Exploring the relational dimension in a smart innovation ecosystem: a comprehensive framework to define the network structure and the network portfolio

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Abstract

This study analyses the relational dimension and the knowledge transfer mechanisms in an innovation ecosystems (IEs), assuming that the bottom-up creation of synergies and cooperative mechanisms between local actors are the drivers of a regional smart growth. More specifically, the study explores the configuration of the network structure and the variety of inter-organizational relationships in a case of a smart IE by capturing the heterogeneous nature of IE demography, whether most studies limit their analyses to inter-firm relationships and at the node-level. Secondly, the paper provides insights into the network portfolio composition, which has been underexplored in IE literature, allowing for the identification of those relationships considered more fruitful to enhance innovation processes from a local perspective. To capture both aspects of IE's relational dimension (i.e. network structure and network portfolio of relationships) our paper adopts an explorative approach, by taking evidence from the empirical study of the Biopharma IE in Greater Boston Area (GBA), which has been exemplified as a successful case. Our empirical study combines two methods, namely social network analysis and expert interviews. Firstly, we conduct a social network analysis to gain insights about the optimal network structure and secondly, we conduct a round of semi-structured interviews with key stakeholders in the ecosystem to explore the characteristics of the desirable network portfolio. Our findings show that a smart IE presents an open network structure with structural holes, a high level of modularity and a portfolio of relationships that privileges informal and non-redundant ties within small communities focused on specific themes.

1. Introduction

The debate on regional growth has been recently characterized by the spread recourse to the concept of *innovation ecosystem* (*henceforth* IE) defined as: "*a network of interconnected organizations,*

organized around a focal firm or a platform, and incorporating both production and use side participants, and focusing on the development of new value through innovation" (Autio and Thomas 2014). Building on this idea, literature has been concerned with an "*explosion of studies related to ecosystems*" (Audretsch et al. 2019 p. 322) that contributed to the scholarly discourse from different angles. The *Regional Ecosystem approach* emphasizes the importance of spatial boundaries and describes the ecosystems by its economic activities (Acs et al. 2017), implementing the ecosystem metaphor to refer to network externalities in terms of complementarity of physical, human, and intellectual resources, for a specific market or niche where large firms, academic institutions and government policies are the most central actors in developing the system and where innovation is the ecosystem's output (Fritsch and Slavtchev 2011; Cooke and Leydersdorff 2006; Asheim and Isaksen 2002; Lau and Lo 2015). The *entrepreneurial ecosystem approach* (Audretsch et al. 2017) has been defined as "*a set of interdependent actors and factors coordinated in such a way that they enable productive entrepreneurship*"(Stam 2015 p. 1765)". Despite the focus on the external business environment common to other approaches (as clusters, industrial districts, innovation systems and learning regions) the entrepreneurial ecosystem approach sees in the entrepreneur, rather than the firm, the main focal point. Differently from other approaches, the entrepreneurial ecosystem perspective considers entrepreneurship non only as a main output of the system and performance measure, but also considers entrepreneurs as key players in the creation and development of the system itself (Cunningham et al. 2017; Acs et al. 2017; Audretsch and Belinski 2017; Stam 2017; Audretsch and Link, 2017; Corrente et al. 2018). Finally, another recent approach i.e., *University ecosystem*, extends the well-established role of Universities in stimulating the regional economic growth, to that of providing leadership in advancing the entrepreneurial society (Audretsch 2014). This literary strand examines the role of individual *knowledge intermediaries*, as technology licensing offices and incubators, that are in support of academic entrepreneurship in establishing spinoff companies or promoting patenting activities based on university research (Backs et al. 2018; Hayter 2017; Lehmann, and Menter 2016; Maia and Claro 2013). However, the approaches described above tend to limit their focus only on three types of actors namely, firms (or entrepreneurs), government and universities typical of the triple helix framework (e.g. Etzkowitz, 1993; Etzkowitz and Leydesdorff, 1995; Budden and Murray, 2015) which are either "*geographically localized or strategically linked to focus on developing a specific technology.* (Jackson 2011, p.3). In contrast, more recent studies emphasize that a "*smart"* innovation ecosystem should rather take the shape of a *quintuple helix*, by adding to the well-known three pillars of the triple helix model, a fourth and a fifth dimension i.e., the *civil society* and the

environment to ultimately achieve a regional smart growth (Carayannis and Campbell, 2009, 2012; Carayannis et al., 2016; Carayannis and Rakhmatullin, 2014). Indeed, smart growth represents today a key topic for both academics and policy makers, with special regard to those engaged in the implementation of the economic development policies of "Smart Specialization Strategy". More specifically, the idea of a smart specialization strategy refers to those national or regional innovation policies aiming at building the regional competitive advantage by developing and matching research and innovation to business needs in order to address emerging opportunities and market developments in a coherent manner, while avoiding duplication and fragmentation of efforts (EU, 2014). This is based on the idea that the region's ability to create the conditions for the emergence of collective learning mechanisms and the ability to conduct research and innovation in multi-dimensional networks are basic requirements of modern societies. The concept of *smart innovation ecosystem* well reflects the principles of the "*smart specialization strategy*" as it refers to a system aimed at achieving sustainable regional growth by leveraging on a horizontal network of relationships that includes not only academic, entrepreneurial and government actors but also the active engagement of civil society and environmental organizations (Carayannis and Rakhmatullin, 2014). Nevertheless, the simple co-presence in a territory of these different types of actors is not a sufficient condition to generate a real smart growth, which requires an actual collaboration among the actors involved (Carayannis and Grigoroudis, 2016). As a result, the assessment of the level of effective collaboration among the regional actors becomes key to understand how "smart" a region is and, more importantly, how to leverage its potential to ultimately define the quality and effectiveness of the innovation ecosystem itself. Consequently, assuming that the mere co-location of innovative actors *per se* does not necessarily identify an IE as such (Russell et al., 2015) and that the bottom-up creation of synergies and cooperative mechanisms between local actors are the drivers for the well-functioning of an IE (Ahuja, 2000), our paper tries to investigate this aspect by analyzing the relational dimensions of a smart IE. In particular, our paper tries to shed lights on two different analytic dimensions: the level of connectivity among the system's actors (network structure) and the portfolio of different types of relationships and forms of cooperation that local actors put in place to produce innovation (network portfolio). Regarding the first dimension, extant studies fail to provide a common agreement about the optimal configuration of network structure, especially regarding its level of closure and openness (Aharonson et al., 2008; Gray et al., 1996; John and Pouder 2006). On the other hand, with regard to network portfolio, most contributions tend to limit their analyses to the observation of formal inter-firm relationships, thus failing to highlight the variety of knowledge channels and the heterogeneous actors' composition,

which are two typical features of innovation ecosystems (see for example. Ahuja, 2000; Eisingerich et al., 2012; Balland et al. 2013; Li et al. 2013; Xie et al., 2014). In order to fill these gaps and in an attempt to capture both aspects of IE's relational dimension (Network structure and Network Portfolio composition), this work aims to answer to the following research questions: (RQ1) What is the configuration of the network structure of a smart IE? And secondly, (RQ2) What is the portfolio of relationships implemented in a smart IE?. To this purpose, our paper adopts an explorative approach by deriving propositions from the empirical study of the Biopharma IE in Greater Boston Area (GBA), which has been exemplified as a paradigmatic case of study in terms of IE successful performance. Our empirical study combines *social network analysis* (SNA) and *expert interviews* that depict a smart IE as characterized by an open network structure and a portfolio of relationships that privileges informal and non-redundant ties within small communities focused on specific themes. The remainder of the paper is organized as follows: section two reviews extant contributions on IE relational dimension. Section three illustrates the research strategy adopted for addressing the theoretical gap and the research techniques implemented for the empirical case study of the Greater Boston Area Biopharma IE. Main results are reported and discussed in section four, before concluding.

