UNIVERSITÀ DEGLI STUDI DI NAPOLI
FEDERICO II

DOTTORATO DI RICERCA IN MANAGEMENT

XXX CICLO

EXPLORING THE RELATIONAL DIMENSION OF LOCAL INNOVATION SYSTEMS. THE CASE OF BIOPHARMA IN GREATER BOSTON AREA

TESI DI DOTTORATO
DI
EVA PANETTI

COORDINATORE:
CH.MA PROF.SSA CRISTINA MELE

TUTOR:
CH.MA PROF. SSA ADELE PARMENTOLA

ACKNOLEDGEMENTS

Firstly, I would like to express my sincere gratitude to my advisor Prof. Adele Parmentola for her continuous support to my Ph.D. study. She introduced me to the academic research by providing an example of rigor and determination. Her guidance helped me in all the time of research and writing of this thesis and I thank her for her teachings and encouragement but also for all critical remarks, which made me engage in a process of continual self-improvement that was key for my growth as a researcher and for the quality of my research. Besides my advisor, I would like to thank the rest of the Parthenope Department of Management and Quantitative Studies (DISAQ) for making me feel part of their community during the last three years. In particular, I am grateful to Prof. Marco Ferretti for believing in me from the very beginning and for pushing me to do things that I would never imagined I could do. I thank him for all the opportunities and motivation he gave me and for teaching me the value of being part of a team and for providing me with an inspiring example of a visionary, dynamic and enthusiast academic, whose relentless work has created actual value for the whole University. I also thank Prof. Marcello Risitano for transmitting me the professional value of the academic job and for all his encouraging words that have been of great comfort during moments of distress. A special thanks goes also to all my fellow mates in room 426 in particular my friends Andrea, Antonella, Daniele and Laura for being so patient with me during working hours and for the wonderful and warm working environment that we have been able to create in the last years characterized by solidarity and mutual support. I also had the honor to enrich my PhD experience with my visiting at the MIT Industrial Performance Center, which has been determinant for changing my perspective about academic research. This opportunity was given to me by Dr. Elisabeth Reynolds that I will never thank enough for her generous support during and after my visiting period and for widening my research perspective through her incredible knowledge and expertise in Biopharma industry and innovation systems. She has been an aspiring example of an incredible strong woman by managing research activities for one of the world leading academic institutions with determination and grace. I am also grateful to all the rest of the MIT IPC members and particularly to Laura, Andre and Zeke who have been my family away from home during my stay in Cambridge. My sincere thanks also goes to Prof. Fiona Murray and Dr. Philip Budden for extending my knowledge and providing me with a more practical approach to the study of Local Innovation Systems and to all the wonderful interviewees for all insightful conversations and for generously dedicating me part of their time despite their busy schedule. A special thanks goes also to Paul Parravano, for showing me more about the uniqueness of Cambridge, for introducing me to amazing people who contributed to my research, and above all for his friendship. Lastly, I would like to thank my family since without their support I would have never been able to embark this – sometimes uncertain – professional path and more importantly, for teaching me the value of work and that of being an honest person. I am grateful to my mother for dedicating all her life to create a serene environment for all our family and to my father for the example of excellence - as a professional and as a man – that he gave to me and my sisters.

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Introduction

In the last decades we assisted to a progressive spatial concentration of innovation activities in specific geographical areas characterized by a vibrant atmosphere due to the synergetic co-location of research centers, innovation –driven enterprises, large corporations and capital providers bound by horizontal and vertical relationships. In many cases, the physical proximity of a diverse community of actors engaged in innovation activities, provides the context for new business formation, socio-economical regional growth and knowledge production at the global and local level, with interesting implications in terms of co-evolutionary dynamics at the social, technological and environmental levels.

Scholars from both management and economic geography have labelled these environments as Local Innovation Systems, which given their implications, have increasingly raised the interest of both academic and political communities. On the one hand, scholars from both management and economic geography have analyzed the conditions and criteria for LIS empirical recognition and judgment (i.e. system boundaries; actors and networks; institutions and knowledge dynamics), as well as the mechanisms for their creation in those regions presenting structural characteristics that may apparently prevent systems of innovation to emerge. On the other hand, institutional and government actors have been increasingly committed to policies to stimulate the emergence of dynamic innovation environments through, for example, the implementation of business accelerator programs, regimes of appropriability of intellectual property, tax incentives, the set-up of incubators and co-working spaces etc. However, the mere co-location of innovation-oriented organizations and the establishment of incentives seem not to be a sufficient condition for LIS emergence. Indeed, as argued in the seminal work of Anna Lee Saxenian (1994), the successful performance of a system of innovation is largely due to the bottom-up emergence of synergetic cooperative mechanisms between organizations in the form of horizontal networks of relationships.

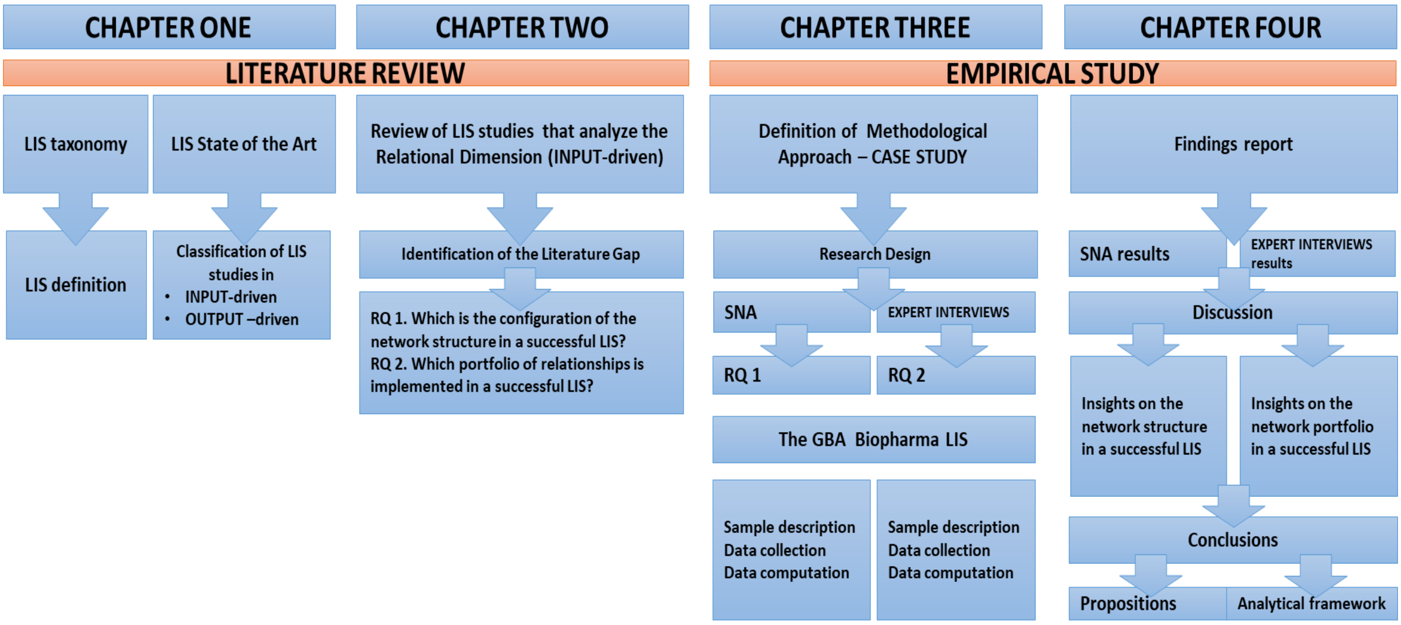
In fact, relationships exert a key role for actors engaged in processes of innovation, as they enhance practices of inter-organizational cooperation that allow them to share risks related to new products and to accelerate their time-to-market, as well as to bring together complementary skills and gain access to financial resources and new technologies. Extant studies on innovation systems have started to analyze the network dimension as a further variable of LIS performance. However, analytical efforts towards the study of LIS relational dimension have been limited and not fully explored. In particular, there seems to be a lack of agreement on the optimal configuration of network structure for the LIS assessment of performance. Additionally, most contributions tend to limit their analysis to inter-firm formal relationships, thus overlooking the heterogeneous nature of system's components and the impact of looser ties.

This thesis is grounded on the recognition of the relevance of relational dimension for the study of LIS as well as on the need to fill the gap in extant literature with respect to two aspects of analysis: network structure and network composition, i.e. the level of connectivity among the system's actors and the portfolio of different types of relationships and forms of cooperation that local actors put in place to produce innovation. While the first aspect relates to the debate as to whether a more open network is preferable than a more closed one, the second issues refers to the fact that, depending on circumstances, inter-organizational relationships may take the form of well-structured and long term relations, as R&D partnerships and joint ventures, as well as that of less formal interactions as in the case of know-how trading. More specifically, this thesis explores which configuration of network structure and portfolio are associated to a high performing LIS, by deriving evidence from the empirical study of the Biopharma LIS in the Greater Boston Area (GBA), which has been exemplified as a benchmark case in terms of LIS successful performance. The work adopts an explorative "critical" case study approach to derive propositions to orient future research, which is invited to test them and consider the results of this work as a benchmark for the study of LIS in emerging regions. Part of this research has been conducted at the Industrial Performance Center (IPC) of the Massachusetts Institute of Technology (MIT) under the supervision of Dr. Elisabeth Beck Reynolds. The IPC has constituted a privileged standpoint for the empirical observation of Biopharma LIS in GBA due to its location at the heart of Kendall Square, where major players of the industry are located, and due to the longstanding academic expertise of the Center in the field of LIS. Additionally, the research design has been influenced by the MIT Innovation Ecosystem Framework that I assimilated at the MIT Sloan School of Management while attending the classes of the Regional Entrepreneurship Acceleration Laboratory (REAL), thought by Fiona Murray and Philip Budden, which have been fundamental for complementing the academic theoretical implications of the work with a more action-oriented approach.

The entire work has been guided and supervised by Adele Parmentola and Marco Ferretti at the Parthenope University of Naples, whose expertise on the theme is documented by their authorships of several publications and books on the theme.

The thesis is organized as follows (Figure 1.0). Chapter one provides a taxonomy of LIS definitions, upon which an original and comprehensive definition of LIS is elaborated. The second part of the chapter offers an overview of the state of the art by classifying LIS studies in two main strands based on the identification of principal drivers of LIS performance (namely, the input-driven and the output-driven approaches) and positions the current work in one of them. The second chapter aims to explore a particular aspect that is studied within the *input-driven approach*, i.e. the relational dimension, where the present work is grounded. To this purpose, the chapter provides an in-depth analysis of key concepts and empirical issues concerning this specific analytical perspective. More precisely, the first section discusses the key role played by networks of relationships within systems of innovation, with specific regard to the benefits deriving from partnering and the impact of network architecture on the access to relational capital. The second section provides an overview of the proximity framework, which highlights the conditions that favor network emergence. Section three introduces the use of the Social Network Analysis (SNA) as an approach for the study of LIS and illustrates the different positions within the debate on the desirable network structure to boost innovation system performance, within network literature. Section four reviews empirical studies adopting a SNA approach for the study of LIS, according to seven specific dimensions. Main findings emerging from the literature review leads to the identification of the literature gap, which is discussed in section five, before concluding. Chapter 3 illustrates and discusses the research strategy adopted for addressing the theoretical gap. The first section provides an overview of the exploratory case study methodology and emphasizes how the selected approach contributes to address the research questions. The second section provides an overview of the selected case study, with particular regard to the relational implications of drug development process, the identification of main players and the illustration and discussion of the typical forms of cooperation and interaction occurring between the industry players. Section 3.3 offers an overview about the research techniques implemented for the empirical study highlighting their points of strength and limitations, most common indicators and fields of application. Section 3.4 illustrates the sample composition, explains the criteria underpinning its selection and the process of data collection and computation. Finally, chapter four reports and discusses the main findings deriving from data analysis and develops an analytical framework for the study of LIS relational dimension. More precisely, the first section provides snapshot metrics of the network structural configuration and identifies its central nodes. Section 4.2 illustrates and critically discusses the results of the round of direct interviews conducted with representatives of different organizations in the Biopharma LIS in GBA with the specific purpose of gaining insights about the preferable network portfolio combination along two specific dimensions, i.e. the impact on knowledge transfer and the importance of spatial proximity. Section 4.3 provides an in-depth discussion of results from both analyses and combine them to achieve a more complete overview about the whole system's functioning and elaborates an analytical framework for future studies. A set of propositions for practitioners are presented in the conclusive section, together with main limitations of the study and suggestion for future research.

Figure 1.0. Structure of the work



CHAPTER 1 – INTRODUCTION TO LOCAL INNOVATION SYSTEM THEORY

The concept of Local Innovation Systems stands upon two basic understandings. Firstly, the shift from the linear conception of innovation process towards the idea of innovation as a result of a systemic and interactive process (Chesbrough, 2003) among actors of different nature (Etzkowitz and Leydesdorff, 1995) and secondly, the relevance of the territorial variable in stimulating innovation (Lundvall and Johnson, 1994). In fact, firms generally do not innovate in isolation but they rather interact with other organizations by bounding themselves into specific ties (Edquist, 2011; Powell, 2005). These interactions are considered to be enhanced when these actors are found in geographic proximity (Asheim, Gertler, 2005) as this is deemed to stimulate collective learning processes (Lundvall, Johnson, 1994; Lawson, Lorenz, 1999; Lundvall, 2010) and those face-to-face contacts for the transfer of tacit knowledge. The System of Innovation approach emphasizes the role of institutions, both governments and research organizations, in influencing the process of innovation. In this vein, the Triple Helix thesis (Etzkovitz, 1993) provides an analytical framework to explain the potential for innovation originating from a more prominent role of the university as well as the hybridization of elements from academia, industry and government to generate new institutional and social formats to elaborate, transfer and implement new knowledge.

The first part of next section (1.1.1) provides an overview about these two strands of research that underlie the definition of a LIS by highlighting the impact of geographic proximity on knowledge transfer dynamics. Section 1.1.2 provides a taxonomy of definitions of LIS and formulates an original one that guides the empirical work of this thesis. Section 1.2 offers an overview of the state of the art of main contributions addressing innovation system performance based on the identification of principal drivers, before concluding.

1.1 Theoretical Background and definition of a LIS

1.1.1 The impact of geographic proximity on knowledge transfer dynamics

Learning is considered as a key concept within innovation system literature. In the late 80s Lundvall (1985, 1988) and Johnson (1991) introduced the notion of *learning – by – interacting*, emphasizing the role of geographic proximity in providing a more direct and easy access to information within users-producers interactions (Lundvall, 1985). More specifically, the authors consider learning as "*a socially embedded process which cannot be understood without taking into consideration its institutional and cultural context*" (Lundvall 1992, p.1). This is mainly explained by the fact that innovation generation represents a process characterized by low levels of predictability and learning plays a central role in this uncertain process, which in turn explains why complex and frequent communication between the parties involved is highly required, with specific regard to the exchange of tacit knowledge (Nonaka and Takeuchi, 1996). The importance of geographic proximity in knowledge transfer processes is further emphasized with the introduction of the notion of *learning region* (Storper, 2005). In this regard, learning is conceived as a *territorially* and *socially* embedded and interactive process (Asheim, 1996), able to drive the successful growth and the innovation performance of regions (Cooke, 1992) thanks to the catalyst role of proximity (Coenen et al., 2004). Networking with other firms and organizations is therefore considered as a "learning capability" (Lundvall and Johnson, 1994) and different kinds of "learning relationships" (e.g. customer-supplier; cross-sectorial) are deemed to be at the core of the innovation process (Johnson and Andersen, 2012).

The impact of geographic proximity on innovation-driven learning dynamics varies according to the nature of knowledge and innovation modes. Lundvall and Johnson (1994) grouped knowledge into four economically relevant knowledge categories:

- *Know- what*, which refers to the knowledge about facts;

- *Know-why,* which refers to knowledge of scientific principles;

- *Know- who*, which refers to specific and selective social relations;

- *Know- how,* which refers to skills (i.e., the capability to do different kinds of things on a practical level) (Lundvall and Johnson 1994, p. 129).

This taxonomy is useful to understand the different channels through which learning takes place. Indeed, while *know-what* and *know-why* can be learnt through codified information (e.g. through reading books or lectures), the other two forms of knowledge are more difficult to codify and may require to be transferred through practical experience. Thus, while *know-why* and *know-what* are more typically produced through the *science, technology, and engineering* (STE)-based innovation, know-how and know-who are generally associated to the *doing, using, and interacting* (DUI)-based innovation. Following Jensen et al. (2007), the STI mode is "*based on the production and use of codified scientific and technical knowledge*", whereas the DUI mode "*relies on informal processes of learning and experience-based know-how*". Main differences between the two modes of learning are shown in Table 1.1

Table 1.1 STI mode vs. DUI mode

STI mode (science driven)	**DUI mode (user driven)**
Aim: Increase the R&D capacity of the actors in the system and increase cooperation between firms and R&D organizations	**Aim:** Foster inter-organizational learning and increase cooperation between in particular producers and users
Typical innovation policy:	**Typical innovation policy:**
Increase the R&D capacity of organizations	Support on-the-job learning and organizational innovations
Support joint R&D projects between firms and universities	Matchmaking activities and building and sustaining existing networks
Support higher education programs	Stimulate trust building and joint innovation projects between actors in the value chain (producers-suppliers – users-consumers)
Subsidies for R&D infrastructure (laboratories, research and technologies centers, research groups, etc.)	Stimulate joint projects between competing and auxiliary businesses
Support (financial) for increasing mobility between academia and industry	
Support for commercialization of research results	

Source: Isaksen and Nilsson, 2011

Asheim and Gertler (2005), building on the concept of learning as an interactive process, add a new dimension in the context of Regional Innovation Systems (RIS) (which will be discussed in the following sections), i.e. *knowledge bases* (Laestadius, 1998).

