central Eastern Europe, i.e. Poland (11 additional regions), Slovakia (3 regions) and Slovenia (2 regions). Together with the increase in the number of nodes, the network also strengthened in terms of edges, with a noteworthy uprise of new inter-regional connections. In particular, CSLs connected 760 pairs of European regions between 2000 and 2004, 1,021 pairs in 2005-2010 and 1,079 in the last span of time 2011-2016, giving evidence of a strong increase of relationships. The new linkages concern both newly established nodes of the network and already existing ones. To give an example, in the 2011-2016 period, the regions of Ile-de-France and Hannover (Germany) were engaged in 22 new cross-sectoral Biopharma operations.

Table 4. Descriptive statistics of the network in the three periods

	2000-2004	2005-2010	2011-2016
Number of nodes	198	220	239
Number of edges	760	1021	1079
Graph Density	0.039	0.039	0.038
Average Degree	7.677	8.917	9.029
Average Weighted Degree	33.485	48.795	40.176

Source: Authors' elaborations based on PATSTAT, Zephyr, and SDC Platinum data

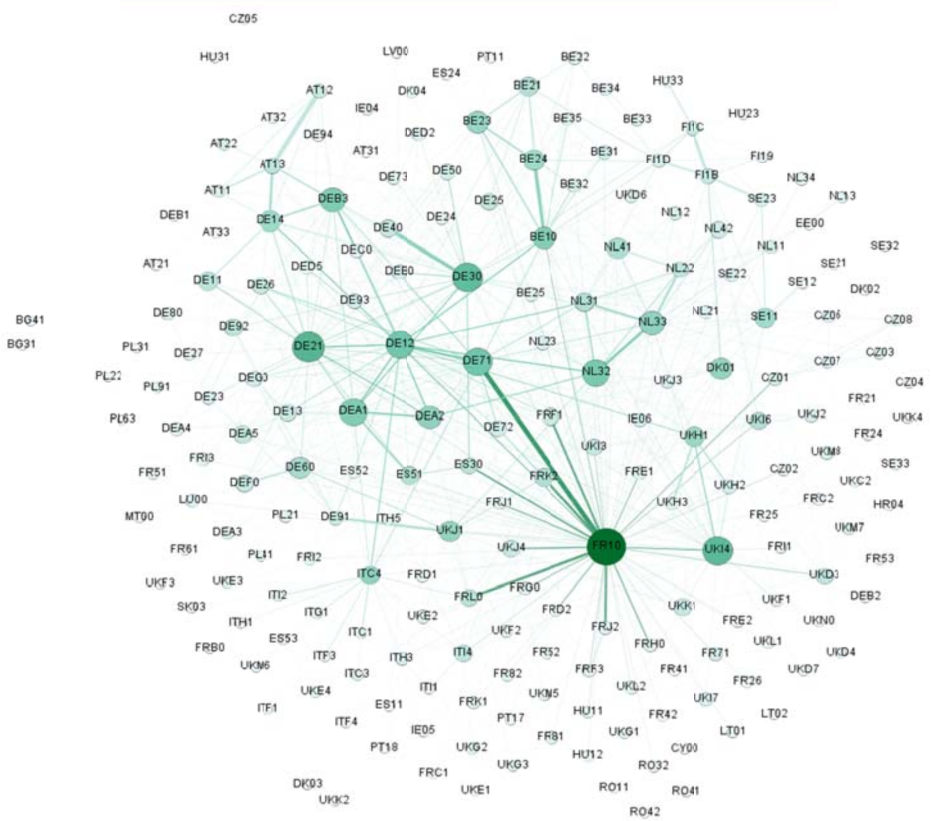
To assess the intensity of relationships within the network, the statistics reported in Table 4, i.e. the graph density, the average degree, and the average weighted degree of the network, may be profitably used. The graph density, measured by the ratio of the actual number of edges to the highest possible number of edges $N(N-1)/2$ within the network,[11] has remained unaltered throughout the considered period (2000-2016), thanks to the substantial rise of connections, despite the remarkable increase in the number of nodes N. The average degree is the ratio of total edges (in our case, couples of regions involved cross-regional CSLs) to total nodes (regions involved in CSLs). Displaying the dynamics of the average degree, Table 4 unambiguously documents that, on average, regions have linked themselves to a growing number of other regions, i.e. 7.7 regions in 2000-2004, 8.9 regions in 2005-2010 and 9 regions in 2011-2016. The average weighted degree of the network is the ratio of the total number of relationships to the total number of nodes, i.e. an index similar to the average degree but assigning different weights to edges according to the number of relationships occurring among nodes. Importantly, while confirming an increasing trend in the connection of regions to cooperate for CSLs between 2000 and 2010, the average weighted degree index highlights that after the crisis (2011-2016), a significant reduction takes place in the overall intensity of relationships within the European network.