2. Theoretical Background

Since early 90s, scholars have started to explore the relational dimension of IE by focusing on two main aspects: the structure of the network of relationships within an IE, and the types of relationships implemented by the different IE's actors. The debate about which relational characteristics ensure a better IE performance has been characterized by contrasting visions from the beginning. The seminal work of Saxenian (1994) represents a first attempt in this sense, suggesting that the more decentralized and horizontal industrial system of Silicon Valley outperformed the Route 128 ecosystem, which, conversely, was recognized as a network dominated by a few large firms, with a high degree of vertical integration characterized by practices of secrecy and corporate hierarchies. The openness argument is also supported by Bresnahan et al. (2001) that consider international links (which are used as a proxy for the level of openness of the network structure) as a key characteristic common to many successful regional clusters around the world. Other studies have recognized that the successful performance of a certain cluster is not necessarily associated to a specific network configuration, as this latter varies across industries and regions (Gray et al., 1996) and it is shaped by the modalities through which

resources are accumulated, capabilities are cultivated (John and Pouder, 2006).Later on, scholars from innovation systems literature have started to empirically study the relational dimension of IE in a more systematic way, by adopting a social network approach (Ter Wal and Boshma 2009; Crespo et al. 2014). These more recent studies analyze both the network structure and the network portfolio and will be reviewed in the next two sub-sections.

Network structure

Network literature is traditionally characterized by two contrasting visions about the desirable structure of networks, namely the *Coleman's network closure* and the *Burt's structural holes* arguments. The debate builds upon the identification of which configurations of network structures are preferable in order to create social capital. Both visions agree on the definition of social capital as a type of capital that can generate a competitive advantage for specific individuals or groups in pursuing their ends. However, the debate contrasts the closure argument Coleman (1988, 1990), according to which social capital is more likely to be created by a network where nodes are strongly connected to each other, and the structural hole argument that supports the idea that social capital is generated through a network where nodes can broker connections between otherwise disconnected segments (Burt, 2002). While adopting a network approach for the study of industry-related networks, the influence of the network structure on innovation performance is not fully explored. Indeed, a significant part of existing literature focuses the analysis at the organizational level (Casanueva et al., 2013), suggesting that the organization's position in the network (expressed in metrics of centrality) influences its innovative performance as it allows a greater access to information (Gulati, 1999; Owen-Smith and Powell, 2004); generates positive effects on organizational learning and reputation (Powell et al., 1996) and increases the number of its direct ties (Ahuja, 2000). More recent contributions that emphasize the geographical dimension, provide a wider range of indicators besides the organization's position in the network, and include structural metrics at the network-level to assess the performance of the cluster as a whole (Balland et al., 2013; Balland, 2012; Capaldo and Messeni Petruzzelli, 2014; D'Este et al., 2012; Dahl and Pedersen, 2004; Powell et al., 1996; Still et al., 2013; Ter Wal, 2014; Cassi and Plunket, 2014). In other cases, a combination of both structural and positional metrics have been used to capture insights at both node and system level (Ahuja, 2000; Broekel and Muellerb, 2017; Giuliani, 2013; Kajikawa et al., 2010; Owen-Smith and Powell, 2004; Russell et al., 2015; Salavisa et al., 2012). As for the structural perspective, the majority of the studies opt for a closed approach (Balland et al., 2013;

Balland, 2012; Capaldo and Messeni Petruzzelli, 2014; Cassi and Plunket, 2015; D'Este et al., 2012; Owen-Smith and Powell, 2004; Powell et al., 1996; Russell et al., 2015; Still et al., 2013) while the open argument has been chosen as a theoretical standpoint in a fewer number of studies (Broekel and Mueller, 2017; Casanueva, 2014; Dahl and Pedersen, 2004; Ter Wal, 2014). In one case, a Small World perspective is adopted (Kajikawa, 2010). Finally, Salavisa et al., (2013) and Giuliani (2013) present a mixed approach able to combine the points of strength and the pitfalls of both views.

Network portfolio

The research body focused on the portfolio of relationships, tend to limit its focus mainly on inter-firm relationships, with the exception of a few studies that, by assuming the heterogenous nature of IE actors, analyze relationships among actors of different nature. A large part of the studies are focused on the effects that the IE's relational dimension exerts on the innovative performance of the firms embedded in it (Ahuja 2000; Xie et al 2014; Li et al 2013). Only a few attempts have been made in order to provide a more comprehensive view about the variety of relationships existing within an IE. As a way of illustration, Eisingerich et al. (2012) explore the nature of factors influencing firms' innovativeness in clusters across different regions and sectors. The study has been conducted in 10 industrial clusters based in Austria and Canada where the authors observe either hierarchical network structures dominated by incumbents in mature industries (automotive and chemicals) and non-hierarchical clusters of younger industries (IT and Biotech) characterized by "firm turnover and smaller firms at the same production stage" and associate the industry maturity to the relative impact of different knowledge channels within the cluster. More precisely, the authors find that while firms' innovativeness in non-hierarchical network structures benefit more from knowledge spillovers from university, firms belonging to more mature industries embedded in hierarchical structures benefit more from inter-firm cooperation and intra-organizational structures that support their business activities. From a similar sectorial perspective, Balland et al. (2013) explore the emergence of inter-firm networks in the video game industry by investigating product co-development inter-firm relationships, suggesting that – as the industry matures – firms tend to prefer to partner over short distances and with organizations that are cognitively similar. Owen-Smith and Powell (2004) are among the first to consider the network organizational heterogeneity as an additional structural property in innovation networks, by analyzing contractual linkages among dedicated biotech firms, public research organizations, VC firms, government agencies and biopharma companies in the Boston biotechnology innovation system, suggesting that the node's organizational form alters the flow of information