The analytical knowledge base "*refers to industrial settings, where scientific knowledge is highly important, and where knowledge creation is often based on cognitive and rational processes, or on formal models*" as in the case of biotechnology, ICT, genetics. University-industry networks turn out to be to be particularly important, as companies tend to rely frequently on results from research institutions for the development of their innovations. The type of exchanged and produced knowledge tends to be codified and its application gives origin to radical innovation more frequently. Radical innovation is typically produced when knowledge is exchanged among actors of different nature through inter-organizational relationships and cooperative mechanisms, capable of stimulating reciprocal learning and thereby processes of innovation (Capaldo, 2004).

Hence, the presence of actors of different nature, with different skills and capabilities and diverse background – universities, firms and local institutions - can boost the creation of radical innovation as far as they exchange non-redundant information.

On the other hand, the synthetic knowledge base "*refers to industrial settings, where the innovation takes place mainly through the application of existing knowledge or through new combinations of knowledge".* It is the case of incremental innovations, which are developed to solve specific problems as for example in the field of industrial machinery or shipbuilding, where products are generally manufactured on a small scale. R&D and University-Industry links tend to be less important compared to the analytic knowledge base, and knowledge is often produced as a result of experimenting, testing, practical processes with a low level of codification. Main characteristics and differences of the two knowledge bases are summarized in Table 1.2.

Table 1.2. Analytic vs. Synthetic knowledge bases

Synthetic knowledge base	Analytic knowledge base
Innovation by application or novel combination of existing knowledge	Innovation by creation of new knowledge
Importance of applied, problem related knowledge (engineering) often through inductive processes	Importance of scientific knowledge often based on deductive processes and formal models
Interactive learning with clients and suppliers	Research collaboration between firms (R&D department) and research organizations
Dominance of tacit knowledge due to more concrete know-ho, craft and practical skill	Dominance of codified knowledge due to the documentation in patents and publications
Mainly incremental innovation	More radical innovation

Source: Asheim and Gertler 2005

The impact of spatial proximity on innovation processes thus manifests itself depending on the frequency and intensity of interactions (especially *face-to-face*) needed to effectively transfer the knowledge and the need of specific infrastructure (e.g. Research institutions or Innovation centers) for its development.

1.1.2 LIS definition

1.1.2.1 Taxonomy of LIS definitions

Extant literature provides a variety of conceptual definitions of LIS. Cooke et al. (1997) and Doloreux (2002) emphasize embeddedness and learning mechanisms as key features of LIS. Indeed, while the former describe LIS in terms of a system "*in which firms and other organizations are systematically engaged in interactive learning through an institutional milieu characterized by embeddedness*", the latter refers to LIS as a "*social system*" where both private and public actors interact with each other in a systematic manner, thus contributing to the regional potential of the region concerned. The network argument is proposed also by Todtling and Kauffmann (1999), who consider LIS as a network inhabited by regional main industry's firms and by those operating in complementary fields whose relations are vehicle for knowledge transfer and production. Similarly, according to Norton

(2007): "*LSI represents the collaboration and networks between companies and other players in the system (national and local government, regulatory authorities, research and training centers, the financial system and markets). It summarizes the diversity of roles of the various parts of the system-roles that are interlinked and interdependent*". In this vein, Morrison (2003) define LIS as "a *set of localized network of actors (firms and organizations) devoted to generate, transform and diffuse knowledge*" and according to Canzanelli and Loffredo (2008) LIS are "*complex systems characterized by interaction between multiple actors and institutions that produce and reproduce knowledge and know- how, govern how they are transferred to businesses and other local organizations, and manage how they are implemented".* Other authors deepen the focus on relationships by emphasizing the interdependencies existing between local actors as in the case of Rahayu and Zulhamdani (2013) that define "*Local innovation system as an intelligent organism which has various organs with their unique tasks in order to achieve the main goal the so called innovation"*. More specifically, these organs include: (i) operational organ (producers, local university, local research institute), (ii) coordinator organ (business culture), (iii) controller organ (business culture and the government), (iv) planner/ intelligence organ (the government), and (v) policy organ (brain) (the government). Asheim and Isaksen (1997) describe LIS as consisting of a "*production structure (techno-economic structures) and an institutional infrastructure (political-institutional structures)*". The catalytic role of institutions and local policies in stimulating the regional innovation performance is also stressed by Muscio (2006) who argues that "*Local innovation systems are based on the generation of regionalized learning systems where some local innovation policies are activated to transfer technologies, to enforce technological cooperation, and to provide support and incentives to innovative networks*". Hamaguchi (2008) provides an interesting contribution on the output dimension by defining LIS as "*as a subset of a cluster, differentiating from other kind of cluster by its very nature of orientation toward creation of products and production methods that are new* *to the industry*", thus emphasizing the specialization and the radical nature of the innovation produced within systems of this kind. A number of contributions have specified the elements or the required conditions for a LIS to exist. According to Gebauer et al. (2005) main LIS components include: *"(i) horizontal and vertical relations among firms (e.g. prime contractors, subcontractors, independent enterprises in similar and/or different industries); (ii) firms' contacts with universities and other research institutions, as well as with technology centers; (iii) the role of government agencies (promotion), interest groups (commercial, technical and information support) and lending bodies (the provision of venture capital)*".

A more specific description of LIS main features, is the one provided by Martin and Simmie (2008), that include: "(i) *Sectorally and institutionally diverse knowledge generating businesses and institutions which can draw innovative ideas from many potential sources;* (ii) *High levels of firm specialization to supply the best in national and international markets;* (iii) *Commercial and marketing know-how, based on knowledge of international market and technological conditions; (iv) A wider social culture that is also tolerant of diversity, and new ideas and ways of doing things; (v) Firms able to exploit knowledge and support knowledge applications by others;* (vi) *High levels of technical sophistication among both producers and users of technology;* (vii) *Economies of scale;* (viii) *International knowledge spillovers from sophisticated customers, including locally-represented multinational companies, providing the local innovation system with information on leading edge knowledge, products and services"*. A more recent study on the creation of LIS in emergent economies (Ferretti and Parmentola, 2015) identifies the following elements as critical for LIS creation: (i) a network of innovative firms, localized in the same area and bound by horizontal and vertical relationships; (ii) a set of research and educational institutions, such as universities and research centers, which generate scientific knowledge that contributes to innovative processes; (iii) a series of infrastructure provisions that incentivize the localization of innovative firms within the given area; (iv) the presence of cooperation mechanisms among all these actors, capable of stimulating reciprocal learning and thereby processes of innovation. Finally, from an ecosystem perspective (Russell, 2011): "*An innovation ecosystem refers to the inter-organizational, political, economic, environmental, and technological systems through which a milieu conducive to business growth is catalyzed, sustained, and supported. A dynamic innovation ecosystem is characterized by a continual realignment of synergistic relationships that promote growth of the system. In agile responsiveness to changing internal and external forces, knowledge, capital, and other vital resources flow through these relationships*". The scholar identifies as actors of the innovation ecosystem: (i) Material resources (funds, equipment, facilities, etc.) and, (ii) Human capital (students, faculty, staff, industry researchers, industry representatives, etc.) that make up the (iii) Institutional entities (e.g. the universities, colleges of engineering, business schools, business firms, venture capitalists (VC), industry-university research institutes, federal or industrial supported Centers of Excellence, and state and/or local economic development and business assistance organizations, funding agencies, policy makers, etc.).

Table 1.3. Taxonomy of LIS definitions

Author (year)	LIS definition	Focus
Cooke et al. (1997)	A system "in which firms and other organizations are systematically engaged in interactive learning through an institutional milieu characterized by embeddedness"	Embeddeness
Asheim and Isaksen (1997)	LIS as consisting of a "production structure (techno-economic structures) and an institutional infrastructure (political-institutional structures)"	Role of policies and regulations
Todtling and Kauffmann (1999),	LIS as a network inhabited by regional main industry's firms and by those operating in complementary fields whose relations are vehicle for knowledge transfer and production	Inter-firm relationships
Doloreux (2002)	"Social system" where both private and public actors interact with each other in a systematic manner, thus contributing to the regional potential of the region concerned	Embeddeness
Morrison (2003)	LIS as " a set of localized network of actors (firms and organizations) devoted to generate, transform and diffuse knowledge"	Inter-organizational relationships; Knowledge production and diffusion

Muscio (2006)	Local innovation systems are based on the generation of regionalized learning systems where some local innovation policies are activated to transfer technologies, to enforce technological cooperation, and to provide support and incentives to innovative networks".	Role of policies; Knowledge transfer
Norton (2007)	"LSI represents the collaboration and networks between companies and other players in the system (national and local government, regulatory authorities, research and training centers, the financial system and markets). It summarizes the diversity of roles of the various parts of the system-roles that are interlinked and interdependent".	Inter-organizational relationships
Canzanelli and Loffredo (2008)	LIS are "complex systems characterized by interaction between multiple actors and institutions that produce and reproduce knowledge and know- how, govern how they are transferred to businesses and other local organizations, and manage how they are implemented"	Inter-organizational relationships; Knowledge production and diffusion
Hamaguchi (2008)	LIS as "as a subset of a cluster, differentiating from other kind of cluster by its very nature of orientation toward creation of products and production methods that are new to the industry"	Radical new knowledge production
Russell, (2011)	"An innovation ecosystem refers to the inter-organizational, political, economic, environmental, and technological systems through which a milieu conducive to business growth is catalyzed, sustained, and supported. A dynamic innovation ecosystem is characterized by a continual realignment of synergistic relationships that promote growth of the system. In agile responsiveness to changing internal and external forces,knowledge, capital, and other vital resources flow through these relationships".	Interdependency of actors at multiple levels; Inter-organizational relationships
Rahayu and Zulhamdani (2013)	"Local innovation system as an intelligent organism which has various organs with their unique tasks in order to achieve the main goal, i.e. innovation"	Interdependency of actors

Source: author's own elaboration

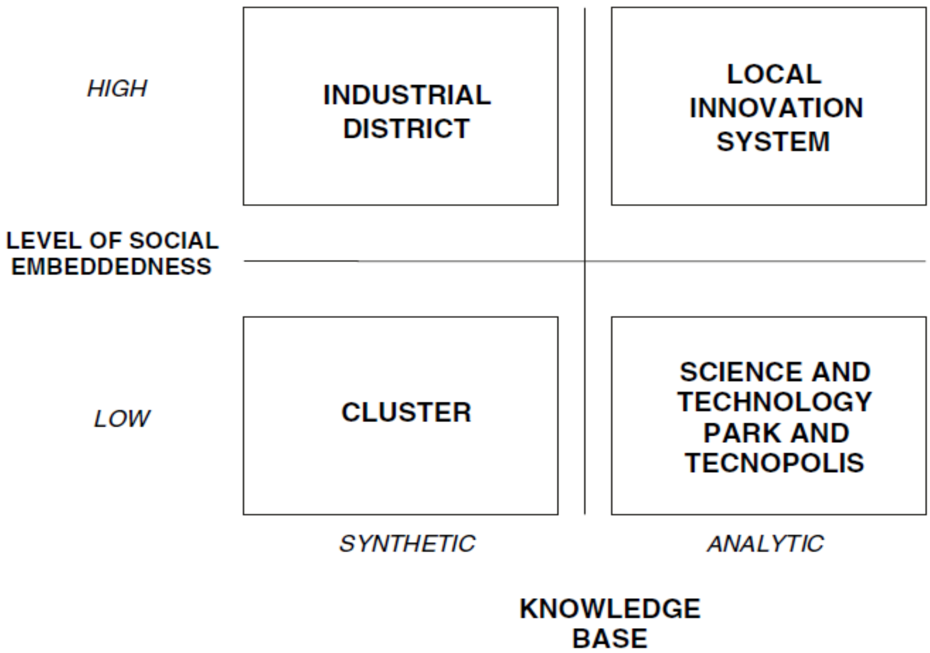
Table 1.4. LIS main components

Author (year)	LIS components
Gebauer et al (2005)	(i) horizontal and vertical relations among firms (e.g. prime contractors, subcontractors, independent enterprises in similar and/or different industries); (ii) firms' contacts with universities and other research institutions, as well as with technology centers; (iii) the role of government agencies (promotion), interest groups (commercial, technical and information support) and lending bodies (the provision of venture capital)".
Martin and Simmie (2008)	(i) Sectorally and institutionally diverse knowledge generating businesses and institutions which can draw innovative ideas from many potential sources; (ii) High levels of firm specialization to supply the best in national and international markets; (iii) Commercial and marketing know-how, based on knowledge of international market and technological conditions; (iv) A wider social culture that is also tolerant of diversity, and new ideas and ways of doing things; (v) Firms able to exploit knowledge and support knowledge applications by others; (vi) High levels of technical sophistication among both producers and users of technology; (vii) Economies of scale; (viii) International knowledge spillovers from sophisticated customers, including locally-represented multinational companies, providing the local innovation system with information on leading edge knowledge, products and services"
Ferretti and Parmentola (2015)	(i) a network of innovative firms, localized in the same area and bound by horizontal and vertical relationships; (ii) a set of research and educational institutions, such as universities and research centers, which generate scientific knowledge that contributes to innovative processes; (iii) a series of infrastructure provisions that incentivize the localization of innovative firms within the given area; (iv) the presence of cooperation mechanisms among all these actors, capable of stimulating reciprocal learning and thereby processes of innovation.
Russell (2011)	(i) Material resources (funds, equipment, facilities, etc.) and, (ii) Human capital (students, faculty, staff, industry researchers, industry representatives, etc.) that make up the (iii) Institutional entities (e.g. the universities, colleges of engineering, business schools, business firms, venture capitalists (VC), industry-university research institutes)
Rahayu and Zulhamdani (2013)	(i) operational organ (producers, local university, local research institute), (ii) coordinator organ (business culture), (iii) controller organ (business culture and the government), (iv) planner/ intelligence organ (the government), and (v) policy organ (brain) (the government).

Source: author's own elaboration

The above-discussed concepts of knowledge base and embeddedness have been used as discriminatory criteria for distinguishing Local Innovation Systems from other forms of territorial agglomerations, i.e. Clusters; Industrial Districts; Local Innovation Systems; Science and Technology Parks (Ferretti and Parmentola 2015) (Figure 1.1). More specifically, LIS distinguish themselves for the high level of social embeddedness and the analytic knowledge base. The high level of social embeddedness stimulates and facilitates phenomena of *collective learning* or *learning through networking* and consequently, knowledge and information transfer. On the other hand, the existence of an analytic knowledge base suggests the co-location of firms and research and educational institutions as well as their close interaction within University-Industry links.

Figure 1.5. The dimensions of innovation systems



Source: Ferretti and Parmentola, 2015

From the review of the above contributions, it emerges a gradual shift from a more static towards a more dynamic conception of LIS over time. More specifically, initial studies in late 90s appeared to be highly consistent with the literature arising around the learning region and the embeddedness, where regional institutions played a major role in stimulating those learning processes channeled by different types of proximity and trust mechanisms. Their focus was on knowledge transfer as a driver for the performance of the single actors – mainly firms – and on the economic development of the region. In early 2000s the complexity of the system was made more evident by the conceptualization of the heterogeneity of LIS actors as a precondition, not only for knowledge transfer, but also for actual new knowledge production. As a consequence, the focus was not necessarily on the socio-economic development of the region hosting the LIS, but rather on the performance of the LIS itself, and more particularly on its innovation output. Later on, with the introduction of the ecosystem perspective, the role of proximity as a catalyst for collective knowledge transfer was further emphasized as stimulating a community of interdependent actors. The focus shifted from the role of the heterogeneous actors' composition to that of inter-actor relationships (both at the individual and organizational level), through which not only knowledge, but also capital, technological capabilities and other vital resources for the system's growth, are channeled. LIS was finally viewed as an intelligent organism where actors proactively respond to changing external and internal forces within a process of continuous and mutual re-alignment, where innovation is not the mere outcome of the system performance, but rather as a solution to those changes. Therefore, the system is not only seen as source of regional competitive advantage, but rather as a tool for technology transition towards more sustainable modes of production and consumption thanks to its ability to align visions and expectations of actors at multiple levels.

1.1.2.2. Local Innovation System: an extended definition

Grounding on extant literature, a Local Innovation System can be defined as a specific and promising geographic area characterized by a flourishing production of new knowledge as a result of the diffused adoption of open-innovation organizational modes and the presence of:

(i) a network of innovative firms, bound by horizontal and vertical relationships;

(ii) a number of large corporations that establish a branch in the area and outsource part of their R&D activities; a set of research and educational institutions, (e.g. universities and research centers) which generate analytic base knowledge that contributes to innovative processes;

(iii) a number of initiatives and programs led by public institutions supporting knowledge exchange and innovation within the region;

(iv) a community of capital risk providers (e.g. venture capitalists, business angels) involved in activities of innovation scouting to diversify their portfolio of investments;

(v) a series of infrastructure and facilities that incentivize the localization of innovative firms within the given area (e.g. incubator);

(vi) a great number of synergetic relationships among all these actors that promote the flow of knowledge, capital, and other vital resources for the growth of the system.

The above definition of LIS refers to an ideal situation where the system is fully developed and grounds on the observation of benchmark cases of success where all the listed elements are in place, e.g. Silicon Valley or Kendall Square in Boston. From an evolutionary perspective, LIS may present all of some of the above elements according to their stage of development. Policies and programs supporting knowledge exchange and innovation within the region are generally key at early stage of LIS development, especially in those emergent economies where it has been observed that government institutions usually undertake a leadership role in creating the LIS (Ferretti, Parmentola 2015). On the other hand, the presence of a community of capital risk providers (e.g. venture capitalists, business angels) is usually typical of fully developed LIS in which the good performance of all other elements makes it appealing for investors to be located in the area. In other words, the physical proximity of risk capital providers may be seen as an indicator itself of the good performance of the system. Additionally, the presence of risk capital providers is strictly related to the regulatory system of the Country hosting the LIS and the extent to which this incentivizes or not private sector risky investments. However, the physical proximity of actors of different nature (Industry, Government and Academia) bounded by a set of innovation -driven relationships seem to be the two basic conditions for the empirical recognition of LIS as such.