The latter indication, consistent with the results of decreasing number of connections for key nodes, and reduction in the importance of Southern and Northern regions of the network, finds support in Figure 1, showing the graphical representation of the Biopharma CSLs network in the three periods. Figure 1 displays an overtime increase in the number of nodes (regions) plotted in the graph, confirming that the network has enlarged over time. On the other hand, the network becomes sparser, meaning that at the end of the period 2011-2016, it is somehow less dense and interconnected with respect to the other periods.

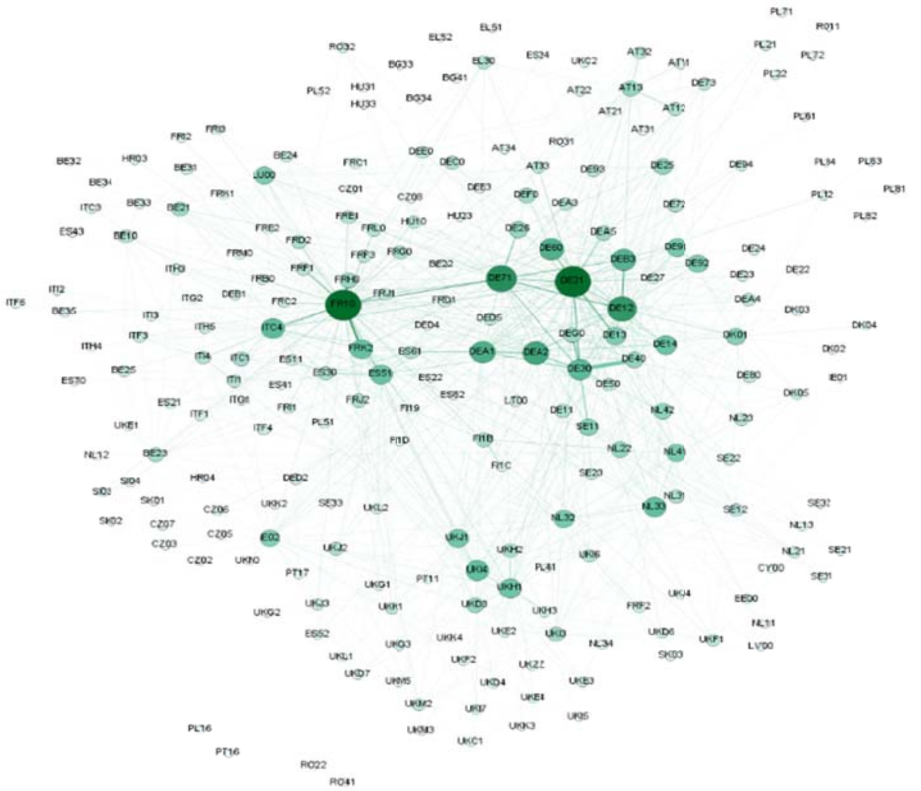
[11] The highest possible number of edges is $N(N-1)/2$, with N being the number of nodes.