through a network. More specifically, they find that the extent to which information is transmitted in a network is a function of whether the key nodes that anchor a network pursue private or public goals, suggesting that institutional and legal arrangements that secure information transfer result from the participants' commitment and effort. Similarly, Broekel and Mueller (2017) study the characteristics of critical links in technology-specific knowledge networks in Germany by empirically analyzing the links among universities, firms, research institutes and other types of organizations and show that first, critical links tend to be formed among regional gatekeepers that offer related knowledge resources and that secondly, the links bridge institutional distances by exploiting the benefits of geographic and social proximity. Moreover, only a limited number of scholars have chosen to address the empirical challenges of considering informal, rather than contractual, relationships in their empirical studies, with the exception of Dahl and Pedersen (2004), who investigate the regional cluster of wireless communication firms in Northern Denmark to study the effect of informal networks among engineers on innovation system growth dynamics, suggesting their key role in knowledge diffusion within the system. Finally, one of the only attempts to provide a more comprehensive picture of innovation systems' relational dimension has been provided by Salavisa et al (2012) who explore networking variety in biotechnology and software innovation ecosystems by considering - at the same time - the different role of both formal and informal inter-firm relationships to access both knowledge and complementary assets, suggesting that their effect is mediated by different knowledge bases. More precisely, the authors find that, as far as biotechnology is concerned, the informal knowledge network tend to be structured in sub-groups with frequent inner connections, i.e. *knowledge epistemic communities* and that university plays a key role as an *informal knowledge provider* thanks to its bridging position among the different communities. From the review of the literature above, it emerges that most contributions employing a network approach for the study of IE performance find contrasting results regarding the effect of network structure. Regarding the network portfolio, existing studies tend to limit their analysis to inter-firm relationships, thus overlooking the heterogeneous nature of the ecosystem's components, which is an important driver for the production of new knowledge. Secondly, these studies tend to privilege the analysis of strong and formal ties, thus overlooking the potential of informal and weaker ties.

3. Methodology

3.1. The methodological approach and research design

To answer to our research questions we adopt an exploratory single case study analysis of the Greater Boston Area (GBA) Biopharma ecosystem. Single case study analysis is particularly useful to deeply understand a complex phenomenon including different dimensions that are not easy to explain through quantifiable variables, as for the study of the IE relational dimension. Despite the advantages above, a single case study analysis has as a main limitation the lack of generalizability of the research results. This limitation can be partially overcome by an appropriate selection of the case. As a method of case study selection, we used the paradigmatic case method (Flyvberg, 2006), which refers to the careful selection of a prototypical case that can reveal key elements of a phenomenon under consideration. Through the observation of a pivotal case study that meets all conditions that we are willing to explore (Yin, 2003; Streb, 2010), this approach allows to formulate propositions to be tested in future research.

The Greater Boston Biopharma ecosystem

The Greater Boston Biopharma ecosystem is along with the Silicon Valley one of the oldest, best-known and most successful IE in the US. Moreover, it is together with San Francisco, one of the two key geographical clusters that nowadays dominate the biopharma landscape thanks to a unique blend of science, entrepreneurship skills, risk-taking culture and spatial concentration especially in the City of Cambridge, where most biotechnology-related companies cluster around Kendall Square, which hosts, among the others, the Massachusetts Institute of Technology (Saxenian, 1994; Breznits and Anderson, 2005; Owen-Smith and Powell, 2004). The rise of biotech industry in the Greater Boston Area (GBA) traces back to the 1970s, with the development of genetic engineering and the establishment of Biogen through the endorsement of the Cambridge City Council after having realized the potential of this new field during a time in which molecular biology was predominant. However, it was not until more recent years that the cluster reached its biggest growth. In 2008, the governor of Massachusetts promoted the *Massachusetts Life Sciences Act* that promised to invest 1 billion dollars for the development of the biotech industry. This led to a tremendous increase of jobs, capital flows and buildings that contributed to turn the area in one of the leading US Life Science cluster for the number of patent ownership per capita, venture capital funding and number of IPOs (JJL U.S. Life Science, 2016). The region is home to many of the leaders in tech and life science (eighteen out of the top twenty drug companies have a major presence in GBA) as well as world-class academic and research institutions as Harvard and MIT. The area hosts approximately 250,000 students across 52 higher education institutions and can rely on the largest concentration of life science researchers in the country, as well as world-class medical

facilities, including the top three NIH-funded hospitals. As a result of direct access to top talent, the GBA ecosystem has attracted a dynamic community of investors. More precisely, VC funding is of 2,580 millions of dollars, which represents the 38% of the total funding of United States in GBA, which in turn, makes the area particularly attractive to innovative entrepreneurs (JJL U.S. Life Science, 2016).

In order to explore the characteristics in terms of both network structure and network portfolio in a case of smart innovation ecosystem we combined a round of expert qualitative interviews with a social network analysis (SNA) of a sampled network localized in GBA. As illustrated in previous paragraphs, the range of innovation- driven relationships include both formal and informal relationships, which are generally excluded from quantitative relational datasets used for SNA. On the other hand, the exclusive use of expert interviews would not allow to gain a comprehensive view about the structure of the network. To overcome these limitations, we complemented both techniques to explore the characteristics of the relational dimension of the innovation ecosystem.

Expert interviews

Expert interviews have been organized and carried out with 9 key informants that occupied leading positions in different organizations having a central role in the IE network. The interviewed organizations were selected in order to ensure that the variety of the ecosystem's population was fairly represented. Therefore, our sample of key informants includes (i) 1 academic institution with a propulsive role in the cluster development; (ii) 1 regional government agency with a focus on biotech industry; (iii) 2 large biopharmaceutical companies (one that de-localized part of its core R&D activities in the area and one that originated in the area); (iii) 1 medium biotech firm; (iv) 4 small biotech firms in pre-incubation, incubation, start-up and growth phases, respectively (De Cleyn and Braet, 2006). The interviewed experts were selected considering their role and in particular, their ability to answer to questions regarding the relationships that their organizations had with other IE members. The investigation method includes the conduction of in-depth interviews with at least one individual in charge of managing R&D cooperation processes within his organization. The list of participants who took part in each interview is reported in Table 1. The interviews have been conducted directly by the authors at the organization's facilities following a predefined protocol. First, by following the classification proposed by Perkmann et al. (2013), each interviewee was provided with a

list of common inter-organizational cooperation practices in the biotech industry and was asked to discuss those types of relationships that were more frequently implemented in their innovation processes and which types of partners were involved in their alliances. Secondly, we asked them about the location of their partners to gain insight about their tendency to establish partnerships with co-located organizations and investigate the main advantages of collaborating with partners in close proximity. Finally, the interviewees were asked to express their opinion about the quality of the relationships, highlighting the main advantages and disadvantages in terms of knowledge transfer. The interviews have been conducted following a narrative approach (Polkinghorne, 1988; Czarniawska, 2004) where the respondents were asked to freely share their opinions with a minimum number of interruptions by the interviewer, which allowed us to learn more about actual events and prevent personal views and theoretical perspectives from interfering with data collection efforts. The interviews were recorded and transcribed as part of the data analysis process. In addition, relevant written documents were collected from both the interviewees and other sources, such as press articles and the internet. By combining the above sources of information, we have been able to reconstruct the more common practices of inter-organizational relationships and identify the relationships that are considered to be more important for the transfer of knowledge.