1.2. The State of the Art

Extant literature tends to appoint the successful performance of systems of innovations to the heterogeneous composition of their components or to their ability to produce new knowledge and to contribute to the regional economic growth. More specifically, existing contributions on the assessment of LIS performance can be divided in two broad groups. The first, which follows an *Input-driven approach*, mainly focuses on the drivers of LIS performance, as the actors' heterogeneous composition (e.g. Etzkowitz, 1993 and Etzkowitz and Leydesdorff, 1995; Budden and Murray, 2015; Carayannis et al, 2006-2016); the spatial dimension (e.g. de la Mothe and Paquet 1998; Cooke 2001, 2004; Asheim and Coenen, 2005); the infrastructural endowment and policy incentives (e.g. R&D expenditure; Venture investments; incubators and acceleration programs) and finally, on the relational dimension (e.g. Saxenian, 1994; Ahuja, 2000, Owen-Smith and Powell, 2004; Russell et al., 2015), with specific regard to the creation of synergetic connections and cooperative mechanisms existing between the system's components. The second group, i.e. *Output-driven approach* privileges the focus on the effects of LIS creation in terms of production of new knowledge and contribution to the regional growth (e.g. Bajmocy, 2012; Campanella, 2014; Guan and Chen, 2010; Lerro and Schiuma, 2015). Next sections provide an overview of main perspectives within the two approaches.

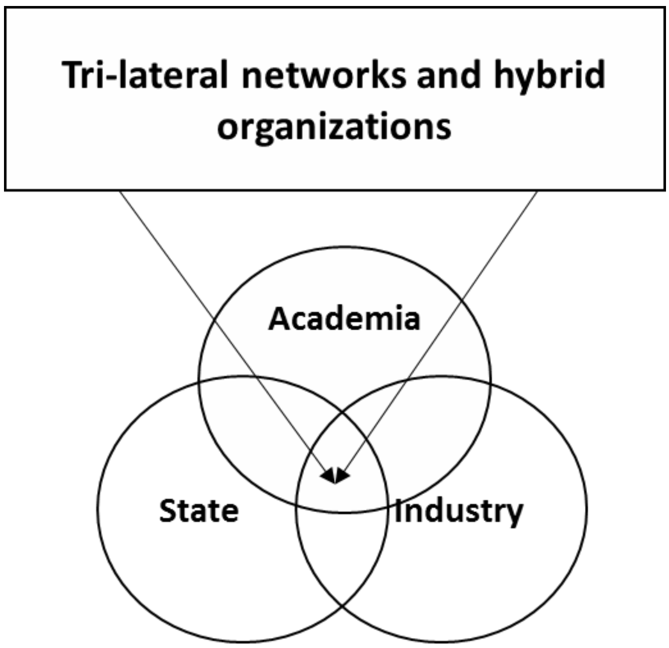
1.2 .1 LIS Input-Driven Approach

This section reviews some of the main contributions appointing the successful performance of systems of innovations, from a structural perspective. In particular, the reviewed studies tend to focus on three main structural elements of LIS: *Actors' Heterogeneity, Territorial boundaries and Relationships.* These input elements are considered as pre-conditions of a LIS successful performance.

1.2.1.1. Actors' Heterogeneity as a Key Performance Indicator of LIS

The Triple Helix framework (Etzkowitz, 1993 and Etzkowitz and Leydesdorff, 1995) has been traditionally employed within the literature of innovation systems, as a valuable framework to explain the dynamics of complex systems in which knowledge production is the result of an interactive and heterogeneous composition of the network. The framework owes its popularity to the introduction of the Industry – University – Government (IUG) networks and the emphasis on the active role of public institutions carried out through a number of initiatives and programs supporting knowledge exchange and innovation within the region (Figure 2). In particular, the presence of government institutions in the network of innovative actors is particularly important as far as it is able to provide a series of infrastructure provisions that incentivize the localization of innovative firms within the area. Due to the potential for innovation deriving from the (non-redundant) transfer of information between different epistemic communities (researchers, managers, policy makers) (Capaldo, 2004), the approach has found fertile ground within innovation system literature. Since its introduction, we assisted to a proliferation of case studies committed to the evaluation of the system, based on its actor base composition.

Figure 1.6. The Triple Helix Model of University–Industry–Government Relations

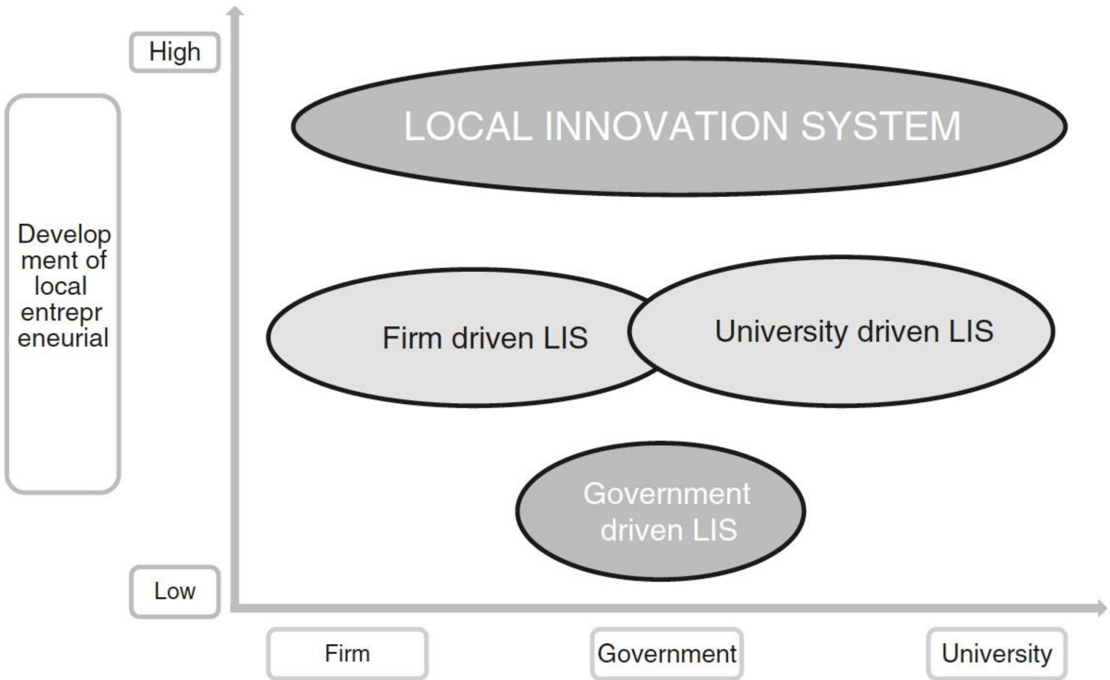


Source: Etzkowitz, 1996

Extant studies not only focus on the physical co-location of the actors and their interactions, but also on their engagement in the creation of the conditions that favor the emergence of LIS through their initiatives and activities. As a way of illustration, Braczyk et al. (1998) propose a classification, which distinguishes three typologies of LIS, i.e. *grassroots*, *network* and *dirigiste*, on the basis of their governance models and the implementation of technology transfer processes.

The *grassroots* model refers to an area where technology transfer is mainly developed and managed at the local level, through the region's own organizations and government structures. In the *network* model technology transfer results from the interplay of institutions at the local, national and global levels. Ultimately, in the *dirigiste* model the technology transfer governance is mostly governed at the central level of national institutions. Ferretti and Parmentola (2015) provide an interesting framework for the classification of LIS (in the specific case of emergent nations), based on the typology of the actor who is taking a leading role in the process of LIS creation and the development level of local entrepreneurial system. More specifically, the creation of a LIS can be driven by one specific actor – a large company, a research institution or a local institution – that can take active role in enacting policies, setting the conditions to incentivize innovation in the local context or make it attractive for innovation firms' localization. The authors identify three typologies of LIS: (i) *government-driven* LIS; (ii) *firm-driven* LIS and (iii) *university-driven* LIS (Figure 1.3).

Figure 1.7. . LIS classification based on the nature of the leading actor



Source: Ferretti, Parmentola (2015)

In this vein, another contribution (Ferretti et al., 2017), while analyzing the development of a (port) innovation system in the City of Rotterdam (NH), focuses on the heterogeneous composition of thesystem with a high level of specialization of the industry (maritime) and provides insights on the *facilitator* role played by the Port of Rotterdam Authority (PORA). Due to PORA's mixed nature of *hybrid organization*, being engaged in both public and private domains with stronger performance requirements - the work presents interesting governance implications. Notably, the authors suggest that Port Authorities engage in cluster management by stimulating exchange of information and face-to-face interactions and by setting their own R&D program, as well as establishing joint ventures and other forms of cooperation with partners who operate in port's hinterlands. More recently, the importance of integrating the perspective of the media-based and culture-based public as well as that of embedding an ecology perspective has been emphasized as beneficial for knowledge-based development processes and policies. Both perspectives enlarged the traditional network composition of innovation systems and enlarged the actor basis to include Civil Society – in the Quadruple Helix model (Carayannis and Campbell, 2009) - and natural environments of society –in the Quintuple Helix (Carayannis et al., 2012).

Unlike the abovementioned systems, that emphasize the spatial dimension of innovation activities, Sectoral Systems of Innovation (SSI) and Technological Innovation Systems (TIS) approaches rely on a particular sector or technology to delimit their system borders. Despite their configuration as a-territorial entities, they maintain the heterogeneity of system's actors as one of the main variables for the innovation systems' assessment. Malerba (2002) define SSI as consisting of three main building blocks: (i) the knowledge and technological domain; (ii) the actors and the networks; (iii) institutions. On the other hand, a TIS is defined as "*a network of agents interacting in the economic/industrial area under a particular institutional infrastructure (…) and involved in the generation, diffusion, and utilization of technology*" (Carlsson and Stankiewicz, 1991) or as the network of actors, rules and material artifacts that influence the speed and direction of technological change in a specific technological area (Hekkert et al., 2007; Markard and Truffer, 2008). Finally, the recent contribution provided by the *MIT Innovation Stakeholder Framework*, besides recognizing the role played by IUG networks in systems of innovation, highlights the importance of the presence of a community of capital risk providers (e.g. venture capitalists, business angels) involved in activities of innovation scouting to diversify their portfolio of investments and providing the context for innovation-driven enterprises (IDE) to start, grow and scale (Budden, Murray 2015). The developers of the *MIT Innovation Stakeholder Framework* identify five key groups of actors that play a crucial in the ecosystem: (i) Entrepreneurs (ii), Risk capital providers, (iii) Large corporations, (iv) Government and (v) Universities (Figure 1.4). Ideally, these five actors should be working synergistically within the innovation ecosystem, through collective action and cooperate to create the necessary conditions for supporting the growth of *innovation-driven enterprises* (IDEs). This specific kind of young firms differentiate from small and medium enterprises (SME) that "*require little startup capital and are handicapped in their ability to grow quickly by a lack of clear competitive advantage*", and rather "*leverages novel ideas and new technologies to establish rapid revenue and job growth potential after initial investment*" (Budden and Murray, 2015).

Figure 1.4. The MIT Innovation Ecosystem Framework

Source: Budden and Murray, 2015

Table 1.5. Actors' Heterogeneity as a Key Performance Indicator of LIS

Theoretical Framework	**Author(s)**	**LIS actors**	**System's boundarie s**	**LIS Classification based based on the acto's leading role**
The Triple Helix framework	Etzkowitz, 1993 and Etzkowitz and Leydesdorff, 1995	Industry – University – Government	Region	---
Local Innovation Systems	Braczyk et al. (1998	Industry – University – Government	Region, Nation and Global	(i) grassroots, (ii) network (iii) dirigiste
Local Innovation Systems	Ferretti and Parmentola (2015)	Industry – University – Government	Region	(i) government-driven LIS; (ii) firm-driven LIS and (iii) university-driven LIS
Quadruple	Carayannis	Industry – University –	Region	---

Helix model	and Campbell, 2009)	Government - Civil Society		
Quintuple Helix	Carayannis et al., 2012	Industry – University – Government - Civil Society - Environment	Region	---
Sectoral Systems of Innovation (SSI)	Malerba, 2002	Industry – University – Government	Technolog y	---
Technologi cal Innovation Systems (TIS)	Carlsson and Stankiewicz, 1991	Industry – University – Government	Industry	---
MIT Innovation Ecosystem Framework	Budden, Murray 2015	Corporate –Entrepreneurship - University – Government - Risk Capital Providers	Region	---

1.2.1.2.Territorial boundaries as a Key Performance Indicator of LIS

A number of approaches, especially from economic geography literature, have for a long time explored the optimal geographic configuration for the well-functioning of a local innovation system. Academic literature on Local Innovation Systems partly takes its roots from the traditional debate existing among the scholars of National Innovation Systems (NIS) (Freeman, 1987; Edquist, 1997) and Regional Innovation Systems (RIS) (Cooke et al., 1997; Asheim, Gertler, 2005). Both perspectives share the belief that innovation originates from a network of institutions in the public and private sector operating in the same territory. However, while the NIS identifies the optimal geographic context with the national boundaries, the latter confines innovation processes within the region, from a meso-level perspective. In other words, while the RIS framework emphasizes the advantages for innovation activities deriving from the emergence of territorial industrial agglomeration, trust mechanisms and cultural proximity, the NIS perspective argues that innovation activities can be better stimulated through a coherent and cohesive set of regulations, policies and incentives at the country level. With specific regard to National Innovation Systems (NIS), scholars emphasize four main components (Freeman, 1987): (i) the role of policy, (ii) the role of corporate R&D in accumulating knowledge and developing advantages from it; (iii) the role of human capital, the organization of work and the development of related capabilities, (iv) the role of industrial conglomerates in being able to profit from innovations emerging from developments along the entire industrial value chain standing upon three main "building blocks" (Lundvall, 1992): (i) Sources of Innovation (Learning and Search and exploration); (ii) Types of Innovation (Radical vs. Incremental); (iii) Non-market institutions (User-Producer Interactions and Institutions) and set-up of actors (especially universities conducting R&D) (Nelson, 1998). Finally, Soete (2012) recognizes the role of social capital (most importantly trust) in the interactive innovation processes. Scholars of geographic economy (Asheim et al., 2003; Asheim and Gertler, 2005), starting from the assumption of the non-homogeneity within countries' regions since many indicators can differ significantly in the areas of the same countries, developed a regionally based approach to Innovation Systems. Doloreux and Parto (2005), identify three main dimensions that characterize the Regional Innovation Systems: (i) the interactions between the actors of the innovation system in relation to the exchange of knowledge; (ii) the set-up and the role of institutions supporting knowledge exchange and innovation within a region; (iii) the role of RIS in regional innovation policy-making. In recent years, several scholars began to question the advantages of considering regions as the fundamental geographic entity for describing the localized nature of innovation systems. Indeed, the LIS perspective, while recognizing the localized nature of innovation, differs from the previous approaches by maintaining the idea that innovation does not necessarily occur within the institutionalized geographic borders of a given area (Bunnel and Coe, 2001; Rantisi, 2002; Moulaert and Sekia, 2003) and may take different spatial configurations through the interplay of national, subnational and transnational systems. As a consequence, scholars started to use the term Local Innovation System, to define a network of locally specialized and locally situated firms, institutions and research agencies, that are involved in a process of collective learning, where this process is not limited to formal geographical borders (de la Mothe and Paquet 1998; Cooke 2001, 2004; Asheim and Coenen 2005).

1.2.1.3. Relationships as a Key Performance Indicator of LIS

Part of the studies approaching LISs from an analytical point of view emphasize the role of relationships between the different actors and organizations of the systems. Social *embeddedness* is one of the key concepts that is applied to the study of innovation systems to explain how non-market relations can favor mechanisms of trust, cooperation, collective learning or learning through interacting and discourage opportunistic behavior (Granovetter, 1985; Lyon, 2000). The concept of *embeddedness* is indeed useful to measure the level of cohesion and actors' integration in the local innovation system. In fact, high levels of cohesion can facilitate knowledge transfer mechanisms and consequently, the LIS development. More specifically, relationships play a crucial role in Local Innovation Systems whether they generate practices of inter-organizational cooperation that allow actors, who are engaged in processes of innovation, to share risks related to new products and to accelerate their time-to-market, as well as to bring together complementary skills and gain access to financial resources and new technologies (Kogut, 1989; Hagerdoorn, 1993; Mowery and Teece, 1993; Eisenhardt and Schoonhoven, 1996; Chesbrough, 2003). As the case may be, relationships take different forms ranging from R&D strategic partnerships to joint ventures or to less structured forms of interaction as in the case of co-organization of events or know-how trading (Uzzi, 1996). But primarily, relationships are a vehicle for new information, or in other words, source of informational advantage (Gulati, 1999) and scholars emphasize their potential for innovation in case of exchange of non-redundant information through ties between actors of different nature (Fagerberg, Martin and Andersen, 2013).

Adapted from the biological sciences, the ecosystem perspective contributes insights on the relational dimension of innovation. The term *innovation ecosystem* has been applied to address the complexities related to innovation (Durst and Poutanen 2013) and the importance of relational capital (Still et al. 2014). Indeed, the innovation ecosystem perspective is based on the premise that communities consist of a heterogeneous and continuously evolving set of constituents that are interconnected through a complex, global network of relationships. These constituents co-create value and are interdependent for survival (Moore 1996; Iansiti and Levien 2004; Basole and Rouse 2008; Russell et al. 2011; Russell, 2015; Basole et al. 2012, Hwang and Horowitt 2012, Mars et al. 2012). As argued by Jackson (2011), "*an innovation ecosystem models the economic dynamics of the complex relationships that are formed between actors or entities whose functional goal is to enable technology development and innovation*". The author argues that the innovation ecosystem includes two different and largely separated economies: (i) the knowledge economy, driven by fundamental research; and (ii) the commercial economy, driven by the marketplace. Of necessity, indeed, the two economies are weakly coupled because the resources invested in the knowledge economy are derived from the commercial sector; this includes government R&D investments, which are ultimately derived from tax revenues. Inter-organizational relationships play a key role in connecting the two economies, especially when the actors involved have the ability to complement their skills for the creation of innovation production and commercialization, as for example the synergies existing between venture capitalists and young start-ups that go beyond exclusively investment relationships to include support and consultancy on business management issues.