Figure 1. Network representation

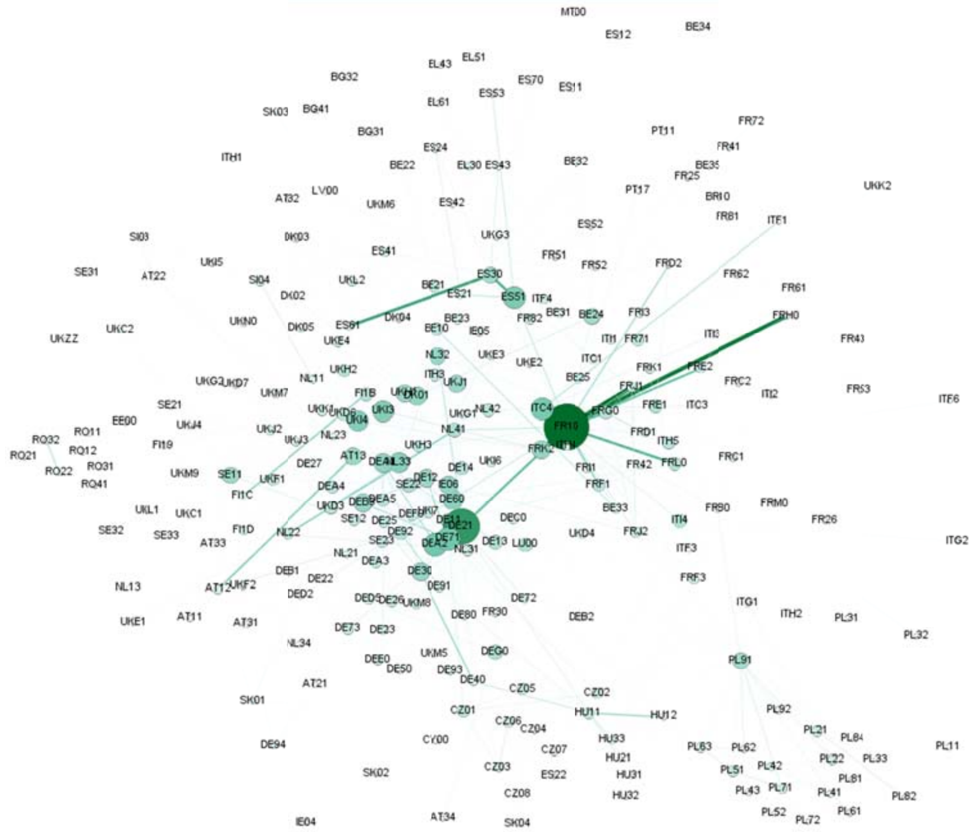
a) Period 2000 – 2004



b) Period 2005 – 2010



c) Period 2011 – 2016



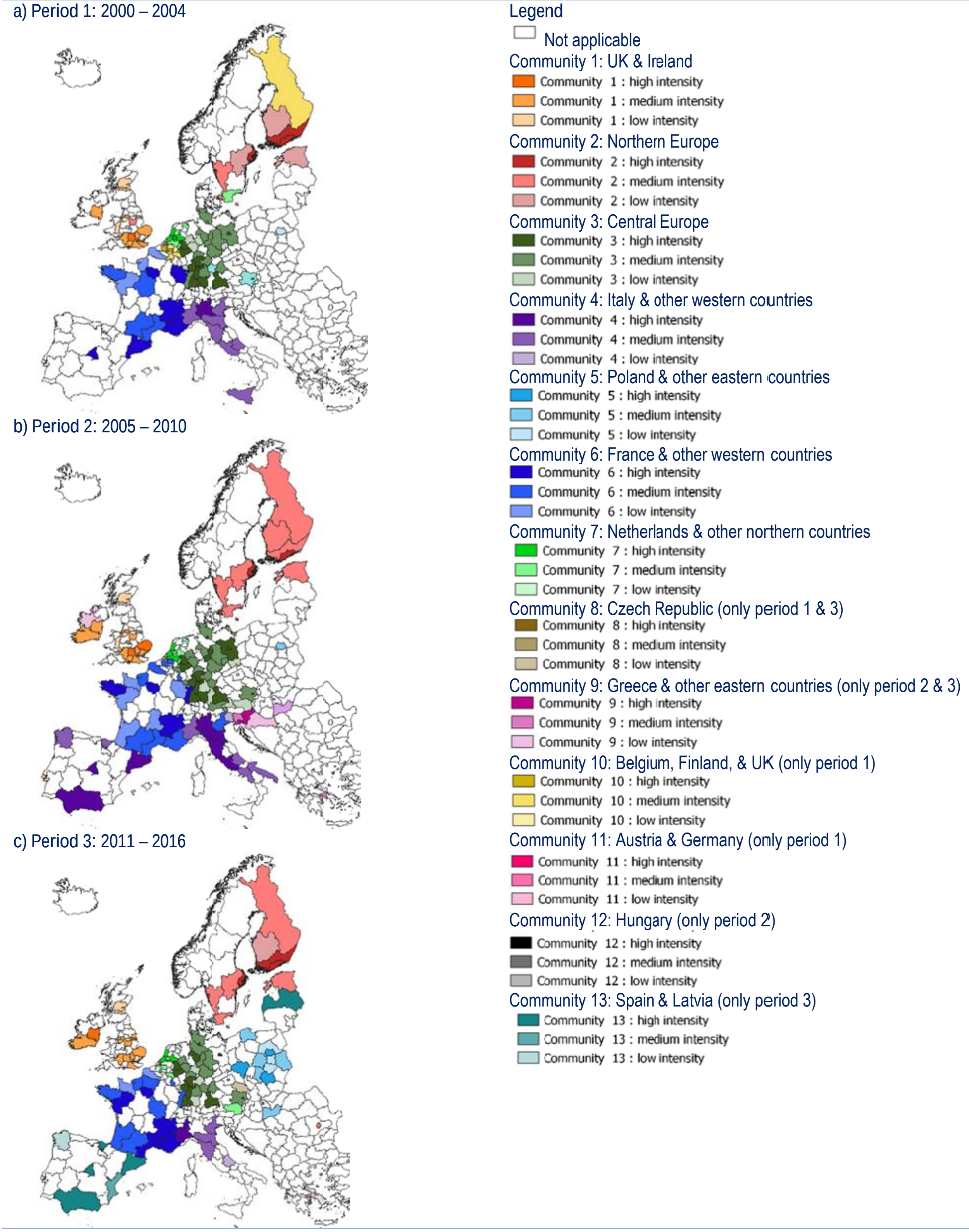
Note: The size and the darkness of the bubble is proportional to the node's eigenvector centrality, whereas the thickness and the darkness of the lines are proportional to the edge's weight

Source: Authors' elaborations based on PATSTAT, Zephyr, and SDC Platinum data

The final part of the analysis is devoted to performing a community analysis to understand better the different geographical patterns of cross-sectoral and cross-regional linkages.[12] The community analysis detects clusters of regions where CSLs are concentrated, identifying larger national or cross-border communities that are the closest linked according to the selected indicators (in our case, co-patenting, M&As and JV&As). Figure 2 illustrates the community analysis for the three periods displaying the evolution of clusters over time, the decline of some of them and the uprise of others.

[12] The suitability of the community analysis here performed is confirmed by the high measure of modularity (0.563 in 2000-2004; 0.542 in 2005-2010 and 0.620 in 2011-2016). Modularity evaluates the relative density of connections between the nodes within communities with respect to that of nodes in different communities.