Table 1. Expert interviews – List of participants

| Position	Organization	Stakeholder
Full Professor	*MIT Dept. of Chemical Engineering*	Academic institution
General Counsel and Vice-President for Academic and Workforce Program	*Massachusetts Life Science Center*	Government
Research Associate	*Novartis*	Large biopharmaceutical companies (foreign)
Senior Vice President, R&D Strategy and External Innovation	*Ironwood Pharmaceuticals, Inc.*	Large biopharmaceutical companies (local)
Alliance Manager	*Alnylam*	Medium biotech firm

Chief Executive Officer	*Revive-med*	Small biotech firm Pre-incubation stage
Chief Executive Officer	*Angiex*	Small biotech firm Incubation stage
Chief Executive Officer	*Kymera Therapeutics*	Small biotech firm – Start-up stage
Chief Executive Officer	*Obsidian*	Small biotech firm Growth stage

Source: authors' own elaboration

Social Network Analysis

To the purpose of the Social Network Analysis, we used information from the MassBio database the freely available membership directory of the Massachusetts Biotechnology Council, that includes the whole population of the subjects ranging from academic hospitals and non-profit organizations to pharmaceutical biotech companies and capital providers, that are dedicated to advancing cutting-edge research in life science industry in Massachusetts. MassBio includes 975 members and provides information on their location, typology and area of specialization. In order to respect the geographical boundaries of the IE concerned by our study, we selected from MassBio population only those organizations with headquarters or branch offices having mailing addresses in the metropolitan areas of Greater Boston and specialized in drug development. The spatial identification of each area included the suburban city names associated with respective identification of that metropolitan area, counting more than 50,000 inhabitants (U.S. Census Bureau, 2015). The final sample counts 450 organizations distributed as follows: 85 academic hospitals & non-profit organizations (universities, research institutes, hospitals, government agencies, incubators); 61 capital risk providers (venture capitalists, corporate venture capitalists, hedge funds, private equity firms); 304 pharma-biotech firms (62 Large firms, 198 SMEs, 44 Start-ups). Figures 1 and 2 report the geographical distribution of our sample and main areas of specialization of nodes' activities.

Figure 1. Geographical distribution – MassBio members in GBA (2012-2017)
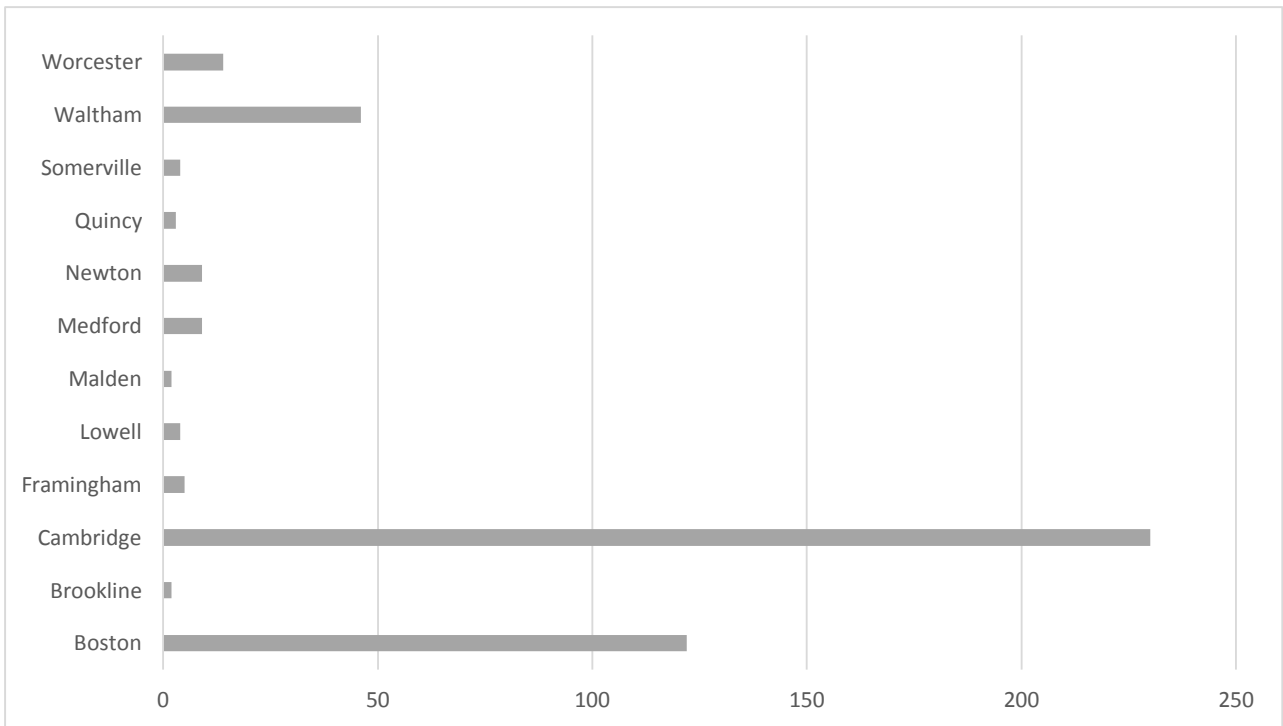
Source: authors' own elaboration from MassBio

Figure 2. Areas of specialization- MassBio members in GBA (2012-2017)
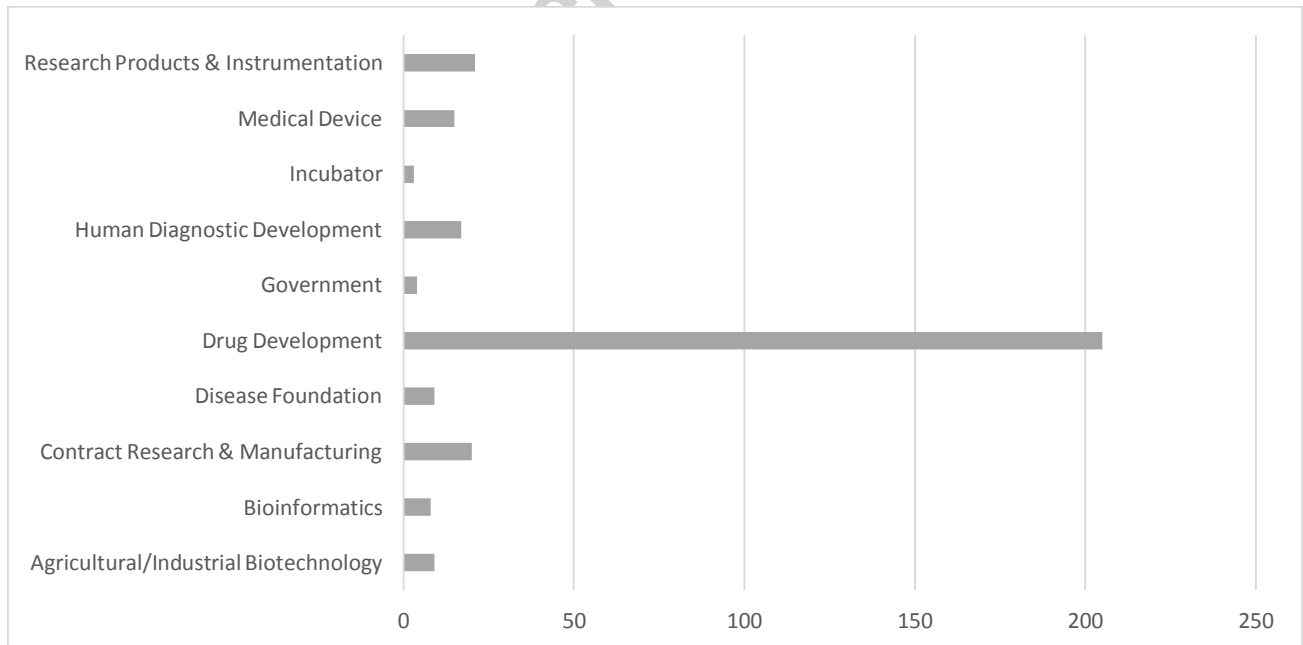
Source: authors' own elaboration from MassBio