When it comes to relations there are at least two aspects to take into account. Firstly, the nature and the characteristics of the ties that compose the network i.e. the *network portfolio*, and secondly, the structural configuration of the network, with specific regard to its characteristics in terms of *closure* or *openness* and the average positions of nodes in terms of *centrality* or bridging function through structural holes, i.e. *network structure*. The seminal work of Saxenian (1994) represents a first attempt to relate the structure of networks to the performance of regional clusters: the more decentralized and horizontal industrial system of Silicon Valley seemed to outperform Route 128 which, conversely, was recognized as a network dominated by a few large firms, with a high degree of vertical integration that privileges practices of secrecy and corporate hierarchies. A great part of contributions addressing the relational dimension for the evaluation of LIS originates from network literature. These contributions are reviewed in the second chapter of the present work, leading to the identification of the literature gap that drives the formulation of the research questions and the realization of the empirical study.

1.2.2 LIS Output-Driven Approach

While the *Input-driven approach* tends to evaluate the innovation systems on the basis of their structural characteristics, the *Output-driven approach* privileges the focus on the effects of LIS creation in terms of production of new knowledge (innovation output) and contribution to the regional growth, from a functionalist perspective.

Literature from different innovation systems' approaches provides a variety of alternative methods and indicators to measure innovation system performance. Based on a study conducted on 108 papers on innovation performance Becheikh, Landry and Amara, 2006 show that there is still a lack of agreement on which indicators to use (Figure 1.5). Some of the reasons behind the heterogeneity of the choices relative to innovation performance indicators can be traceable to:

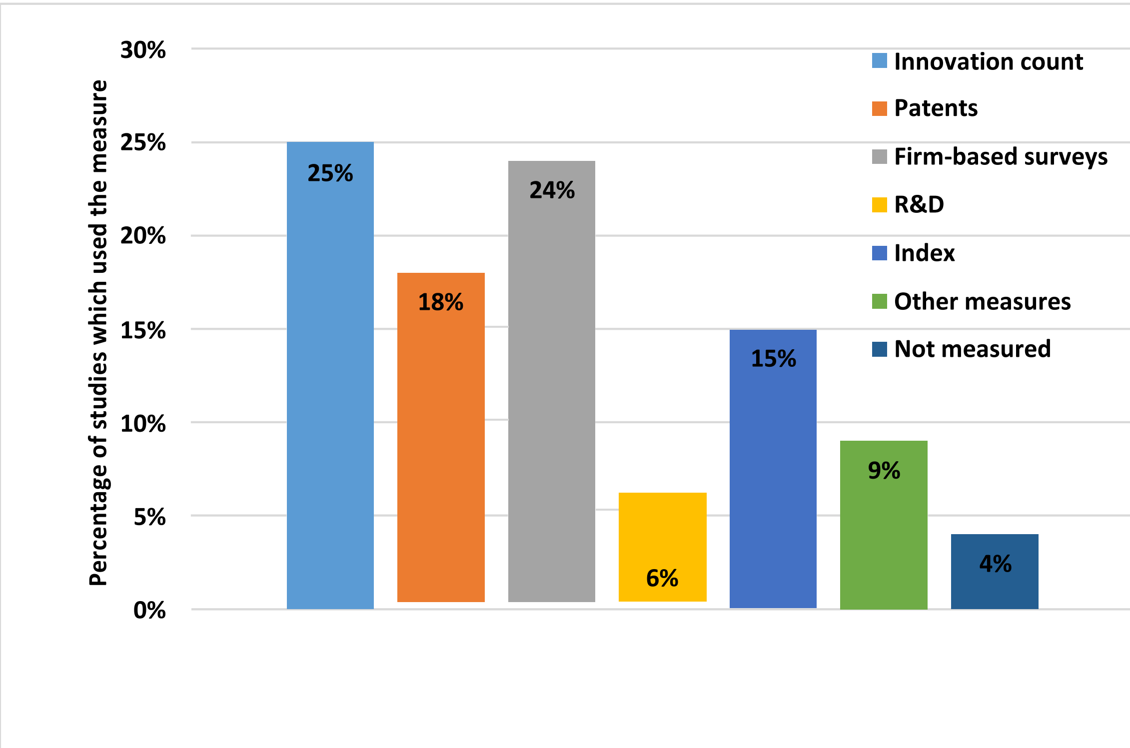
- The *complex nature of innovation systems*, which makes it difficult to find a single indicator for measuring the multiple dimensions of the system in terms of actors, dynamics and impacts;
- The *lack of a commonly accepted definition of innovation itself*. More specifically, measuring choices depend on the type of innovation under analysis (radical vs. incremental or product

vs. process);

- The *unclear distinction between innovation capacity and innovation performance* itself. In other words, the question is whether focusing on the number of innovations produced in a specific time-frame or rather on the creation of environments and competencies capable of sustaining learning and innovation in the future.

Innovation involves multidimensional novelty (OECD, 1997) and therefore, key problems with innovation indicators concern the underlying conceptualization of the object being measured, the meaning of the measurement concept and the general feasibility of different types of measurement. Edquist and Zabala (2009f) clarify the difference between innovation capacity and innovation performance through the concepts of input and output. However, any indicator both input and output, shows its limitations. Table 1.5 summarizes some of the main advantages and disadvantages of the most common used indicators.

Figure 1.5. Most common innovation performance metrics



Source: author's own elaboration from Becheikh, Landry and Amara (2006)

Current major indicators include input indicators such as R&D data (Archibugi and Coco, 2005), data on patent applications (Audretsch, 2004), bibliometric data (citations and scientific publications). However, these metrics present some limitations, especially if these are used as single indicators. Firstly, R&D data are considered to be indicators of innovation capacity rather than performance (Eggink, 2012), as well as being considered as a measure that overestimates innovation (Audretsch, 2004; Becheikh et al., 2006; Greenhalgh and Rogers, 2010) as not all R&D expenditures do necessarily lead to innovation and conversely not all inventions are the result of R&D investments. Secondly, patents, even if these are used in many studies as a measure of innovation output, are considered by some scholars as "intermediate output" since they are deemed to measure *inventions* rather than *innovation*, and not all inventions are patented (Fagerberg, Srholec and Verspagen, 2009; LeBel, 2008). Finally, even publications are criticized as their quality can vary widely between countries. As Archibugi and Coco (2005) noted, English-speaking countries risk to be over- represented as most journals monitored by the Institute for Scientific Information (ISI) are published in English. In the last decades, innovation surveys have become popular in order to achieve more directly innovation-focused indicators to explore the whole process of innovation. In particular, the Community Innovation Survey (CIS) that provides statistics analyzed by types of innovators, economic activities and size classes aims at developing and incorporating data on:

- Non - R&D inputs, such as expenditure on activities related to the innovation of new products (R&D, training, design, equipment acquisition, etc);
- Outputs of incrementally and radically changed products, and sales flowing from these products;
- Sources of information relevant to innovation;

- Technological collaboration;
- Perception of obstacles to innovation, and factors promoting innovation (Fagerberg, 2005).

Table 1.5. Most common used indicators of innovation performance

Metric	Advantages	Disadvantages
R&D Expenditure	Comparability time/countries	Overestimation of innovation; Time-lag not considered
Patents	Availability of detailed statistics; Inventions are usually commercialized	Intermediate output indicator; Time-lag not considered
Innovation Counts	Tangibility of innovation output	Favor radical innovation; Favor product innovation
Scientific Publications	Availability of detailed statistics	Favor English-speaking countries; Quality can vary widely over countries
Royalties and License fees	Comparability time/countries	Acquisition of technology/Creation of technology

Source: author's own elaboration

In order to overcome the problems of choice among input/output indicators, in the last 15 years, there has been a proliferation of composite indicators, which became very popular within Innovation Systems literature. Indeed, scholars in the field, due to the systems' complex nature, tend to use composite indicators to overcome the possible problem of implementing an incorrect or inaccurate single variable (Greenhalgh and Rogers, 2010). Some approaches tend to define innovation system performance in terms of functions achieved (Hekkert et al. 2007, Bergek et al., 2008) and provide a set of indicators for each specific function (Hekkert et al. 2007). Carlsson et al. (2002) for example, measure innovation in terms of generation, diffusion and use of knowledge, displaying some possible measurements (Rickne, 2001) that may be combined for an effective evaluation of the system (Figure 6). Other contributions define innovation system performance as the capacity of knowledge institutions to exploit the results of scientific research, focusing on patents, licensing, applied research projects; spin-offs (Acs et al, 2002; Fontes, 2005; Mustilli et al., 2012).

Figure 1.6. Examples of performance metrics for an emerging technological system

Indicators of generation of knowledge	Indicators of the diffusion of knowledge	Indicators of the use of knowledge
Number of patents	Timing/the stage of development	Employment
Number of engineers or scientists	Regulatory acceptance	Turnover
Mobility of professionals	Number of partners/number of distribution licenses	Growth
Technological diversity, e.g. number of technological fields		Financial assets

Source: author's own elaboration from Rickne, 2001

There has been significant effort derived by international organizations that try to assess the innovative performance at the national and regional scale to inform political interventions. As in the case of the *Revealed Regional System Innovation Index* (RRSI) based on the *European Innovation Scorecard (EIS)* or the *Global Competitiveness Index* (GCI) but also from innovation literature as in the case of the *ArCo Index* developed by Archibugi and Coco (2004) that was constructed as the average of eight different indicators reflecting various aspects of technological capability (Table 1.6). These indexes combine both input (e.g. R&D expenditures) and output (e.g. patents and scientific publications) snapshot indicators to provide a picture of the system performance as complete as possible. An interesting contribution (Bajmocy, 2012) elaborates the Local Innovation Index, a functionalist approach, that assesses the system's performance based on 26 indicators (Table 1.7), which are classified according to four functions, i.e. knowledge creation; knowledge exploitation; innovation background infrastructure and links.

Table 1.6. Composite indicators of Innovation System Performance

RRSII (Ue)	ArCo technology Index	Global Competitiveness Index (WEF)
1. population with tertiary education	1. patents	1. capacity to innovate
2. participation in life-long learning	2. scientific articles	2. quality of scientific research institutions
3. employment in medium-high and high-tech manufacturing	3. internet penetration	3. company spending on R&D
4. employment in high-tech services	4. telephone penetration	4. university-industry research collaboration

5. public R&D expenditure	5. electricity consumption	5. government procurement of advanced technology products
6. business R&D expenditure	6. tertiary, science and engineering enrolment	6. availability of scientists and engineers
7. High-tech patent application	7. mean years of schooling	7. utility patents
	8. literacy rate	8. intellectual property protection

Source: authors' own elaboration from Bajmocy, 2012

Table 1.7. The Local Innovation Index (Bajmocy 2012)

Local Innovation Index			
F1. Knowledge creation (KC)	**F2. Knowledge exploitation (KE)**	**F3. Innovation background infrastructure (BI)**	**F4. Links (LINK)**
(1) Government R&D expenditures (per capita)	(1) Average number of valid home patent applications for four years (per capita)	(1) # of newly registered enterprises (total number of enterprises)	(1) # of patent co-applications as an average of four years (total number of co-applications)
(2) Basic research expenditures (per capita)	(2) Corporate R&D expenditures (per capita)	(2) # of entries and exits (total number of enterprises)	(2) # of microregions that have co-application links with the given micro-region as an average of four years
(3) # of teaching staff in higher education institutions by location of headquarters (per capita)	(3) Applied research expenditures (per capita)	(3) # of population with maximum primary education subtracted from 100% (population aged 18-24),	(3*) # of majority or exclusively foreign-owned companies (per capita)
(4) # of teaching staff in higher education institutions by place of education (per capita)	(4) Experimental research expenditures (per capita)	(4) # of employees with tertiary education (number of employees)	(4) Net turnover of majority or exclusively foreign-owned companies (total number of companies)
(5) # of graduating students (per capita)	(5) # of enterprises at high- and medium-tech manufacturing (total number of enterprises)	(5) # of inhabitants with tertiary education (population aged 7 or above)	(5) Total staff of majority or exclusively foreign-owned companies (total staff of companies)
(6) # of students attending tertiary education (per capita)	(6) Number of enterprises at hightech KIBS (total number of enterprises)	(6) Number of ISDN lines (per capita)	(6) Net turnover from export sales (total net turnover of companies)
	(7) Number of full-time bachelor and master students (per capita)	(7) Number of enterprises at KIMS (total number of enterprises)	

Source: author's own elaboration from Bajmocy, 2012

1.3 Summary

This chapter aims to provide a definition of Local Innovation System and, secondly, to offer an overview of the state of the art regarding the study of LIS systems performance. Based on the identification of the drivers of LIS successful performance two main approaches are identified within the literature of innovation systems: the *input-driven approach* and the *output-driven approach*. Table 8 summarizes the main focal points of both streams. This work positions itself in the first stream of studies (*input-driven approach*) and more specifically, focuses on the relational dimension of LIS. This work aims to provide a theoretical framework for the study of the relational dimension of LISs, based on the assumption that the mere co-location of LIS's actors *per se* does not necessarily identify a LIS as such (Russell, 2015) and that the bottom-up creation of synergies and cooperative mechanisms between local actors are the drivers for the well-functioning of a LIS given the advantages in terms of knowledge transfer, access to resources and pooling of complementary capabilities (Ahuja, 2000) thus contributing to both innovation creation and regional economic growth.

Table 1.8. LIS Input-driven and Output –driven approaches

	INPUT-DRIVEN APPROACH		**OUTPUT- DRIVEN APPROACH**	
Perspective	Structural		Functional	
Focus	**Main actors' composition**	e.g. Etzkowitz, 1993 and Etzkowitz and Leydesdorff, 1995; Murray, Budden 2015	**System innovation and Economic output**	e.g. Bajmocy 2012; Campanella 2014; Guan and Chen, 2010; Lerro and Schima, 2015
	Spatial Dimension	e.g. de la Mothe and Paquet 1998; Cooke 2001, 2004; Asheim and Coenen 2005		
	Relational Dimension	e.g. Saxenian, 1994; Ahuja, 2000 Oven-Smith & Powell, 2004; Russell et al., 2015		

Source: author's own elaboration

CHAPTER 2. LOCAL INNOVATION SYSTEMS AS NETWORKS OF RELATIONSHIPS

From the review of studies on the drivers of local innovation systems' performance reviewed in Chapter one, two main approaches have been identified, namely the input-driven and the output-driven approaches. This chapter aims to explore a particular aspect that is studied within the input-driven approach, i.e. the relational dimension, where the present work is grounded. To this end, the next section will provide an in-depth analysis of key concepts and empirical issues concerning this specific analytical perspective. More precisely, the first section discusses the key role played by networks of relationships within systems of innovation, with specific regard to the benefits deriving from partnering and the impact of network architecture on the access to relational capital. The second section provides an overview of the proximity framework, which highlights the conditions that favor network emergence. Section three introduces the use of the Social Network Analysis (SNA) as an approach for the study of LIS and illustrates the different positions within the debate on the desirable network structure to boost the innovation system performance, within network literature. Section four reviews empirical studies adopting a SNA approach for the study of LIS, according to seven specific dimensions. Main findings emerging from the literature review leads to the identification of the literature gap, which is discussed in section five, before concluding.

2.1 Innovation networks: key concepts

By definition, a network is a set of nodes (e.g. persons, organizations) linked by a set of relationships between them (Fombrun, 1982) and networks of innovating firms are identified in different configurations: supplier-user networks, networks of pioneers and adopters, regional inter-industrial networks, international strategic technological alliances, and professional inter-organizational networks (DeBresson and Amesse, 1991). According to economic sociology, whether operationalized in informal ties among individuals (Granovetter 1985, Uzzi 1996), interlocking affiliations among corporations (Mizruchi 1992, Davis et al. 2003), or formal, contractually defined, strategic alliances (Eisenhardt and Schoonhoven 1996, Powell et al. 1996), networks represent a key component of markets due to their ability to channel and orient flows of information and resources within a social structure. Innovation literature generally appoints networks as critical to innovation process with specific regard to knowledge – intensive sectors, where innovation involves the transformation of the results of scientific results into marketable products and services.

2.1.1 Benefiting from innovation networks

Depending on the choices about the preferred mode of commercialization, firms may decide to operate only in the upstream phases of the value chain, thus focusing on production and then selling their intellectual property or rather opt for a full or partial engagement in downstream operations by developing and selling their products directly to the market (Arora, 2002). In both cases, relationships with external organizations play a crucial role but depending on firm's location in the value chain they assume different forms, ranging from licensing agreements and venture investments for the development of the technology (as in the first case) to strategic alliances for gaining access to the market for the product commercialization. In particular, young small firms operating in knowledge-intensive industries, such as biotechnology or software development, are those that are more likely to benefit the most from networking, with specific regard to (i) *reputation advantages*; (ii) *access to information* and (iii) *resource mobilization*.

(i) *Reputation advantages*. Primarily, social networks play a particularly important function during the early stages of business formation and development as they provide *credibility and legitimacy* to the young business thus decreasing the high level of uncertainty and risk perception related to technologies that have not yet proven their efficacy on the market (Moensted, 2007).

(ii) *Access to information.* Secondly, networks are a vehicle for new information, or in other words, source of *informational advantage* (Gulati, 1999) especially about the quality and location of resources. Network literature emphasizes their potential for innovation in case of exchange of non-redundant information through ties between actors of different nature (Fagerberg, Martin and Andersen, 2013).

(iii) *Resource mobilization.* Finally, networks can be exploited for *mobilizing the resources* required during the innovation process (Stuart and Sorenson, 2003). Actors operating in knowledge-intensive industries may require both technological and non-technological resources. While the former highly depend on the knowledge base that prevails in the industry and are generally channeled through R&D projects, S&T partnerships, patents (both in co-development and provision practices), non-technological resources generally refer to *complementary assets* (Teece, 1986), that are required to commercialize and capture value from the technology as for example, financial capital, manufacturing or marketing services, regulatory knowledge, etc.