Figure 2. Geographical analysis of cross-sectoral and cross-regional communities



Note: The coloured regions in the map indicate the cluster of regions with a number of cross-sectoral and cross-regional linkages above the median. Each community is indicated in different colours. Within each community, the different shades of the same colour indicate the intensity of cross-sectoral linkages for each region (high, medium and low).
Source: Authors' elaborations based on PATSTAT, Zephyr, and SDC Platinum data

Two major outcomes can be observed. The first one concerns the patterns of development of the overall network, based on the increase in the number of nodes and clusters (communities increased from 9 in 2005-2010 to 11 in 2011-2016), the reinforcement of Western and Eastern nodes and clusters, and marginalisation of some areas in the North and especially in the South of Europe. In particular, in Western Europe, the Spanish community remarkably enlarges over time, thus significantly contributing to the entire network enlargement. Between 2000-2004, only two Spanish regions were active in cross-sectoral and cross-regional operations, mostly in partnership with French regions. Between 2010 and 2016 (when the Spain and Latvia community arises, see Figure 2c), cross-sectoral operations involve ten different Spanish regions, while a substantial increase in the number of firms and employees of the biopharma sector occurs in the whole country (see data in Table 1). In the same years, in Eastern Europe, three new communities arise a cross-border community covering most of the Polish regions and two Hungarian regions, and two country-based communities located respectively in the Czech Republic and in Greece. The Polish community is particularly large, with CSLs strongly increasing over time. The other two communities are still emerging, including only a few regions centred around the capital cities, namely the Prague region for the Czech community and the Attica region for the Greek one. The observed emergence and enhancement of Eastern European regions into the EU Biopharma network might have been favoured by several factors. The 2004 and 2007 EU enlargements were likely to play a crucial role in fostering the integration of firms operating in Eastern European countries within the EU Biopharma network, and government policies effectively supported this evolution. For instance, Poland granted special attention to the Biopharma sector, considered as a priority industry, through the European Structural and Investment Funds (Polish Information and Foreign Investment Agency, 2013). Thanks to the support to investments, the Polish Biopharma industry has notably developed in the last decade, moving towards the production of innovative drugs (Tyl et al., 2018).

Conversely, in the same years, other areas and communities have lost their importance and reduced the number of cross-regional CSLs. As seen above, this is, for example, the case of some Irish, British, Scandinavian, Austrian and German regions, even when the boundaries and composition of their communities remained relatively stable over time. The case of the worst decline in CSLs (especially in co-patenting activity) concerns the Italian community, particularly the regions of Central and Southern Italy. In years 2011-2016, together with a significant drop in the number of operating firms in the Biopharma industry[13], companies and inventors operating in Campania, Apulia, Tuscany and Latium, which had increased the number of CSLs during the 2005-2010 period in particular with Spanish counterparts, strongly reduced their participation in cross-sectoral and cross-regional operations both within the national range and with non-Italian actors. The reasons for this evolution might be several: the features of industry in those regions, characterised by a dualistic structure, with relatively few high-tech producers and a large pool of traditional small-sized firms, with marginal activity in research and innovation (Leoncini et al., 1996); the scarcity of links between basic research organisations and potential users, with little incidence of public policies (Vittoria and Lubrano Lavadera, 2014); the generalised productivity slowdown of the Italian economy in the last couple of decades (Bugamelli and Lotti, 2018); the impact of the global financial and economic crisis started in 2008-2009, which significantly affected the expenditure in R&D in Italy e particularly in Southern regions (OECD, 2021).[14]

The second finding of our analysis is that in the most recent period (2011-2016), Biopharma has recorded increasing CSLs across national borders only in few regions. This is the case, for example, of some core regions of the Biopharma industry, which consolidated around three well-established cross-border communities, i.e. Germany and Austria, Scandinavia and UK and Ireland. However, in most cases, for example, France, Spain and Italy, cross-regional CSLs mainly took place within national borders. This evidence, consistent with the above-observed reduction in the overall network interconnection, suggests that in the years 2011-2016, a process of regionalisation within national boundaries of CSLs may have taken place.