To reveal insights about the network structure of the ecosystem under analysis, we mapped the relationships occurring among the above sampled organizations by relying on two sources of relational data. More precisely, to collect data on venture deals, we used the *Preqin Dataset* (Preqin Ltd. 2017), which is a comprehensive and historical database on the private equity industry offering detailed information and analytics on firms, funds, deals and portfolio companies dating back to 1999 on over 5,000 funds and 11,000 hedge funds. We selected venture deals (i.e. Series A-E/Round 1-5; Grant; Seed; PIPE; Add-on; Venture Debt) between portfolio companies and investors located in Massachusetts (U.S.) completed within the last five years (2012-2017) in biotechnology and pharmaceutical industries and matched with our sample. To gather information on the other kinds of formal relationships, i.e. R&D cooperation partnerships (including Trial Collaboration); licensing agreements (including reverse licensing); purchase of intellectual property (including product or technology swap; spin-out and spin-off; joint ventures), we collected data from the *Strategic Transactions Database* (Pharma & MedTech Business Intelligence) that summarizes deals by type, industry and sector from 1995 to date. We collected this information within 2012 – 2017 time frame. We have finally integrated these two databases into a single dataset on networks consisting of 450 nodes and 323 links. The links are non-directed in order to measure small world properties (Kajikawata, 2010). In total, we observed 148 venture deals and 141 strategic alliances (Table 2).

Table 1. Data sources

	Preqin dataset Preqin Ltd. 2017	**Strategic Transactions Database** (Pharma & MedTech Business Intelligence)
Source of Data	Comprehensive and historical data on the private equity industry offering detailed information and analytics on firms, funds, deals and portfolio companies dating back to 1999 on over 5,000 funds and 11,000 hedge funds	Summaries of deals by type, industry, and sector. 1995 to date.
Ecosystem entities	BigPharmas, Biotech firms, Start-ups; Risk Capital providers	BigPharmas, Biotech firms, Start-ups; Risk Capital providers; Academic, Hospital and non-profit institutions

	Venture deals (148)	Strategic Alliances (141)
Types of relationships	between firms and investors co-located in the GBA	R&D and Marketing – Licensing; Purchase of Intellectual Property; Spin-Out; Spin-Off; Trial Collaboration; Reverse licensing; Product purchase; Product or Technology Swap; Joint Venture; Intra Biotech Deals; Marketing-Licensing

Source: authors' own elaboration

To present data in a visual form we used *NodeXL*, an interactive network analysis software that implements a set of key functionalities for visual network analytics and metrics computation. We used a force-driven algorithm where nodes repel each other and edges pull the connected nodes together to gain insights on the spatial structure of relationships (Russell et al., 2015). In graph theory, force-driven layout reveals the macro-level structure of the network including the key clusters, the key brokers in the network, as well as possible structural holes (Burt, 2002). Also, color-coding was added to provide information about the frequency of the tie (measured by counting the number of interactions in the referred time-frame). Tie data allowed us to calculate measures of network structure that we used to evaluate the level of embeddedness of the network and to classify individual ties by their type: (i) R&D strategic alliances (i.e. R&D co-development and clinical trials), (ii) venture deals, (iii) joint ventures, (iv) IP transfer (which includes licensing agreements, product purchase, technology swap and acquisition of intellectual property rights); (v) spin-off/spin-out. Our final network counts 166 connected nodes and 323 edges, in which venture deals represent the most frequent type of interaction (56%), followed by R&D strategic alliances (21%) and IP transfer (21%) Finally, joint ventures and academic spin-offs / corporate spinouts represent only the 2% of the network portfolio, each..

3. Findings

Network structure

Table 3 reports the top twenty actors that occupy the focal positions in the network in terms of degree centrality, betweeness centrality and closeness centrality. In our sample, top positions in terms of centrality are occupied mainly by large pharmaceutical companies with a venture arm (e.g. *Astrazeneca Pharmaceutical, LP; Pfizer, Inc.; Celgene*) and large venture capital firms (e.g. *New Entreprises*

Associates; Third Rock Ventures; Polaris Partners). Similar results are obtained by identifying the top 20 actors for betweeness centrality but, differently from degree centrality's top positions, the list of actors with the greatest level of betweeness centrality includes, apart from big pharmas and venture capital firms, also smaller biotech firms and startups (e.g. *Catabasis Pharmaceuticals; Syndax Pharmaceuticals; Unum Therapeutics; Neon Therapeutics*). A different hierarchy is achieved by computing metrics of closeness centrality. Top positions are in this case occupied by smaller manufacturing biotech firms (e.g. *Gen9, Inc.; Ginkgo BioWorks; GreenLight Biosciences*) and to a lesser extent by big pharmas and venture capital firms (e.g. *Pfizer, Inc., Moderna, AstraZeneca Pharmaceuticals LP, Rhythm Pharmaceuticals*, *Inc., Merck & Co., Inc., Wellington management*).

Table 3. Top 20 actors for centrality scores – Greater Boston Area (2012-2017)

Vertices	Degree Centrality	Vertices	Betweeness Centrality	Vertices	Closeness Centrality
AstraZeneca Pharmaceuticals LP	12	AstraZeneca Pharmaceuticals LP	1640,51	Gen9, Inc.	1
Third Rock Ventures	12	Moderna	1559,50	Ginkgo BioWorks	1
Pfizer, Inc.	12	RA Capital	1481,03	GreenLight Biosciences	1
Celgene	11	Ra Pharma	1391,16	Kodiak Venture Partners	1
Moderna	9	Third Rock Ventures	1348,30	Rapid Micro Biosystems, Inc.	1
New Enterprise Associates	9	Pfizer, Inc.	1324,32	TPG Biotech	1
Fidelity Management & Research Company	9	Rhythm Pharmaceuticals, Inc.	1204,02	INVESCO Asset Management	0,16
CRISPR	9	Celgene	1197,55	SciFluor Life Sciences, LLC	0,14
Unum Therapeutics	8	New Enterprise Associates	1140,36	Vedanta Biosciences	0,14
Novartis	8	MPM Capital	1139,84	Allied Minds	0,1
AbbVie Biotech Ventures	8	Lightstone Ventures	1029	PureTech Ventures	0,1
Merck & Co., Inc.	8	Fidelity Management & Research Company	990,36	Pfizer, Inc.	0,002
MPM Capital	7	Wellington management	965,92	Moderna	0,002
Wellington management	7	CRISPR	958,27	AstraZeneca Pharmaceuticals LP	0,002
Syndax Pharmaceuticals	7	Catabasis Pharmaceuticals	899	Rhythm Pharmaceuticals, Inc.	0,001