2.1.2 Why network structure matters: the impact of network architecture on resource mobilization

Access to resources through social networks has been the object of analysis of both literature on social networks and entrepreneurship as well as literature on innovation networks. The former considers that entrepreneurial activities are essentially social processes that are *embedded* in networks of social relationships among individuals (Aldrich and Zimmer, 1986; Uzzi, 1997), which, in combination with the social environment, highly affect the business formation and development (Huang et al., 2012). On the other hand, literature on innovation networks emphasizes the role of networks in giving access to *critical resources* (especially technological and scientific knowledge) in alternative or in combination to the market (Ozman, 2009), which make them key during the early stages of business formation and development.

However, resource mobilization through networks may vary according to specific dimensions of network architecture. Salavisa et al. (2012) identify, from extant literature, four aspects affecting the process of resource access, namely *network size*, *network composition*, *network positioning* and *relational structure*.

As far as *network size* is concerned, following Burt (2000) the larger is the network, the more complete and diverse is the set of available resources and entrepreneurs can use indirect ties to enlarge their personal network and gain access to a larger quantity of assets.

With regard to *network composition*, there is a traditional debate whether main advantages can be traceable to the concepts of *heterophily* and *homophily*. On the one hand, scholars (Burt, 2002; Nooteboom, 1999 and Baum et al., 2000) emphasize the benefits of actors' diversity in terms of non-redundant exchange of knowledge and information. On the other hand, a network homogenous composition can make solid and long-term partnerships more likely and enhance mechanisms of trust and collective problem solving (Powell et al., 1996). As for *network positioning*, a position of centrality in the network has been considered to give advantages in terms of new partnership formation (Ahuja, 2000, Gulati and Gargiulo, 1999); access to key resources and business economic and innovation performance (Powell et al., 1999). Finally, *relational structure* is a concept relative to nature of ties (strong vs. weak; formal vs. informal; simple vs. multiplex) that the network's actors choose to establish with their partners in order to gain resources. Contrasting visions characterize the debate on which relational structure ensures a better performance and main arguments relate to the trade-off existing between the potential for innovation deriving from weak and informal ties and the trust-based exchange of information resulting from strong ones. The long-standing debate on the optimal network structure will be in-depth analyzed in section 2.3.

2.2 What drives tie emergence: the proximity framework

2.2.1 The role of proximity in the emergence of knowledge networks

The role of proximity in favoring practices of knowledge transfer and the emergence of inter-organizational relationships has increasingly gained the attention of scholars from organizational and management studies (Oerlemans and Meeus, 2005; Knoben and Oerlemans, 2006; Ritter and Gemunden 2003; Molina-Morales et al., 2014; 2015; Presutti et al., 2013) as well as from regional and urban studies (Kirat and Lung, 1999; Huber, 2012). In economic geography the issue concerning the positive relationships between geographic proximity and tie formation has for long time been one of the most debated question (Morgan, 2004). The intuitive positive association of between spatial distance and tie formation has been empirically validated in a number of studies (e.g. Bell and Zaheer, 2007; Maggioni et al., 2007; Abramovsky and Simpson, 2011). Additionally, also other forms of proximities have been proven to act as substitute of geographic concentration in stimulating network formation (see e.g. Singh, 2005; Agrawal et al., 2006; Sorenson et al., 2006; Ponds et al., 2007; Breschi et al., 2010). A stream of studies within Evolutionary Economic Geography has provided significant contribution to this field of research, through the elaboration of an analytic framework – the proximity Framework – that extends the notion of proximity to multiple dimensions and allows isolating geographical proximity as only one of the potential factors stimulating the emergence of networks. Originating from the French school of proximity dynamics

(Gilly and Torre, 2000; Torre and Rallet, 2005; Carrincazeaux et al., 2008) that represents the first attempt to combine geographical proximity with other forms of similarities (i.e. the organizational proximity), the *Proximity Framework* owes its popularity to the work of Boschma (2005) that analyzes the relationship existing between proximity and innovation. The author starts from the assumption according to which "*geographical proximity cannot be assessed in isolation*" and that "*geographical proximity per se is neither a necessary nor a sufficient condition for learning to take place*" and proposes a framework that combines five dimensions of proximity i.e. *cognitive, organizational, social, institutional* and *geographical proximity*, which are deemed to positively influence the emergence of knowledge networks. The underlying idea is that practices of inter-organizational cooperation are more likely to occur if the parties show certain similarities. In other words, the involved actors should present a certain level of *homophily* (Mc Pherson et al., 2001) not limited to the spatial co-location.

2.2.2 Geographical Proximity

In its simplest form, the term refers to the physical distance that separates two organizations and their economic activities (Gilly and Torre, 2000) and that is deemed to enhance face-to-face interactions. More recently, scholars have distinguished co-location and geographical proximity with the aim to specify that actors can share geographic proximity even without being co-located by the means of the c.d. *temporary geographic proximity* (Torre, 2008) that allows two organizations to interact through visits, meetings and conferences. Traditionally, geographical propinquity has been considered as a source of competitive advantage in the literature of agglomeration economies (Rosenthal and Strange, 2001), technological cluster s(Porter, 1998) and Italian districts (Becattini et al., 2009). Beyond material factors, such as the reduction of transport and logistics costs or access for the use of common technological platforms, spatial proximity has also been deemed as a condition enhancing the particular transfer of tacit knowledge, a key driver of innovation processes and its stickiness (Bathelt et al., 2004) in networks of local systems of innovation (Audretsch and Feldman, 1996; Howells, 2002; Tallman et al., 2004)

2.2.3 Cognitive proximity

This dimension of proximity refers to the conditions of similitude that facilitate the emergence of ties among actors sharing common knowledge bases and competences (Nooteboom, 2000; Knoben and Oerlmans, 2006). More specifically, this particular kind of proximity is deemed to drive the c.d. *absorptive capacity* (Cohen and Levinthal, 1990) within interactive learning processes among the parties involved in the relationships. However, organizations cooperate in order to gain access to external and new knowledge, which in turn requires a certain degree of cognitive distance between the involved parties. As a consequence, this leads to a trade-off between the novelty of the exchanged information (deriving from different knowledge bases) and the efficacy of communication (resulting from similar knowledge background (Balland, 2012)). Consequently, cognitive proximity is considered as one of the key decisions driving the choice of future partners.

2.2.4 Organizational proximity

This category of proximity indicates that actors belonging to the same organization, or to the same *corporate group*, show a greater tendency to share knowledge and innovate. More in detail, this category refers to *the degree of strategic interdependence between two organizations, and it reduces uncertainty about the behavior of the future partner".* This proximity occurs between partners belonging to the same organization, that is between parent companies and subsidiaries. According to Boshma (2005) the degree of organizational proximity depends on the extent of autonomy and control induced by their tie. More specifically, actors sharing a high level o f organizational proximity tend to avoid more easily unintended knowledge spillovers and decrease the uncertainty rate, which, in turn, leads to a reduction in the costs of collaboration "*by providing an easier exchange of engineers, working groups or meetings*" (Balland 2012) as well as a more available exchange of relevant information about the knowledge bases of the involved parties, with good results in terms of efficacy of the collaboration and cognitive matching (Balland, 2012).

2.2.5 Institutional proximity

Following Edquist and Johnson (1997), institutions are defined as a "*set of common habits, routines, established practices, rules, or laws that regulate the relations and interactions between individuals and groups*". Consequently, a distinction can be made between formal institutions (e.g. laws and rules) and informal institutions (as habits and cultural norms) that, according to Boshma, implies both the idea of economic agents sharing a common language, law systems, regulations and language that provide the basis for coordinating and collective action. This type of proximity is therefore considered to reduce uncertainty and transaction costs. Therefore, institutional proximity can be regarded as an enabling factor that provides the stability required for interactive learning to take place. On the other hand, institutional proximity may also be a source of local inertia when restructuring of old and rigid structures meets resistance from conservative actors who see in change a threat to their vested interests, leaving no room for "*experiments with new institutions that are required for the successful implementation of new ideas and innovations*" (Boshma, 2005).

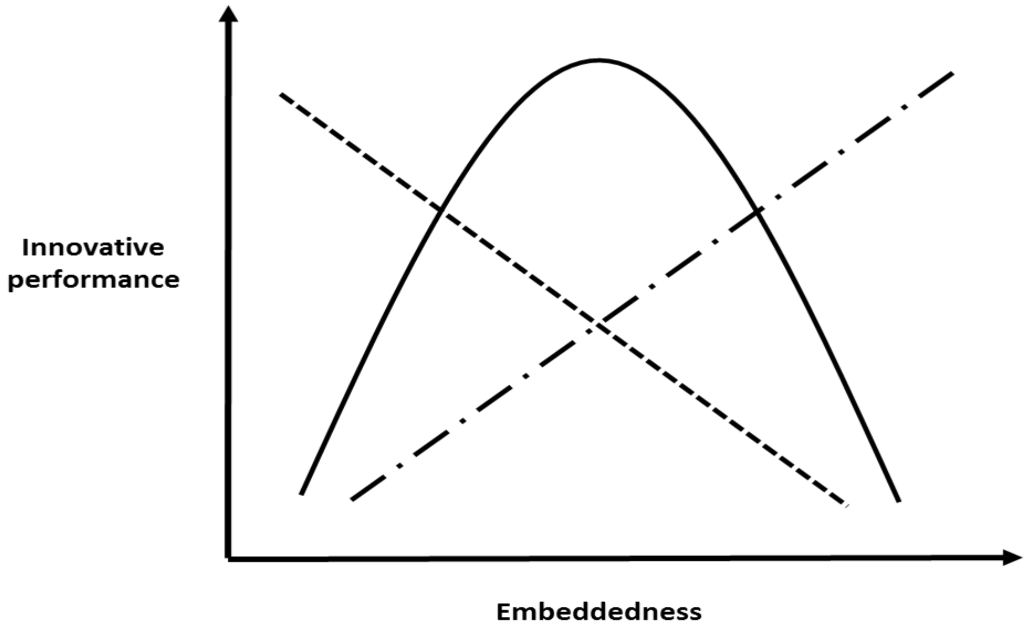
2.2.6 Social proximity

The idea of social proximity is generally expressed through the concept of *embeddeness* (Polanyi, 1944; Granovetter, 1973), and emphasizes the crucial role played by individual and personal ties -

the *old boys network* - in establishing economic relationships on the basis of trust mechanisms. Balland (2012) shows that actors are more inclined to bond ties with individuals that share their same behaviors in relational dynamics. More precisely, social proximity refers to reputation and trust effects resulting from experience achieved through past collaborations and repeated interaction among the actors over time. Personal relationships, friendships and mostly trust, enhance the transfer of informal communication that induces organizations with a common partner to cooperate with each other.

To sum up organizations are more likely to cooperate with each other when they present similar knowledge bases, belong to the same corporate group, share common norms, values and routines, are embedded in a common social context or when these are co-located in the same geographical region (Balland, 2012). According to the proximity framework, geographic proximity may ease interactive learning but does not represent a sufficient condition and neither a necessary one. More precisely, spatial propinquity is not necessary because it can be replaceable by other types of proximity to address the problems of coordination and secondly, it is not sufficient since learning processes need a certain extent of cognitive proximity to be efficient. However, besides stimulating tie formation, all different forms of proximity also play a role in increasing the effectiveness of knowledge transfer and novelty generation. As shown by Boshma et al. (2002) with specific regard to social proximity, there is a positive relationship between *embeddeness* and innovation performance (Fig. 2.1).

Figure 2.1. The relationships between embeddedness and innovative performance



Source: Boshma, 2002

2.2.7 The risks of "too much proximity"

The advantages of proximity in terms of more efficacy in communication, discouragement of opportunistic behavior and limitation of unintended local knowledge spillovers have been widely discussed in the literature and found common agreement. However, it is argued that an environment with organizations in excessive proximity can be detrimental as far as proximity shapes a condition of *knowledge overload* (Granovetter, 1973) as a result of an excessive network "closeness" that can be harmful for new knowledge generation and prevent learning to take place (Geldes et al., 2015). This phenomenon has also been referred to as the "*proximity paradox*" (Broekel and Boschma, 2011; Cassi and Plunket, 2014) and depicts a condition of too much proximity. Such a condition, is considered to cause some undesired effects that may hinder innovation to take place (Boshma, 2005) with particular regard to *lock-in mechanisms* deriving from a too closed network or local inertia as a result of extremely rigid institutions that are resistant to change, as well as lack of sources of novelty due to redundancy of information between agents and organizations sharing a common knowledge base and high level of cognitive proximity. A significant number of empirical contributions demonstrate how excessive cognitive proximity could eventually reduce inter-organizational knowledge exchange, and too high level of closeness between partners on any proximity dimension could be harmful for their innovation performance. As a way of illustration, Ben Lataifa and Rabeau (2013) investigate the reasons and the mechanisms through which proximity may impede the creation of new entrepreneurship. In this vein, Molina-Morales et al. (2015) explore the potential negative effects resulting from the diverse forms of proximity and show that the existence of cognitive and institutional proximities negatively affect tie generation in the later stages. In order to meet some of these inconveniences, Boshma (2005) proposes a set of adjusting mechanisms that can be traceable to the achievement of a knowledge base consisting of a diverse, yet complementary set of capabilities; the constitution of more loosely coupled networks; the combination of both embedded and market relations between agents; a mixed innovation system model between *local buzz* and opening to extra-territorial linkages and finally a common institutional system that guarantees checks and balances (Table 2.1). Moreover, the role of geographical proximity has been the object of further criticism by a stream of studies that emphasizes the *virtualization* of inter-firm relationships – as a result of globalization– and downsizes the role of spatial concentration in network development (Fitjar and Rodriguez Pose, 2016).

Table 2.1 The proximity framework

	Key dimension	**Too little proximity**	**Too much proximity**	**Possible solutions**
1. Cognitive	Knowledge gap	Misunderstanding	Lack of sources of novelty	Common knowledge base with diverse but complementary capabilities
2.Organizational	Control	Opportunism	Bureaucracy	Loosely coupled system
3.Social	Trust (based on social relations)	Opportunism	No economic rationale	Mixture of market and embedded relations

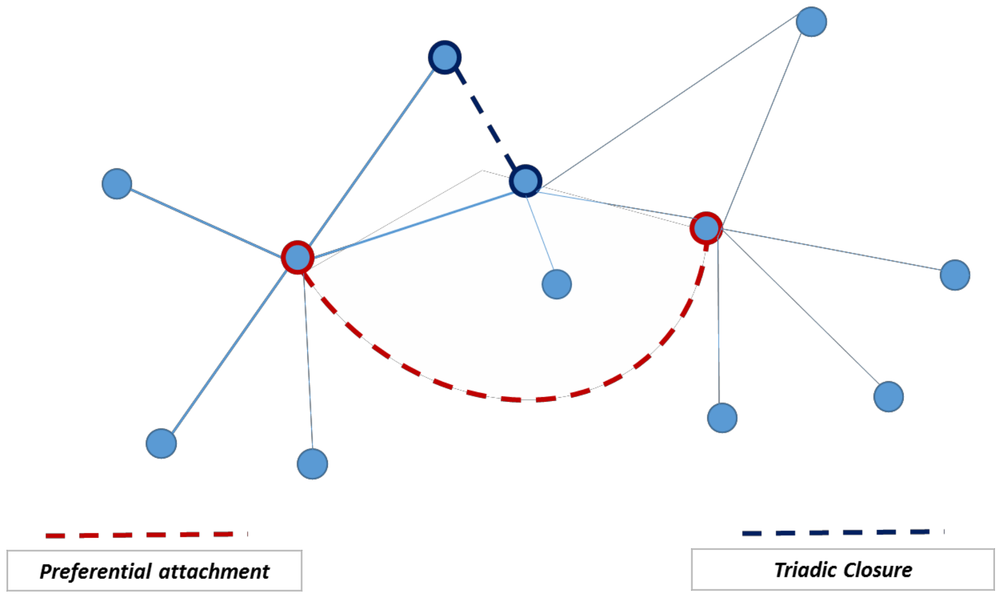
4.Institutional	Trust (based on common institutions)	Opportunism	Lock-in and inertia	Institutional check and balances
5.Geographical	Distance	No spatial externalities	Lack of geographical opennes	Mix of local "buzz" and extra local linkages

Source: author's own elaboration from Boshma 2005

2.3 The Social Network Approach for the study of Innovation Systems

Social Network Analysis (SNA) has been widely implemented for the sociological study of individuals and organizations (Wasserman and Faust, 1994; Welser et al., 2007), as well as for the assessment of nested structures of inter-firm relationships (Moody and White 2003; Halinen et al. 2012). In particular, studies within economic geography have paid increasing attention to relational issues (Dicken et al., 2001; Bathelt and Gluckler, 2003; Yeung, 2005) and provided a rich narrative on spatial dynamics of evolution. However, despite their valuable contribution, these studies have been the object of criticism by a number of scholars who appoint the lack of formalization and scientific rigor as one of the main weaknesses of this approach (see e.g. Giuliani and Bell, 2005; Cantner and Graf, 2006; Grabher, 2006; Gluckler, 2007; Sunley, 2008). Balland et al., (2013) argue that these flaws in relational approach can be partially overcome through the use of network analysis, as it "*allows for a quantitative investigation of inter-organizational interactions*". More specifically, networks' main components are actors (nodes) and their relationships (edges) and visual network analysis can serve as a tool for revealing the flow of information, know-how and financial resources among different actors (Russell et al. 2011). Relational metrics can allow for a deeper understanding of system's emergent structures, patterns and transformation dynamics (Freeman, 2002) as well as for a comparative analysis over time and across regions. As a result, scholars in economic geography have increasingly adopted network analysis within their methodology choices (Murdoch, 2000; Grabher and Ibert, 2006; Bergman, 2009; Ter Wal and Boschma, 2009) with specific regard to the study of certain endogenous structural network effects (Gluckler, 2007) such as *transitivity* or *preferential attachment* mechanisms in driving network evolution. More precisely, while the former refers to the c.d. *triadic closure*, that is the tendency of two unconnected nodes to tie with each other in case they share a common partner (Davis, 1970; Holland and Leinhardt, 1971), the latter refers to the attractiveness exerted by nodes in a position of high centrality within the network that leads new entering nodes to partner with them (Barabasi and Albert, 1999) (Fig. 2.2). Apart from the drivers of network evolution, many scholars have increasingly focused on the effects and implications of structural characteristics of networks on the knowledge transfer and innovation performance. Contrasting visions have characterized this specific stream of studies, which are illustrated in the next section.