Several factors can explain this trend. The increase in the number of local Biopharma firms and their upgrading in functional abilities may have induced a substitution of remote with geographically closer agents in carrying out CSLs. Also, CSLs may have been somehow affected by a more general drift toward regionalisation in inter-firm relationships, favoured by a political attitude more inclined to enhance national economies, reshoring investments, and so on.[15]

To summarising, in the period we consider the overall network has strengthened thanks to a substantial increase in inter-regional connections. The network has shown a clear tendency to enlarge toward the East (Poland) and West (Spain), with a concomitant reduction in the activity of peripheral nodes in the Southern and Northern borders of the network. Consequently, the geographic centre of gravity of the European Biopharma industry has moved eastward, with new clusters being formed in Eastern European countries, particularly in Poland, and less favourable dynamics in Western Europe, where especially Southern Italy regions are progressively losing their relevance. Finally, the network has become sparser, so that at the end of the period 2011-2016, it was somehow less dense and interconnected with respect to the previous periods.

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[13] In 2008, the number of Biopharma enterprises active in Italy was 3,999, while in 2016, that number decreased to 3,448.

[14] Between 2008 and 2011, the ratio of expenditure on R&D to gross domestic product increased by 6.60% in EU28, 6.36% in France, 7.30% in German, 24.54% in Poland and only 3.62% in Italy. On the regional detail, see Nascia and Pianta (2018).

[15] It is widely recognised how in the last decade the political climate has conditioned (and reduced) the extent of value chains and the size of international trade flows (Hoekman, 2015; IBRD & World Bank, 2017; 2019).

5. Conclusions and policy considerations

Aiming at contributing to the nascent literature on emerging industries and cross-sectoral linkages, this paper focuses on Biopharma, one of the most important emerging industries in Europe, characterised by a large and increasing number of cross-sectoral activities, as well as technological transformations led by continuous innovation. The investigation, carried out using the network analysis tools, focuses on cross-sectoral and cross-regional co-patents, M&As, and JV&As taking place in the Biopharma European network. Looking at three distinct time periods, 2000-2004, 2005-2010 and 2011-2016, the study illustrates the dynamic transformation that occurred at network, cluster and node level, to draw an overall picture of the evolution of the different geographical areas, in terms of reinforcement or weakening of agglomerations and emergence of new regional patterns.

Our main finding is that in the years we consider, European companies and researchers operating in the Biopharma industry have been increasingly involved in the cross-sectoral collaboration. In particular, the progress of Eastern Europe, Poland above all, is remarkable. As in that geographical area, Biopharma companies are organising themselves into new clusters; the overall European Biopharma industry is progressively moving its centre of gravity towards the East. At the same time, in Central and Northern Europe, core regions of the Biopharma industry have consolidated their primary role around well-established cross-border communities in Germany and Austria, Scandinavia and UK and Ireland. In Western Europe, Spanish regions have increasingly involved in cross-sectoral activities, while in Italy, central and southern regions have partly lost their relevance within the overall network. Finally, more recently, a tendency to establish more links within national borders rather than across the borders has emerged.

Considering the importance of inter-sectoral ties in steering economic development and industrial transformation through knowledge spillovers, innovation transfers, and other virtuous interactions, the geography of cross-sectoral activities is of great interest for European and national policymakers. Therefore, the analysis carried out in this paper, showing how the industrial and the technological evolution of the Biopharma industry is affecting European regional agglomerations, can support policymakers in understanding potential future developments of the industry and stimulating firms to collaborate. In this light, future research could consider a longer time horizon and combine technological with geographical data to single out each community's technological trajectory and sectoral focus. A finer-grained analysis investigating each community's technological specialisation might inform policymakers about the geographical structure of the European Biopharma industry and about technological new trends occurring in each community. This might, in turn, facilitate the differentiation of policy efforts according to the specific features of each regional community in terms of industrial development and technological knowledge.

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