Alexandria Venture Investments	7	Syndax Pharmaceuticals	838,57	Merck & Co., Inc.	0,001
Atlas Venture	7	Unum Therapeutics	792,34	Wellington management	0,001
Sanofi Genzyme	7	Neon Therapeutics	720,94	Novartis	0,001
Polaris Partners	7	Novartis	685,48	WaVe Life Sciences	0,001
RA Capital	6	Alexandria Venture Investments	671,87	Syndax Pharmaceuticals	0,001

Table 4 reports network structural metrics of density, average degree, modularity and small worlds properties (average path length and clustering coefficient). Our analysis shows that GBA Biopharma IE presents a low value of density (0,0026) and a low-medium average degree value (1,178). Also, the network presents a high number of connected components (289) where modularity scores 0,510. The GBA innovation ecosystem presents relatively high values of average geodesic distance (4,428), and relatively low for clustering coefficient score (0.014). Visualization of the GBA network is provided in Figure 3 that highlights the tendency of forming dyadic and triplets forms of interactions and includes labels for the most central actors. However, due to the lack of exact benchmark parameters for network structural metrics in the network literature, these results mean to be taken as a reference for future comparative analysis.

Table 4. Social Network Analysis Metrics - Greater Boston Area (2012-2017)

# nodes	444
# edges	323
Ratio edge-to-node	1,41
Network Diameter	13
Average Degree	1,178
Graph Density	0,0026
Modularity	0,510
Connected components	289

Avg. Clustering Coefficient	0,014
Average Geodesic Distance	4,428
Average Betweenness Centrality	91,827
Average Closeness Centrality	0,015
Average Eigenvector Centrality	0,002

Source: authors' own elaboration

Figure 3. The GBA Biopharma IE

Social media network connections
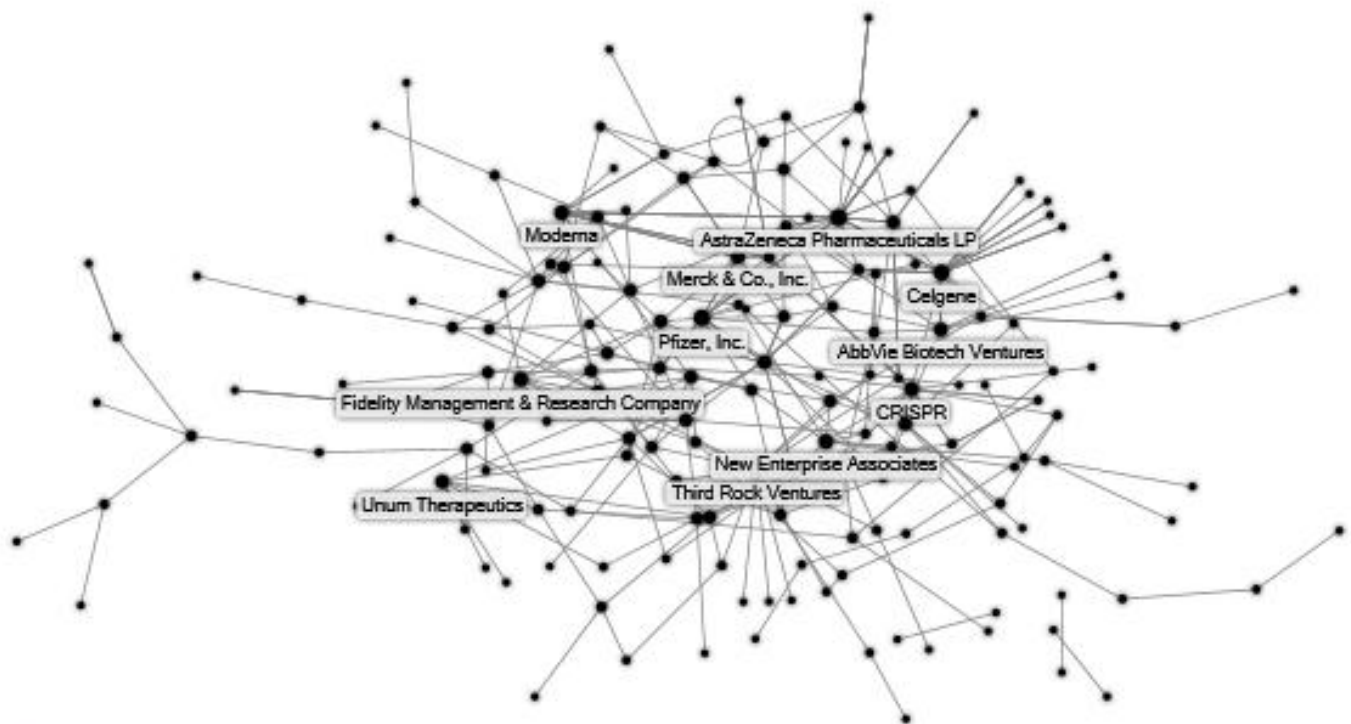
Vertex Properties

1   12

Degree   Size

Created with NodeXL Basic (http://nodexl.codeplex.com) from the Social Media Research Foundation (http://www.smrfoundation.org)

Network portfolio

From the analysis conducted on the GBA Biopharma ecosystem, it emerged that the most frequent practices of innovation- driven interactions, including informal relationships are*: (i) Value Added Supply Agreements (ii) Venture Capital and Seed Investments (iii) Agreements for the Access and Use of Infrastructure (iv) Co-participation in Thematic Associations and Symposia (v) Board Interlocks (vi) Formal and Informal Industry-University Agreements for the Mobility of Human Resources (vii) Sponsored Research (viii) Intellectual Property Transfer* and *(ix) R&D Strategic Alliances*.

As for the contribution of the specific type of relationship to the knowledge transfer, some relationships seem more effective than others. With regards to *Co-participation in Thematic Associations and Symposia*, as in the case of the Neuroscience Consortium - which was created by Mass Life Science with the aim of filling the gaps in research funds through the organization of periodical operative meetings between different stakeholders in the field of neurodegenerative diseases - it emerged that this practice was particularly important for knowledge transfer as it allows the "*sharing of experiences in the pre-commercial phase*", i.e. target identification and validation. One of the main issues is that "*failures in the industry are not generally published and therefore, bringing around the table different stakeholders allows avoiding the duplication of efforts, including mistakes*" (cit. Massachusetts Life Science Agency). According to the experts, other indirect benefits to knowledge transfer deriving from this type of practice, regard primarily the achievement of time and cost efficiencies in relationship-seeking activities and secondly, the alignment of visions and missions of the different epistemic communities by promoting dialogue among them and leading to a collective resolution of problems.