Figure 2.2 Networks' endogenous effects: Preferential attachment; Triadic Closure

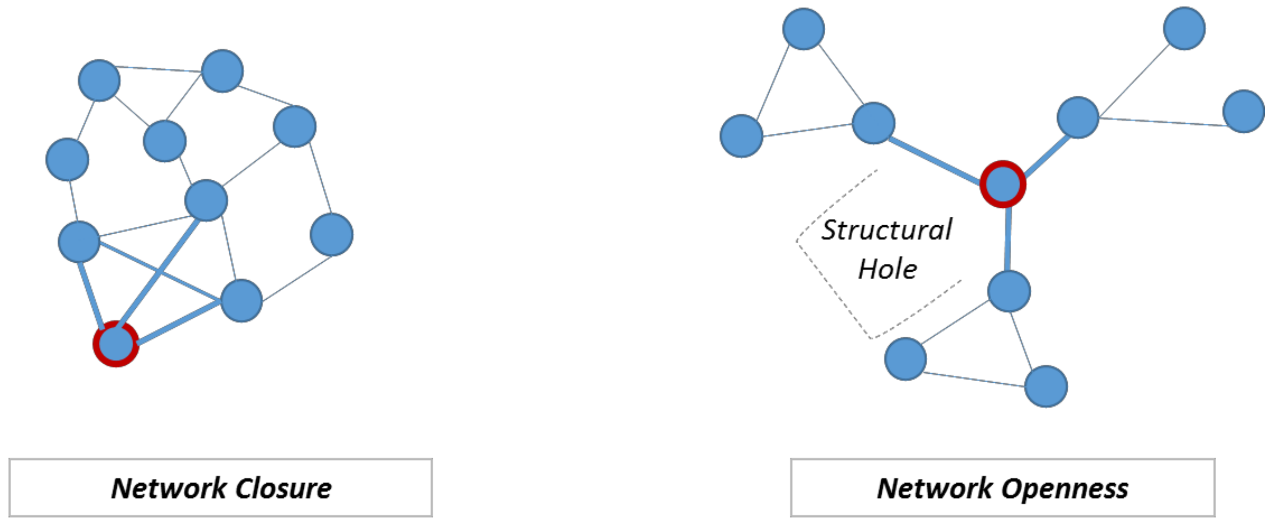


Source: author's own elaboration from Gluckler, 2007

2.3.1 The debate on the desirable network structure: key concepts

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 hole* arguments. The debate is about 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*, 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) (Fig. 2.3).

Figure 2.3 Coleman's Network closure vs. Burt's Structural hole



Source: authors' own elaboration

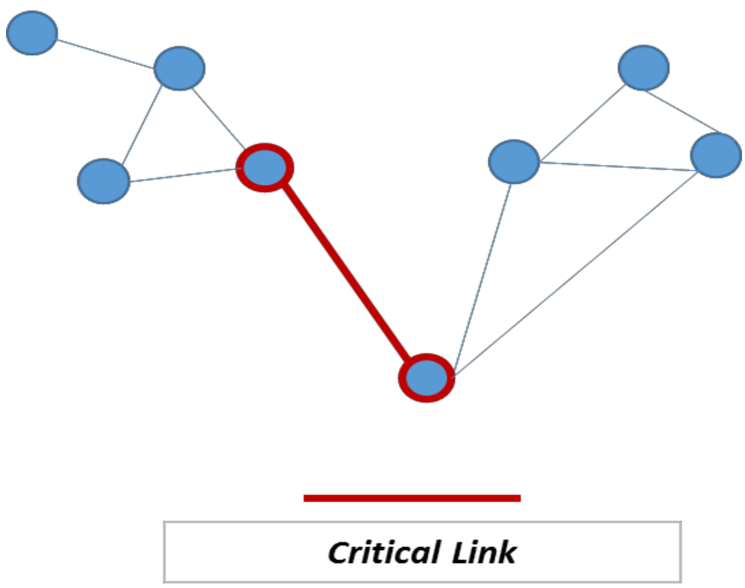
2.3.1.1 Network closure

Coleman (1988, 1990) is one of the most prominent authors of the closure argument. His view emphasizes the importance of strong ties as they encourage the emergence of cooperative mechanisms; promote the development of shared social norms and trust and uncertainty reduction. Typically, closed and cohesive networks are characterized by frequent, reciprocal and repeated interactions where the involved parties usually have the possibility to cross-check information resulting from direct ties by the means of indirect paths in the network (Cassi et al., 2012). The combination of these properties is deemed to generate trust mechanisms within partnerships of collaboration (Walker et al., 1997; Buskens, 2002; McEvily et al., 2003) which in turn, strengthen the motivation and level of commitment to share knowledge within the relationship (Reagans and McEvily, 2003), with specific regard to the exchange of complex as well as sensitive knowledge (Zaheer and Bell, 2005). On this subject, Gargiulo and Benassi (2000) and Beckman et al. (2004) show how in situations of high levels of risk, market uncertainty and costs related to opportunistic behavior, actors tend to prefer to embed themselves in dense and close network structures, as in the case of US venture capital networks (Sorenson and Stuart, 2008). The repeated exchange among stable members is deemed to improve coordination and access to social capital. Therefore, the availability of social capital turns out to be function of the *closure* of the network surrounding them. In Coleman's view, closed networks are the source of social capital as they provide a better access to information and discourage opportunistic behavior (Coleman, 1988; Walker, Kogut, and Shan, 1997; Rowley, Behrens, and Krackhardt 2000) as "*closure facilitates sanctions and makes less risky for people in the network to trust one another*" (Burt, 2002) due to the threat of reputation loss. Cohesive and dense networks are likely to have similar information and thus provide redundant information benefits. Additionally, this perspective suggests that redundant ties among firms may result in a collective action's resolution of the problems.

2.3.1.2 Structural Holes

Conversely, Burt's structural hole theory (1992, 1997, 2002) emphasizes the role of weak ties and the lack of network closure. The argument considers social capital as a function of brokerage opportunities and relies on concepts that originated in sociology during the 1970s, namely the *strength of weak ties* (Granovetter, 1973) and *betweenness centrality* (Freeman, 1977). This perspective can be considered as an extension of the Granovetter's argument about the strength of weak ties that suggests that a greater amount of information is more easily obtained through weak rather than strong and long-term relationships. More specifically, the high costs related to the maintenance of close relationships would limit the number of "ties" that an organization can have. Secondly, since weak ties do not generally encompass a regular-basis interaction, they may access to less redundant information compared to strong ties. Network *betweenness* is an index proposed by Freeman that indicates the extent to which a node brokers indirect connections among all other nodes in the network. The holes in social structure, i.e. Structural holes, provide a competitive advantage for those actors whose connections span the holes, which in turn act as buffers separating non-redundant sources of information. Therefore, structural holes provide the possibility of brokering the flux of information between the nodes and "*control the projects that bring together people from opposite sides of the hole*" (Burt, 2002). Additionally, firms who are positioned in structural holes may have more opportunity to brokerage activities, by serving as bridges among relatively unconnected parts of the network. In the end, the availability of information is not limited to the function of a firm's ties only, but also to those retained by third parties, i.e. network configuration. *Critical links* represent another class of ties that has gained increasing attention in the network literature (Fig. 2.4). These links have the function of connecting poorly or otherwise disconnected sub-networks in a way that when, for some reason, they dissolve, then the entire network collapses, including the process of knowledge transfer among its members. Due to the critical links' function to connect sparsely linked parts of the network, they have often been referred to as "bottlenecks" (Sytch, Tatarynowicz, and Gulati 2012) or 'bridges' (Glückler 2007). However, "*while every critical link can be classified as a weak tie, the same is not necessarily true of the reverse. Critical links are crucial for the structure and integration of the complete network, while weak ties may only have local relevance*" (Broekel and Mueller 2017).

Figure 2.4. Critical Links



Source: Broekel and Mueller 2017

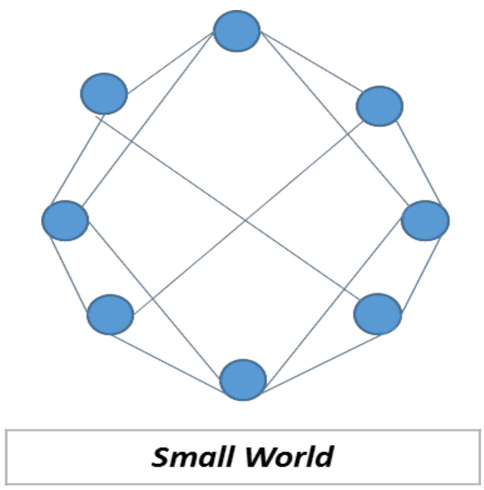
2.3.1.3 Gatekeeper organizations

Tightly connected to the structural holes' argument and the importance of *critical links*, studies within systems of innovation literature have regarded with increasing interest the role of the intermediary organizations (Hargadon and Sutton, 1997) or the c.d. *gatekeeper* actors, which are defined as actors holding a brokerage position between an actor group's internal or external partners (Gould and Fernandez, 1989). With particular reference to their role within innovation networks, Allen (1977) introduces the definition of *technological gatekeeper,* i.e. R&D professionals provided with the particular intellectual ability to absorb information from external sources and make it available and accessible to other employees of the company that he works for. The brokerage position has been proved to positively impact the performance of those organizations that rely on them to access external information (Hargadon, 1998). More recently, the concept of gatekeeper has been transferred to the geographical context by Giuliani and Bell (2005) who emphasize the role of *regional gatekeepers* in embedding local systems of innovation in global innovation networks. More precisely, the innovation performance of regional systems of innovation is deemed to be highly affected by the presence of a small number of regional gatekeeper organizations (Giuliani and Bell, 2005; and Graf and Krüger, 2011). Indeed, a growing number of scholars (see e.g. Gertler, 1997; Bathelt, Malmberg, and Maskell 2004) recognize their important function in importing and diffusing new knowledge within the region, thus contributing to limit the risk of *lock-in phenomena* without preventing organizations from exploiting the benefits deriving from local *embeddedness* (Glucker, 2007). More specifically, Graf and Krüger, (2011) emphasize the crucial role played by regional gatekeepers' absorptive capacity, which enables them to establish long-distance relationships to fill the cognitive gap existing between regional actors and external networks. Broekel and Muellerb (2017) make a clear distinction between *network gatekeepers* and *regional gatekeepers*. While the former *"are defined on the basis of a complete network"*, the latter are defined as organizations linking the regionally embedded network to an external network. Indeed, while regional gatekeepers "*are always gatekeepers from a network perspective, the same does not necessarily apply the other way around*" (Broekel and Muellerb, 2017). Morrison (2008) empirically verifies the tendency of regional gatekeepers to engage with organizations that are external to the region and specialized in complementary or similar assets and technologies, which suggest how cognitive proximity in this case, may act as a substitute of geographic proximity and compensates for spatial distance.

2.3.1.4 Small worlds

Watts and Strogatz (1998) suggest that the structure of networks may present the benefits of both strong and weak ties. For this specific configuration, the authors refer to the *Small Worlds* (Travers and Milgram, 1967), i.e. particular types of networks characterized by a shorter path length and a higher clustering coefficient. In other words, in these network the actors are close to almost all other elements through a smaller number of interconnecting paths, despite the large number of nodes (Fig. 2.5). The first property of Small Worlds -*shorter path length* - sustains network closure and for this reason, it is expected that knowledge and information circulate through the small world network more easily and quickly. Thus, a network with a small path length can be considered as one with fewer structural holes (benefit of weak ties). On the other hand, the second property - *higher clustering coefficient* - suggests that a larger social capital is accumulated, which leads to collective problem resolution (benefit of strong ties). However, following Ahuja (2000), the optimal structure of inter-firm networks ultimately depends on the objectives of the network members. The high degree of density and redundancy of linkages within local cliques ensures the formation of a common language and communication codes that enhances reciprocal trust and supports the sharing of complex and tacit knowledge among actors (Breschi and Catalini, 2010); the shortcuts linking local cliques to different and weakly connected parts of the network, ensures a rapid diffusion and recombination of new ideas throughout the network and allow to keep a window open to new sources of knowledge, thereby mitigating the risk of lock-in that could arise in the context of densely connected cliques (Cowan and Jonard, 2004).

Figure 2.5. Small world network configuration



Source: author's own elaboration

2.4 Review of empirical studies adopting a network approach for the study of local innovation systems

This section reviews a number of empirical studies adopting a network approach for the study of local innovation systems. The contributions are analyzed according to five main analytical dimensions: (i) the analytical perspective employed to trace the system's boundaries (sectorial; technological or geographical); (ii) the network nodes' composition according to the nature of the actors engaged in the relationships; (iii) the choices in terms of network portfolio of relationships that are used for the collection of relational data; (iv) the scholars' position within the longstanding debate around the optimal network structure; (v) the choices about level of analysis (node/system) and the (vi) following network indicators (structural/centrality); and finally, when applicable, (vii) the interpretation of innovation performance through the use of specific metrics. Next sections will discuss in details the above-mentioned analytical aspects. A summary of the review is reported in Table 2.3.

2.4.1 Definition of network boundaries

Studies that analyze network characteristics generally focus on a single sector or on particular geographic area, or the combination of the two. Some authors privilege to emphasize the sectorial perspective and focus their analysis on industry-related networks, as in the case of Salavisa et al. (2012), who argue that firms' networking behavior is particularly affected by sectorial differences. Indeed, depending on the industry, firms are provided with different types, sources and modes of access to resources required for innovating, which in turn affects the whole network's architecture. More specifically, it is the *nature of knowledge* exploited and the *organization* of *innovative activities* to affect the type of resources required and the modes of access to them that ultimately influence the network architecture. From a more evolutionary perspective, Balland et al., (2013) focus their analysis on the emergence of inter-firm networks in the global video game industry and argue that the factors that drive network formation vary according to the stage of development of the industry life cycle. In particular, the authors find that organizations tend to partner over short distances - thus presenting a higher level of geographic proximity – and with organizations with more similar knowledge bases- i.e. in greater cognitive proximity - as the industry matures. Similarly, D' Este et al., (2012) investigate the role of geographical proximity in university-industry networks in the field of Engineering and Physical Sciences in UK. Finally, from a knowledge-based perspective, Capaldo and Messeni Petruzzelli (2014) explore the impact of geographic and organizational proximity on the innovative performance of 1.515 inter-firm dyadic knowledge- creating alliances in the electric and electronic equipment (EEE) industry. Other contributions shift the focus on technology, as in the case of Balland (2012) that explore the global navigation satellite system (GNNS) to understand the influence of proximity on the evolution of collaboration networks in the framework of European Union R&D partnerships. Broekel and Mueller (2017) apply the proximity framework by empirically studying the characteristics of critical links in 132 technology- specific subsidized knowledge networks in Germany demonstrating that critical links tend to emerge among inter-regional gatekeepers with similar knowledge bases and complementary resources. From an exclusively regional standpoint, Still et al. (2014) provide an analytical framework to understanding the network dynamics underlying the Finnish ecosystem at multiple levels for an heterogeneous sample of actors. Russell et al (2015) offer an evidence-based approach to exploring the relational infrastructure of spatially defined innovation systems in the three metropolitan areas of Austin, (Texas, US); Minneapolis, (Minnesota, US); and Paris (France). However, most of the reviewed empirical contributions tend to opt for the combination of both sector and regional perspectives as in the case of Ahuja (2000) that develops a theoretical framework to relate the entrepreneurial innovation performance by taking evidence from the empirical study of collaborative linkages in Japan, United States and Western Europe in the chemical industry. Owen-Smith and Powell (2004) explore the role of spatial propinquity and organizational form in altering the flow of information in the Boston biotechnology ecosystem by performing a network analysis on human therapeutics biotechnology firms located in the Boston metropolitan area. Kajikawa et al. (2010) conduct a comparative analysis on eight regional Clusters in Japan to explore the role of bridging organizations in different industries. Casanueva et al. (2013) select the geographically localized footwear cluster in the region of Valverde (Southern Spain) as an empirical context to study the effects of firms' position in the network on their innovation performance. Ter Wal (2014) analyzes the evolution of inventor networks in German biotechnology arguing that the role of geographical proximity decreases as the technological regime experiences a shift from tacit to more codified knowledge. Giuliani (2013) employs Stochastic Actor-Oriented Models (SAOM) to measure network dynamics and examine the micro-dynamics underlying the emergence of new knowledge ties in the Chilean wine cluster. Finally, Dahl and Pedersen (2004) explores the regional cluster of wireless communication firms in Northern Denmark to study the effect of informal networks on innovation system dynamics of growth.

2.4.2 Network nodes' composition

It is well established in the literature of innovation systems that the heterogeneous nature of system's components represents one of the main drivers of its performance. Previous sections have indeed focused on the advantages in terms of new knowledge production deriving from the exchanges of information, capabilities and experiences between actors of different nature and the virtuous cooperation practices through the I-U-G networks have been appointed as the engine for the emergence of local innovation systems. From an empirical standpoint, the ability to capture – and assess- the diversity of actors' composition within innovation networks still remains a challenge. Except for a few cases (Dahl and Pedersen, 2004; Ter Wal, 2014) where the network analysis is at the individual node level (i.e. inventors and engineers), a great part of the contributions that are reviewed in this chapter 2, focus their analysis on inter-firm relationships, thus enabling to gain insights on the characteristics and dynamics of a certain aspect of the network and capture the specificities in more depth. Ahuja (2000) emphasizes the role of inter-firm networks as an information channel in terms of both *information collection* and *information processing*. More precisely, the network between firms is deemed to provide benefits as an information gathering device through which firms can obtain information about the successes and failures of contemporary research activities (Rogers and Larsen, 1984), thus allowing to benefit from indirect experience and to avoid replicative efforts. Secondly, the network can act as an information-processing or screening device through which, for example, a firm can detect relevant developments in complementary technologies to solving specific issues at hand. Still et al., (2013) analyze the network of firms in Finland by focusing on the different roles and positions of larger and established companies, start-up and investors. Kajikawa et al. (2015) build a large dataset of firms to analyze the multiscale structures of eight inter-firm networks and compare their small *world* properties upon which classifying firms in hub or peripheral nodes. Russell et al. (2015) combines both the resource dependency and the coalition perspective suggesting that inter-firm networks are complex systems characterized by "*co-evolving actors engaged in collaboration and co-opetition (...) as well as the emergence of collective invention*". Balland et al. (2013) study the dynamics of inter-firm networks along the game industry life cycle, by including in their sample both *developers* and *publishers*. Casanueva et al. (2015) explore the role of innovation networks in mature industries by studying relationships between 52 small and medium-sized firms presenting similar structural characteristics, as size in terms of employee numbers, with specific regard to manufacturers and auxiliary firms. Capaldo and Messeni Petruzzelli (2014) start from the identification of ten 'focal' companies (based on their degree of innovativeness in the industry) to build the network resulting from focal companies' R&D alliances. Finally, Salavisa et al. (2015) focus on the network of R&D intensive small and medium enterprises in software and biotech industries. However, network literature is showing an increasing commitment in analyzing local innovation systems in their whole complexity by meeting the methodological challenges that the study of diverse inter-organizational networks involves, starting from the study conducted by Owen- Smith and Powell (2004) who focus their attention on formal relationships between dedicated biotechnology firms, public research organizations, venture capital firms, government agencies and large companies in the pharmaceutical/chemical/healthcare industries (Fig. 2.7). Balland (2012) include, among the actors of GNSS industry, organizations with heterogeneous institutional forms, including large companies, small and medium-sized enterprises, research institutes, public agencies or non-profit organizations. Similarly, D'Este et al. (2013) focus on research collaborations existing between university and industry and finally, Broekel and Mueller (2017) investigate I-U-G networks for research grants by distinguishing among *executing* and *receiving* organizations, including (in the first category) large organizations as multinational companies and non-university research institutes.

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2.4.3 Network portfolio of relationships

Extant literature acknowledges the existence of diverse types of relationships. However, partly due to methodology constraints, the study of formal ties appears to be prevalent with specific regard to R&D and commercial agreements, licensing agreements for technology transfer, patent co-development (Ahuja, 2000; Baum et al., 2000; Castilla et al., 2000; Cloodt et al., 2010; Gulati, 1995; Gulati, 1999; Hanaki et al., 2010; Owen-Smith and Powell, 2004; Powell et al., 1996). With specific regard to the contributions that have been studied in this session, a large part of the studies under review opt for R&D intensive relationships as in the case of Balland (2012) and Broekel and Mueller (2017) that rely on co-participation in R&D projects and subsidized joint R&D projects, respectively.

In this vein, D'Este et al. (2012) focus on publicly funded university-industry research partnerships as a preferential source of relational data, which are defined as "*a transport vehicle of intended and unintended knowledge flows*". In some cases, (Ahuja, 2000) R&D partnerships are combined with financial relationships in the form of both direct and indirect ties to understand their effect on innovation performance. Capaldo and Messeni Petruzzelli (2014) and Ter Wal (2014) employ a particular type of knowledge-intensive alliances, i.e. joint patents, which are defined as an example of *knowledge- creating alliance* that differ from licensing and technology transfer that, in turn, are referred to as *knowledge-accessing* and *knowledge transfer alliances,* respectively. Indeed, according to the authors, "*Being aimed at the joint development of new knowledge, knowledge-creating alliances require partners to combine heterogeneous knowledge and share knowledge resources that are complex and tacit to a large extent*" (Capaldo and Messeni Petruzzelli,2014), thus requiring a high level of interdependence. Similarly, Balland et al., (2013) rely on relationships for product co- development to collect relational data in creative industry. Conversely, Kajikawa et al. (2010) focus on a more traditional set of customer-supply relationships**.** Other studies resort to a wider portfolio of relationships (Powell, 1996; Oven-Smith and Powell, 2004; Russell et al., 2015) spanning from R&D relationships and IP transfer to commercial, manufacturing, and investment ones. However, more recent contributions start to address the empirical challenges deriving from the analysis of informal networks (Arenius and DeClercq, 2005; Dahl and Pedersen, 2004; Kreiner and Schultz, 1993; McEvily and Zaheer, 1999; Østergaard, 2009; Shane and Cable, 2002; Weterings and Ponds, 2009) for which data are to a certain extent more difficult to collect. More precisely, the study of informal ties in reviewed contributions has been addressed by investigating interactions in the form of casual contacts between firms' employees (Dahl and Pedersen, 2004) or friendship, trust, tacit and explicit information exchange (Casanueva, 2013). Finally, some scholars adopt an aggregate approach (Cainelli et al., 2007; Cantner et al., 2010; Elfring and Hulsink, 2003; Fuller-

Love, 2009;Gilsing and Duysters, 2008; Giuliani and Bell, 2005; Van Geenhuizen, 2008; Yli-Renko et al., 2001; Todtling et al., 2009; Zhao and Aram, 1995) by considering both types of formal and informal ties and eventually provide a comparative analysis (Cantner and Graf, 2006; Johannisson and Ramìrez- Pasillas, 2001; Todtling et al., 2009; Trippl et al., 2009; Uzzi, 1997;1999). In a few cases (Salavisa et al., 2012) the two typologies of networks are considered simultaneously. The authors while comparing the sectorial differences in two German knowledge networks in the fields of molecular biology and software for telecommunications studied both formal and informal networks and distinguished them according to the type of resources that they allow to capture, i.e. *complementary assets* and *knowledge* (Table 2.2). The complementary asset network includes all relationships to acquire both tangible resources (e.g. financial capital, distribution channels, equipment and facilities) and intangible ones (e.g. business management knowledge, information, consultancy services), and include *commercial partnerships, service provision* (legal, accounting, IP, marketing), *agreements for the provision of facilities* and *funding relations*. On the other hand, the knowledge network consists of all relationships that allow knowledge and technology transfer and production as in the case of R&D projects, S&T Partnerships, Patents (partners and providers) and licensing agreements.

Table 2.2. Complementary assets and Knowledge networks

	Formal	**Informal**
Complementary assets	Funding sources Facilities providers Service providers (legal, accounting, IP, marketing) Commercial partnerships	Managerial knowledge Information
Knowledge	R&D Projects S&T Partnerships Patents (partners; providers) Origin of the technology (if formally transferred)	Innovation (new ideas) S&T knowledge Origin of technology (if informally transferred)

Source: author's own elaboration from Salavisa et al., 2012

In addition to the resource type, the authors distinguish the nature of the relations as informal or formal. While the latter refer to codified agreements with a clear definition of roles and duties through contracts, informal relationships generally originate from personal ties and spontaneously. However, the scholars argue that the difference in this case is not always clear-cut and that, in some cases, the actors may establish both forms of ties with the same organization, especially when "*formal ties are frequently based on previous informal relations*" (Salavisa et al., 2012).

2.4.4 Network structure perspective

While adopting a network approach for the study of industry-related networks, a significant part of existing literature focus their analysis at the firm level (Casanueva et al., 2013), suggesting that the position in the network, expressed in metrics of centrality, influences its innovative performance as it allows a greater access to information (Gulati, 1999; Oven-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 emphasize the geographical dimension and provide a wider range of indicators not limited to the organization's position within the network, but also 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, 2015). 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 under review 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; Oven-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 standpoint in a fewer number of studies (Broekel and Muellerb, 2017; Casanueva, 2014; Dahl and Pedersen, 2004; Ter Wal, 2014). In one case, the Small World perspective is implemented (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.

2.4.5 The relationship between network characteristics and innovation performance

Extant literature provides a number of contributions that address the relationship between network characteristics and innovation performance. Empirical findings, in general, support the theoretical relation (Bell, 2005; Bell & Zaheer, 2007; Chiu, 2009) between centrality and innovation, which has been widely explored and validated in the literature (Ahuja, 2000; Tsai, 2001). Innovation outcomes have been interpreted in a number of ways, such as alliance governance (Dyer and Singh, 1998; Sampson, 2004), characteristics of the search processes conducted within the alliances (Capaldo and Messeni Petruzzelli, 2011) and various aspects of the inter-organizational networks where the relationships are embedded (Ahuja, 2000; Baum et al., 2000; Capaldo, 2007). However, the performance of inter-organizational networks still remains a relatively unexplored area (Osborn and Hagedoorn, 1997) with specific regard to innovative performance of alliances (Hoang and Rothaermel, 2005). Powell et al. (1996) measure innovation performance in terms of ability to establish future R&D alliances and to contribute to firm's growth. Ahuja (2000) assesses the effects of a firm's ego-network on innovation by developing a theoretical framework that associates three specific characteristics of a firm's ego network, i.e. direct ties, indirect ties, and structural holes to the firm's innovation output, which is measured in terms of patents. In a similar vein, Oven-Smith and Powell (2004) demonstrate how membership and centrality in a geographically co-located network positively affects innovation by appointing patents as a proxy for innovation performance.

Capaldo and Messeni Petruzzelli (2014) explore the effects of geographic propinquity on knowledge-intensive alliances' performance by considering the number of citations of joint patents (used as relational data) as an appropriate metric for innovation performance. Finally, Casanueva et al. (2013) analyze the influence of centrality and structural holes in tacit and explicit knowledge networks on firms' innovation performance, being this measured in terms of product and process innovation.

Table 2.3. Empirical studies adopting a network approach for the study of local innovation systems

	Analytical perspective	**SNA Metrics**	**SNA Approach**	**Type of ties**	**Network Portfolio**	**Nodes**	**Innov. perf. metrics**
Ahuja, 2000	Sectorial/Regional	Structural/Positional	Closure/Open	Formal	Finance; R&D	Firms	Patents
Balland et al., 2013	Sectorial	Structural	Closure	Formal	Product co-development	Firms	---
Balland, 2012	Sectorial	Structural	Closure	Formal	Co-participation in EU R&D projects	Large companies, small and medium-sized enterprises research institutes, public agencies or non-profit organizations	---
Broekel and Mueller, 2017	Sectorial/Technological	Structural/Positional	Open	Informal	Subsidized joint R&D projects	Universities firms, research institutes and miscellaneous organizations	---
Capaldo and Messeni Petruzzelli, 2014	Sectorial	Structural	Closure	Formal	Joint patents	Firms	Number of patent citations
Casanueva et al., 2013	Sectorial/Regional	Structural	Open	Informal	Transmission of tacit and explicit knowledge	Firms	Product and process innovation
Cassi and Plunket, 2015	Regional	Structural	Closure	Formal	Co-inventorship relations	Individuals	---

D'Este et al., 2012	Sectorial	Structural	Closure	Formal	Collaborative Research Grants	Universiti es Firms	---
Dahl and Pedersen , 2004	Sectorial/Regional	Structural	Open	Inform al	Information exchange	Individual s (engineers)	---
Giuliani, 2013	Sectorial/Regional	Structural/Positi onal	Mixed approach	Inform al	Technical support (inbound and outbound)	Firms	---
Kajikawa et al., 2010	Sectorial/Regional	Structural/Positi onal	Small Worlds	Formal	Customer-Supply relationships	Firms	---
Oven-Smith and Powell, 2004	Sectorial/Regional	Structural/Positi onal	Closure	Formal	R&D; Finance; Commercial; IP transfer	Firms, Gov. agencies; PROs; VC	
Powell, 1996	Sectorial	Positional	Closure	Formal	R&D; Finance; Commercial; Custom-Supply; IP transfer.	Firms	# R&D ties (t+1); Growth (t+1)
Russell et al., 2015	Regional	Structural/Positi onal	Closure	Formal	R&D; Finance; Commercial; Custom-Supply; IP transfer; Manufacturin g	Firms	---
Salavisa et al., 2012	Sectorial	Structural/Positi onal	Mixed Approach	Formal	Knowledge and Complement ary Assets relationships	Firms	---
Still et al., 2013	Regional	Structural	Closure	Formal	R&D; Finance; Commercial; Custom-Supply; IP transfer; Manufacturin g	Firms	---
Ter Wal, 2014	Sectorial/Regional	Structural	Open	Formal	Co-inventorship relations	Individual s	---

Source: author's own elaboration

2.5 Literature Gap and Summary

This chapter aims to explore the key concepts underpinning the relational dimension as a driver of local innovation systems' performance and illustrate the relative analytical challenges through the analysis of main contributions in the field. Based on reviewed studies in section 2.5, the following gaps in the literature have been identified:

- There is no general agreement on the optimal configuration of network structure (e.g. Closure network vs. Structural Holes);
- Most contributions employing a network approach for the study of innovation systems' performance limit their analysis at the node-level and mainly focus on inter-firm relationships, thus overlooking the heterogeneous nature of a system's components, which is an important driver for the production of new knowledge.;
- Most studies limit their analysis to strong and formal ties, overlooking the potential for informal and weaker ties;
- Extant literature tends to limit the analysis to network structure and does not address the variety of inter-organizational relationships, thus failing to gain insights into the optimal network portfolio composition.

In order to fill these gaps and in an attempt to capture both aspects of LIS's relational dimension (Network structure and Network Portfolio composition), this work will explore: (RQ1) What is the configuration of the network structure of a successful Local Innovation System? And secondly, (RQ2) What is the portfolio of relationships implemented in a successful Local Innovation System? This next chapter will provide a more in depth explanation of the reasons underpinning the formulation of the above research questions and address the relative methodological challenges through the development of an exploratory study of the Biopharma innovation system in the Greater Boston Area.

CHAPTER 3 – METHODOLOGY

This chapter aims to illustrate and discuss the methodological approach selected for addressing the theoretical gap identified in the previous chapter through the review of extant literature on the relational dimension of LIS.

The first section provides an overview of the methodology and emphasizes how the selected approach contributes to addressing the research questions. Section 3.2 provides background information on the industry of the selected case study, with particular regard to the features of drug development process, the importance of geographic proximity in the sector and its demography composition. Additionally, the second part of this section is dedicated to the illustration and discussion of the typical forms of cooperation and interaction occurring between the industry players. Section 3.3 offers an overview about the research techniques implemented for the empirical study highlighting their points of strength and limitation, most common indicators and fields of application. Section 3.4 provides a sample description, explains the criteria underpinning its selection and illustrates the process of data collection and computation, before concluding.

3.1 Methodology approach and research design

3.1.1 Formulation of research questions

This chapter aims to explore the key concepts underpinning the relational dimension as a driver of local innovation systems' performance and illustrate the relative analytical challenges through the analysis of main contributions in the field. Based on reviewed studies in the second chapter, it emerged a lack of general agreement about the optimal configuration of network structure with particular regard to its level of closure and openness. Furthermore, from a methodological perspective, most studies tend to limit their analyses to the observation of formal and inter-firm relationships, thus failing to highlight the variety of network portfolio and the heterogeneous actors' composition, which are two typical features of local innovation systems. In order to fill these gaps and in an attempt to capture both aspects of LIS's relational dimension (Network structure and Network Portfolio composition), this work will explore: (RQ1) Which is the configuration of the network structure in a successful Local Innovation System? And secondly, (RQ2) Which portfolio of relationships is implemented in a successful Local Innovation System?

3.1.2 The methodological approach

In order to answer these questions, this work conducts an exploratory, data-driven and quali-quantitative empirical case study. Case study research allows the exploration and understanding of complex issues and its robustness as a research strategy it is particularly appreciated when an in-depth and holistic approach is required. Indeed, a case study approach allows examination of real-life situations, develop theories, assess policies and programs and permits to give guidelines for strategic interventions (Soy 1997; Baxter and Jack 2008; Yin 2009, 2015). More specifically, this study conducts an exploratory single case study. Compared to multiple or collective case studies, a single case study is more adequate when the case itself is either a representative or typical case, either acritical case as in the current study. Indeed, Yin (1994, pp. 38-41) proposed four strategies for case study selection according to the purpose of the case inquiry, namely the critical case, the extreme case, the unique case and the prelude case strategies. These strategies are used for; testing, formulating or extending a theory, documenting a rare and unique case, investigating a phenomenon that is inaccessible to scientific research, and piloting a case in preparation for a multiple case design, respectively In our case, a critical case study would allow for formulating propositions to be tested in future research starting from the selection of a case study that meets all conditions that we are willing to explore. On the other hand, among all types of case study researches (i.e. explanatory, exploratory and descriptive), the exploratory case study is selected as it is particularly appropriate to research contexts that lack hypotheses (Yin, 2003), as in this case, and where the research environment limit the choice of methodology (Streb, 2010). In fact, exploratory case studies do not start with prepositions and hypothesis deriving from prior literature review, but they rather develop descriptive analytic frameworks to redirect future empirical research, (Hartley, 1994) as in this current study. Another aspect that is worth mentioning is that a case study design approach should not be confused with qualitative research, as it can indeed implement a mix of both qualitative and quantitative techniques. In fact, an important aim of the case study, is that of capturing the complexity of a single case of study by integrating different levels of analysis, theoretical approaches and research techniques (Kohn, 1997 and Johansson, 2005). This process is generally referred to as *triangulation*, i.e. a process where different methods and research techniques are combined to achieve a better validation of the study (Johansson, 2003). For this reason, a case study is generally referred to as a research strategy rather than a method (Kohlbacher, 2006).

3.1.3. Research design

The empirical case study in the current work, is articulated in two phases.

- Firstly, I developed a network analytic study of strategic alliances and financial relationships among business, academic, corporate, start-up and government entities.