As for the *Agreements for the Access and Use of Infrastructure*, it emerged that the advantages in terms of knowledge transfer reside in the spillover effect of the environment provided by hosting organizations. Apart from the well-known advantages in terms of visibility and costs efficiencies deriving from renting a space within an innovation center, it is also the opportunity of *casual encounters* with industry operators that enhances the chance of knowledge exchange. Also, incubators and accelerators generally offer services of business consultancy to scientists and engineers that lack capabilities in this field. Furthermore, according to the experts, the embeddedness itself is favored by the presence of incubators and co-working spaces that multiply the networking opportunities thanks to their strategic design that promotes casual encounters.

From the interviews, *Venture Capital and Seed Investments* relationships turn out to be ground for the transfer of new knowledge due to the complementarity of the skills between innovative firms' scientific know-how and investors' support for business operations. As reported by Kymera's CEO, especially in the case of funding VC, the start-up is usually provided with support on every aspect of the business management, including assistance for hiring the right people and for seeking potential partnerships to exploit the developed innovation at its best. In this case, the importance of interpersonal relationships is mainly explained by the frequency of interactions required – especially at the seed stage - and the need of establishing trust mechanisms with the partners. While exploring the relationship between Kymera and Atlas Venture – a VC company headquartered in Kendall Square - it emerged that it is not uncommon for VCs to host their portfolio companies in their office spaces. Also, especially in the case of VC founders, relationships tend to be long-term, thus implying an investment not only in money but also in time, which – as reported by Alnylam's CEO – "*allows for a more efficient corporate resource management*". Finally*, Formal and Informal Industry-University Agreements for the Mobility of Human Resources* are deemed by the experts to be one of the most fruitful relationships in terms of knowledge transfer. The *Massachusetts Life Science Internship Challenge* and the *Northeastern Co-Op* (Cooperative Education and Career Development) are some of the examples appointed as best practices in promoting knowledge transfer between industry and academia. The former provides a platform to facilitate the placement of college students in life science by subsidizing paid internships hosted by companies in the area, while the latter constitutes a powerful learning model that promotes intellectual and professional growth by integrating classroom learning with practical experience. In so doing, to the one hand, real-world experience enhances the potential for innovation of academic human capital and on the other, the employer partners pursue a cost-effective strategy for hiring and training talented workforce.

4. Discussion

With regards to the *network structure*, low levels of density suggest that the GBA network is relatively sparse (Balland et al. 2012) and characterized by the presence of structural holes (Ahuja 2000). The average degree value, which indicates the average number of partners for each organization, suggests a low-medium level of engagement of the network actors in partnering with organizations found in spatial propinquity (Kajikawa et al 2010; Still et al. 2010 and Salavisa et al. 2012). Also, indicators at

the meso-structural level suggest a high tendency of the network to divide into modules (i.e. groups, clusters or communities) in which nodes have dense connections with those belonging to the same module but sparse connections with nodes in different modules. Additionally, by analyzing the network from a *small world* perspective (Watts and Strogatz 1998), the relative high values for the average geodesic distance and relatively low score for the clustering coefficient confirm the network's structural tendency toward a more open configuration and to accumulate a more diversified relational capital through the frequency of less redundant and weaker ties (Kajikawa et al. 2010). Finally, since centrality metrics are typical indicators of engagement and influence (Freeman 1989), large pharmaceutical companies with a venture arm and large venture capital firms (which occupy top centrality positions) are suggested to have a propulsive role in the ecosystem's development and to act as buffers spanning the structural holes and thus holding a brokering position.

As for the *network portfolio*, the relationships with high scores for knowledge transfer are mainly characterized by a low degree of formalization, i.e. *venture capital and seed investments, co-participation in thematic associations and symposia* and *agreements for the access and use of infrastructure* and *HR mobility between industry and academia*. With reference to *VC and seed investment*, despite the higher level of formalization, it emerged that it is mainly the exchange of complementary skills (business support and scientific capabilities) and the advantages in terms of reputation for the startups within VC portfolio to play a major role. More specifically, the form of the observed types of relationships, with specific reference to the way through which transfer of information occurs and future partnerships arise, appears to be mainly based on trust, personal interaction and reputation effects without the necessity of long term and binding contracts. This suggests that the composition of a network portfolio is predominated by the presence of weak ties. Also, these relationships involve actors of different nature and disciplines and are characterized by their ability to foster cross-disciplinary interaction and match complementary resources (financial and technical) and capabilities (business support and scientific capabilities), which suggests that the network is characterized by non-redundant ties. While comparing the results deriving from both analyses, findings from SNA are coherent with the outcome of expert interviews that suggest that an open network with non-redundant ties is preferable in terms of positive impact on innovation system performance. More specifically, informal relationships that link universities and firms as the *co-participation in thematic associations and symposia, the agreements for the access and use of infrastructure* and the *HR mobility*

from industry and university seem to be those that are more fruitful for the development of innovation activities (see Figure 4).

Figure 4. Network portfolio in Biopharma IE in Greater Boston Area
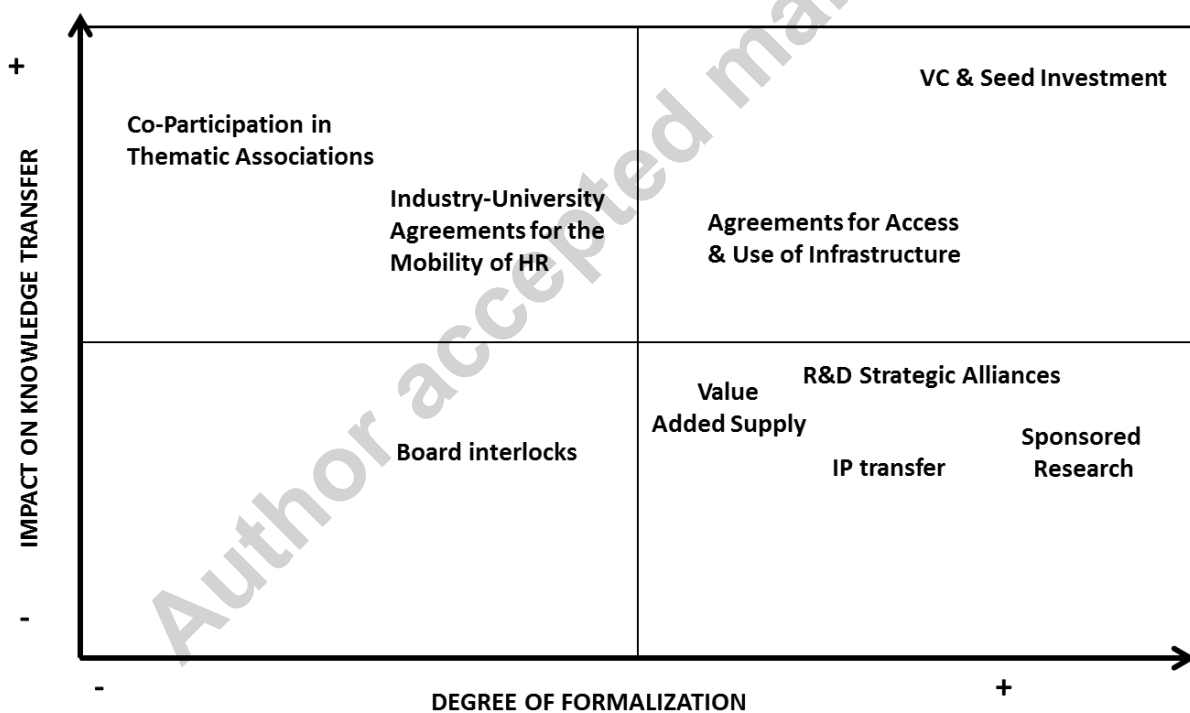
Source: authors' own elaboration

This network portfolio is coherent also with the tendency, at the structural level, of being divided in small groups where interactions occur more easily, as in the case of specific thematic associations (e.g. the Neuroscience Consortium or the Massachusetts Biotechnology Council) or sector-specific

innovation centers (e.g. Lab Central), so as to form *local innovation communities* that focus their joint effort on specific R&D targets within the innovation ecosystem. These *local innovation communities* are therefore characterized by a high intensity knowledge transfer through organizations of different nature and a high frequency of personal interactions, yet with a low degree of formalization, co-localized in the same geographical area.

Our analysis of GBA Biopharma IE allows us to delineate a comprehensive framework that describe all the aspects of the relational dimensions of IE and that can be tested in the future on other IEs (Figure 5). Our analysis reveals that a smart Innovation Ecosystem presents the following characteristics:

(i) an open network structure with structural holes (+ distance among the actors, - network density)

(ii) a high level of modularity in which nodes have dense connections with those belonging to the same module but sparse connections with nodes in different modules (+ connected components);

(iii) a portfolio of relationships dominated by informal ties, with specific reference to the way through which the transfer of information occurs and future partnerships arise, that are mainly based on trust, personal interaction and reputation effects (+ personal face-to-face contacts) without the necessity of long term and binding contracts (- binding contracts);

(iv) non-redundant ties involving actors of different nature and disciplines, which stimulates the innovation potential of the exchanged information and the transfer of different (and complementary) practices to tackle with specific research challenges (+ heterogeneity of actors) and the complementarity of the resource exchanged (+ complementarity of resources)

(v) the presence of *local innovation communities* which reflects the tendency of actors from different epistemic communities to convene in small groups around specific thematic areas where knowledge transfer occurs through loose ties whose frequency is ensured by their spatial proximity and that are able to span the structural holes typical of the open structure of the network.

These results are in contrast with the strand of reviewed literature whose empirical results suggest the tendency of innovation systems' actors to partner more with organizations which are

cognitively similar (Balland et al. 2013). Conversely, these results are in line with those studies that demonstrate that personal contacts represent an important channel of knowledge diffusion (Dahl and Pedersen 2004) and that show how critical links and organizations with brokering positions compensate the negative effects of network dispersion for the ecosystem's innovation performance by spanning structural holes and ensuring the exchange of non-redundant information (Casanueva et al. 2013; Broekel and Mueller 2017) and finally, with those studies suggesting the tendency of science-based innovation systems' networks (as Biotech) to form small sub-groups, i.e. knowledge epistemic communities, characterized by frequent inner connection and informal channels of knowledge diffusion (Salavisa et al 2012).

Figure 5. Characteristics of a smart IE from a relational perspective
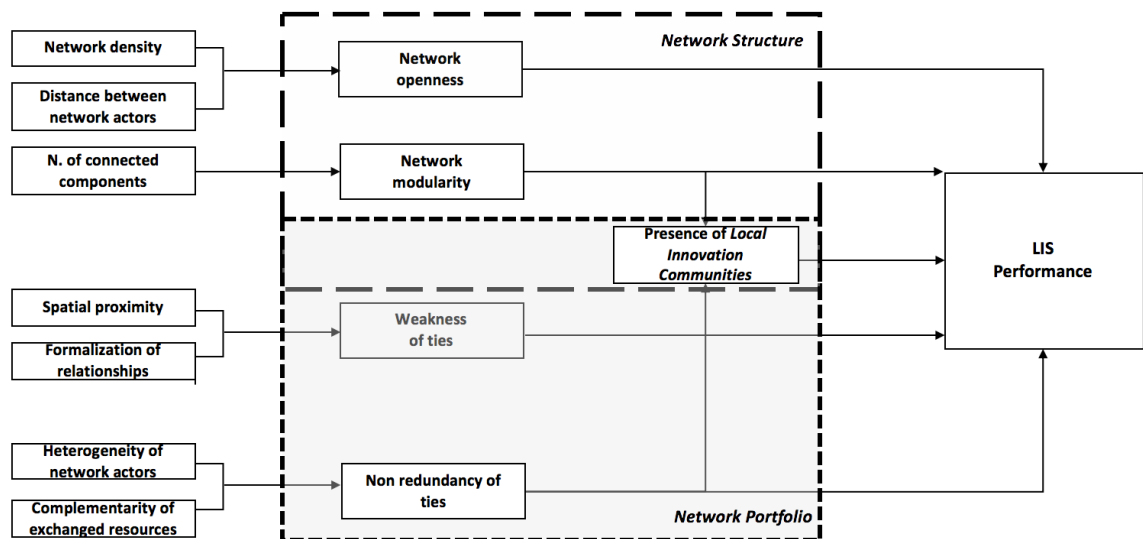
6. Implications, limitations and future researches

This study offers a more comprehensive view about the relational dimension of local innovation ecosystems by taking into account of both network structure and the quality of its relationships. Additionally, from a methodological perspective the study contributes to meet the challenges related to the adoption of a holistic approach, by capturing the heterogeneous nature of IE demography when most studies limit their analyses to inter-firm relationships and at the node-level. Finally, the study provides insights into the network portfolio composition, which has been underexplored in IE literature, allowing for the identification of those relationships considered more fruitful to enhance innovation processes from a local perspective. Our study has many practical implications both for the companies that can define which kinds of relationships are more fruitful to enhance their processes of knowledge transfer and for policy makers and those actors willing to undertake an active role in the development of an IE in their own regions suggesting the relational configuration that a smart IE should have. However, this study represents a first attempt to gain insight about the interaction dynamics among government, university, industry and civil society in a smart IE. The analysis of a single case study, even if it refers to an exemplar case, does not allow for the generalization of the results to other cases. Moreover, the limited number of expert interviews and the use of indirect source of data do not allow us to completely understand the complexity of the IE with specific regard to informal relationships. Also, the paper explores the relationships among university-firms-government and financial investors but neglect to deepen the role of the other two helices of smart growth i.e., civil society and environment. Future studies are invited to overcome this paper's limitations to achieve a more complete analysis of the phenomenon ,for example by extending the analysis to organizations that represent the environment and the civil Society. Moreover, the framework that we proposed can be tested in different geographical and industrial contexts in order to verify is replicability. Finally, a comparative study with other IEs at different stages of development would contribute to a greater extent of validation of the propositions.

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