Secondly, I conducted a round of interviews with key stakeholders in the ecosystem in order to gain insights into the desirable network portfolio mix in terms of both strong and weak ties, for the transfer of knowledge. The results of the Social Network Analysis (SNA) suggest insights about the optimal network structure (RQ1), as SNA has been widely used and proved its efficacy for representing the features of the network structure configurations by providing visual and quantitative information on the level of openness and closure through a variety of specific indicators. However, the exclusive use of this methodology does not allow capturing the whole variety of relationships occurring within an innovation ecosystem. More specifically, the relational data available in databases are usually indicators of formal relationships (financial, commercial and R&D). However, it is widely accepted that one of the main advantages deriving from geographical propinquity is the opportunity to exchange information through informal channels resulting from the establishment of personal relationships among co-located actors. These informal ties are generally excluded from quantitative relational data and to overcome this limitation and gain insights about network portfolio, SNA technique is complemented with qualitative expert interviews. The conversation with opinion leaders allow for insights on the advantages of being in spatial proximity with partners and on the specific types of relationships best contribute to the knowledge transfer and to the innovation process (RQ2).

3.2 The selection of the case study: The Greater Boston Biopharma LIS

3.2.1 Industry setting: innovation-driven relationships in Biopharma Industry

3.2.1.1 Main features of the Biopharma industry

The term “biopharmaceutical” refers to the evolution of the pharmaceutical industry since its emergence in late 1800s, when it was predominantly chemistry-based, to include the more recent birth of biotechnology from the 1980s, which is based on living cells and molecules. More specifically, biotechnology refers to the whole set of technologies that employ and manipulate living cells and molecules with the aim of developing products and solutions that find their application in human health, agricultural production as well as other industries (de Andrade, 2013). As long as almost every pharmaceutical company is engaged in the development of biotech-related drugs, the distinction between *pharma* companies and *biotech* firms is increasingly less meaningful compared to past years. Nowadays, biopharmaceuticals cover the 20% circa of the whole pharmaceutical market and it represents its fastest growing branch. The present empirical study focuses on the process of biotech-based drug development, which consists of three main stages (Bianchi et al., 2011; Reynolds and Uygun, 2017) (Figure 3.1):

(i) *Drug discovery,* including the following activities:

- *Target identification and validation*, that involves the selection of a gene or protein as a potential cause of a specific disease followed by a validation phase through the observation of data about the interactions of the target with human organisms. This stage requires a number of tools and procedures, e.g. cross-species studies, growing cell cultures, biomarkers for the measurement of biological functions.
- *Lead identification and optimization*. At this stage a new compound is developed with the aim of addressing the specific target identified in the previous steps and transformed in the active principle for the future drug through the addition of excipients.

(ii) *Drug development.* During this phase the drug has to undergo through a series of testing rounds, articulated in:

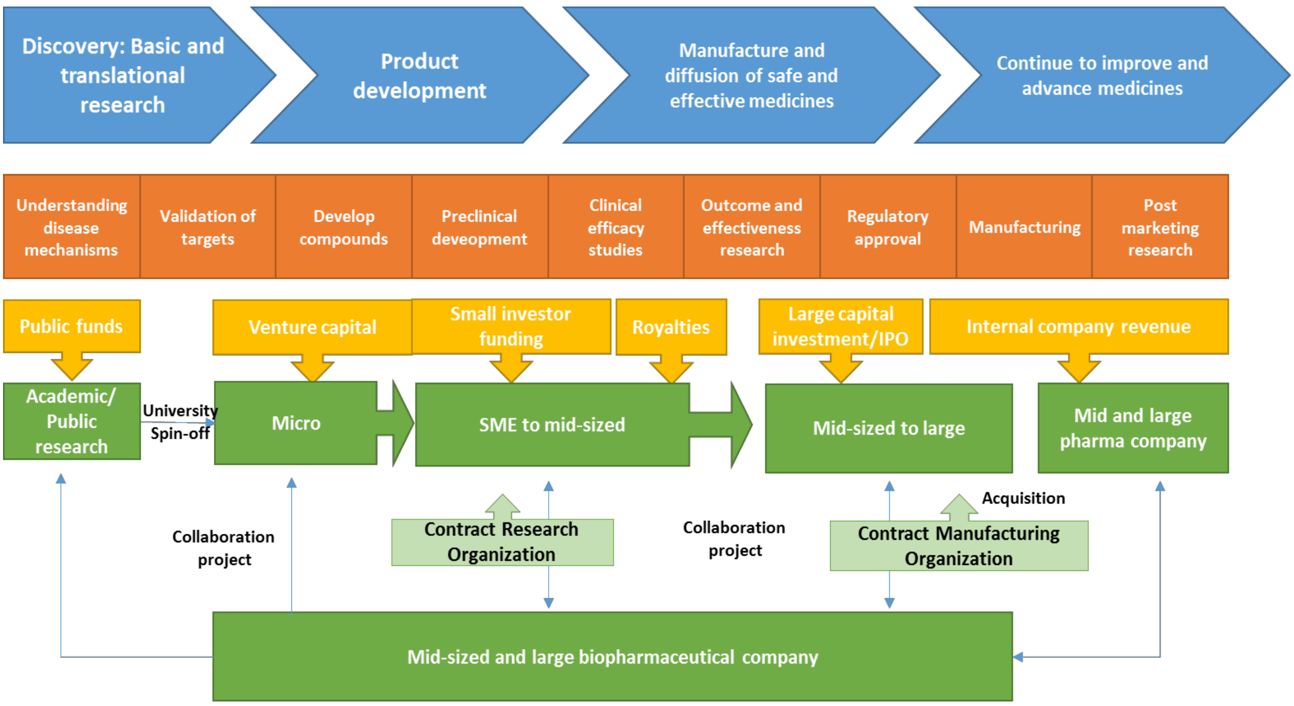
- *Pre-clinical tests*, where the new drug is initially tested on animals and subsequently subject to a first approval by public authorities, before proceeding with the development.

- *Clinical tests*, which are articulated in Phase I, Phase II and Phase III. During these stages the drug is tested on human patients in order to validate the safety and to evaluate the efficacy of the new product. In case the response to these tests is positive, the new drug can be approved by public authorities to be commercialized in the market.

In general, the above phases, i.e. drug discovery and drug development may take from ten up to fifteen years.

(iii) *Drug manufacturing at commercial scale.* During this phase, a master cell line containing the gene to develop a specific protein is developed, as well as a large number of cells to manufacture the protein. Afterwards, the protein is isolated and purified to be ready for patient use, before being transferred in large bioreactors for scale-up. The *biomanufacturing* process is one of the most complex and riskiest industrial processes, due to its high level of vulnerability to any slight change in the environment, which can potentially alter the drug quality and nullify its efficacy.

Figure 3.1. The Biomanufacturing Value Chain



Source: author's own elaboration from CRA, 2014

3.2.1.2 The importance of geographical proximity in the Biopharma Industry

The biopharmaceutical industry is characterized by a multidisciplinary structure that is typical of science-based sectors. One of its peculiarities is exemplified by the tendency of the biopharmaceutical firms to cluster in a small number of geographical regions and to be significantly dependent on public research institutions for scientific capabilities and skilled labor (Audretsch and Stephan, 1996). Indeed, the industry is usually portrayed as a succession of highly specialized activities, each of which is in need of cooperation among both private and public organizations. It has been argued that the development of a biopharma product requires the establishment of complex knowledge ecosystems (Reynolds et al., 2016) and following Oven-Smith and Powell (2004), geographic propinquity and network centrality represent two sources of competitive advantage for the industry's actors. Further explanation for the importance of relational capital and geographic proximity can be traceable to a number of reasons. Firstly, the lengthy of the R&D life cycle, which requires a stable and supportive institutional environment. Secondly, the idea that the survival and the competitiveness of firms in biopharma sector is mainly based on continuous and technical innovation (Powell et al., 1996), which makes crucial to gain access to new (and often tacit) knowledge and capabilities through both localized information spillovers as well as strategic alliances networks with a broader geographical scope. Finally, the high risks and costs associated to the R&D biopharma activities increase the dependence on risk capital, most notably public funds and venture capital. A recent study developed by TUFTS University (Milne and Malins, 2012) estimates that the average cost for developing a biotech based drug (from its early discovery to its commercialization) is of $2.6 billion dollars approximately (of which $1.4 billion in direct costs), which explains why the availability of risk capital providers is so important. Apart from the specific characteristics of the R&D activities, there are two broader factors that contribute to explain the key role of inter-organizational cooperation in the industry. One reason can be traceable to the fact that public-private collaborations have been further fostered by the enactment of Bayh-Dole Act by U.S. Congress in 1980, which stimulated the emergence of new generation of academy-industry partnership models. The act stimulated the commercialization of government-funded research as it allowed universities and other non-profit entities to guard the property of patents resulting from research funded by federal grants. Indeedprior to this, university laboratories had served primarily as centers for basic biological research efforts, without particular concern for commercial application. With reference to

Biopharma industry, the Bayh-Dole act created an environment that fostered partnerships for a rapid translation of scientific research into market-directed health care applications, thus increasing the innovation *appropriability* (Teece, 1986). Secondly, as emphasized by Ter Wal (2014), biotechnology industry has been interested by a shift in the technological regime from a predominantly generic to a more specialized knowledge base, known as the *second biotechnology revolution* (Gambardella, 1995). The advancements made in chemical engineering in 1980s, driven by small biotech firms, brought a more rational approach to the development of new chemical substances and drug design. A large part of these firms, generally referred to as *dedicated biotech firms* (DBF), were originating from academic spin-offs and were highly specialized in biotechnology research and the realization of products with high commercial potential. However, their main limitation was the lack of resources required for clinical trials and strict bureaucratic approval procedures. Thus, from the mid-1980s, big pharmaceutical companies began to provide financial support to DBFs for the development and commercialization of their products.

3.2.1.3 Demography of Biopharma Industry

Before illustrating the portfolio of relationships typical of Biopharma industry, it is worth mentioning between whom these interactions occur. The industry is characterized by a heterogeneous demography where we can distinguish at least five different categories of stakeholders, namely *Dedicated Biotechnology Firms (DBFs), Lead Firms, Contract Manufacturing Organizations (CMOs), Contract Research Organizations (CROs), Public Research Organizations. DBFs* usually originate as start-ups, founded by university-affiliated researchers with the aim of commercializing a specific technology or product resulting from research endeavor. As long as the skills required to bringing a product to the market are often too complex to be contained in a single firm (Powell et al., 1996), DBFs oftentimes rely on their relationships with competitors, domestic and international suppliers, public and private research institutions, technology transfer offices, universities, hospitals and public funding agencies to fill their knowledge gaps and fulfill those functions required for the development and exploitation of their product or technology (i.e. basic and applied research, clinical testing, marketing, regulatory engagement, distribution). Once they validated the early stage efficacy of their drug, DBFs can take two alternative pathways of growth. On the one hand, these firms can initially seek for dilutive funding, by the means of a series of VC funds, and ultimately through IPO. In alternative, DBFs can be acquired by a large pharmaceutical or biopharmaceutical company. However, due to high rate of failure in the early phases of DBF development, their capability of bearing the risks related to drug development may be hindered. In fact, it is generally after the achievement of a certain level of initial success that DBFs can raise their expectations about their rapid growth through VC or acquisition. *Lead Firms* refer to large pharmaceutical or biopharmaceutical companies that often undertake a facilitator role in the management of networks of biotechnology start-ups, university laboratories and international suppliers to bring a drug to the market. *Contract Manufacturing Organizations (CMOs)* also referred to as contract development and manufacturing organization (CDMO), are firms that provide a set of services ranging from drug development to drug manufacturing, on a contract basis. Main services include pre-clinical and Phase I clinical trial materials, late-stage clinical trial materials, registration batches and commercial production. Their proliferation is in line with the pharmaceutical companies' tendency to outsource a part of R&D operations to focus most of their efforts on drug discovery and marketing, thus expanding its technical resources without excessively increased overhead costs. Similarly, *Contract Research Organizations (CROs)* are engaged in bioassay development preclinical and clinical research, clinical trials management (patient recruitment and data collection) and drug safety testing. Their main function is indeed that of supporting large firms in meeting the complex regulatory pathway underpinning drug development and commercialization. *Public Research Organizations* comprehend universities and no-profit institutes that are engaged in research that is valuable to industry. These are deemed to play a key role in the knowledge production on a research frontier and they allow for a pursuit of more open technological trajectories as they, compared to for-profit organizations, create different selection environments for early stage research. The Biopharma ecosystem demography is also characterized by the presence of venture capital firms and public agencies that undertake the role of capital risk providers as well as that of facilitator and business support, as it will be illustrated in the empirical case in the fourth chapter.

3.2.1.4 Forms of collaboration in the Biopharma Industry

The practices of cooperation within Biopharma Ecosystems occur during the whole innovation pipeline and present different degrees of formalization depending on their scope. In this section the main forms of inter-organizational relationships are illustrated. Some of them are typical of most industries while others are more specific to Biopharma sector. One of the most traditional forms of innovation-driven cooperation occurs through partnering in R&D strategic alliances. This refers to the development of research programs through a formal relationship between two or more parties to pursue a set of agreed upon goals. while remaining independent organizations, for a specific target where all parties contribute in a joint endeavor. Generally, it is based on the complementarity of the skills and assets between the partners involved. Similarly, co-patenting refers to relationships established through the co-development and co-ownership of patents by universities and other organizations. Another common practice is Sponsored research. In this case, it is common that large firms fund a program of R&D that is developed entirely or mostly by an academic research group or a smaller company. Depending on the degree of engagement of the funding organization, this type of relationship may take follow a *fee-for-service* model where the commissioner presents a hands-off approach. Joint clinical trials, which generally involve academic medical centers; DBFs and big pharmaceutical companies represent another typical practice of cooperation in biopharma. This regards the cooperation in conducting trials of products on subjects for FDA approval (Powell et al., 1996). IP transfer represents a widespread practice in the biotech industry. Indeed, it is frequent for small biotech firms and academic research groups working on innovative approaches to act as technology providers throughout -licensing agreements with the aim of monetizing a certain innovation that can potentially become the seed of a drug discovery or solve a technical problem in an existing large company's ongoing project. The frequency of the interaction between the licensee and licensor usually varies according to the degree of originator approach in actively monitoring and control the use of the IP as well as providing support and guidance for its implementation. The issues pertaining to the appropriability of the developed innovation also underpins the spin-off generation, i.e. the creation of a separate company from part of an existing firm. This is considered as a form of relation due to the high level of interaction with the originator-organization. Following the increasing specialization that characterizes R&D activities in the field and the level of inter-organizational competitiveness, we assisted to the proliferation of the c.d. Value Added Supply agreements. It is a common practice for biopharma organizations to outsource specific non-core R&D operations (e.g. clinical data monitoring, chemical reference compound synthesis) typically to CROs. While many of these are highly standardized practices that do not require a high level of interactions and are regarded as usual buyer-seller transactions, there is a significant number of supplier arrangements that become real partnerships, with a close integration of operations and benefits in terms of cost and time savings for the customer. The reasons of establishing collaborative supply arrangements may be traceable to the high level of customization that requires the customer's participation to the delivery of the process. Venture Capital (VC) and other private capital (as Business Angel seed investment or Corporate Venture Capital (CVC)) has been key to fostering start-ups in the biopharmaceutical industry due to the high costs and risks of the industry R&D process. Traditional VC and CVC can assume multiple forms ranging from funding to transformative technologies with potential to be turned into a variety of products to investing exclusively in existing companies in return of equity. Finally, a more traditional form of inter-organization cooperation is the joint venture, which is common across diverse industries and envisages the constitution of a third independent organization as a result of the joint effort of two or more parties with shared vision and goals. The types of partnerships illustrated above mainly exemplify forms of formal and contractual relationships that tend to be strong and long-term. However, it has been widely recognized the high potential for innovation resulting from less formal types of interactions. As a way of illustration, Interlocking directorates represent an informal channel of information exchange as this practice refers to the presence of the same person in the respective Boards of Directors of two or more organizations. Also, there is a growing interest in the establishment of formal and informal agreements for the mobility of human resources among industry and university through internship programs and targeted job placement policies. Another common practice in the industry is exemplified by the agreements for the access and use of infrastructure, which provide access to infrastructures in an innovative center to allow or facilitate the exercise of certain research activities for both companies and research groups often governed by contracts as for example incubators, that are areas of services designed to accommodate new businesses that can benefit of the shared use of expensive equipment as well as cheap office space and business consultancy services. Finally, the co-participation to thematic associations or consortia is a newer form of collaboration regarded as a burgeoning area of partnerships. The association or the consortium may bring together resources, direct research pathways and gather experts from the industry with the aim of enabling a specific research endeavor that could not be undertaken by a single organization alone. A more complete list of the most common is implemented practices of inter-organizational relationships is provided in Table 3.1.

Table 3.1. Practices of inter-organizational relationships

	Definition	Type of tie	Partners	Source
Strategic R&D partnerships	Development of research programs with other organizations for a specific target to pursue a set of agreed upon goals while remaining independent organizations effort	Formal	DBFs; pharmaceutical corporations, research institutes; university labs	Powell et al., 1996; Oven-Smith and Powell, 2005
IP transfer	In-licensing and out- licensing agreements to commercialize the results of scientific efforts or purchase rights to partner's idea	Formal	DBFs; pharmaceutical corporations, research institutes; university labs	Ensing, 2017 ; Powell et al, 1996; Oven-Smith and Powell, 2005; Bianchi et al., 2011
Sponsored Research	Large organizations fund an R&D program that is developed entirely or mostly by research institutions	Formal	Pharmaceutical corporations, research institutes; university labs	Ensing, 2017
Joint Clinical trials	DBF has partner conduct trials of products on subject for FDA approval	Formal	Research hospitals; firms specializing in clinical hospitals	Powell et al, 1996; Oven-Smith and Powell, 2005
Value Added Supply Agreements	Outsourcing of non- core R&D activities based on long-term and highly customized agreements	Formal	Large Chemical or Pharmaceutical Corporations; CROs; CMOs	Powell et al, 1996; Oven-Smith and Powell, 2005; Kajiwata 2010; Capello and Faggian, 2005; Ensing, 2017
Joint venture	DBF invests funds (and usually human/scientific capital) in a partner	Formal	Other Biotech firms	Powell et al, 1996; Oven-Smith and

				Powell, 2005
Venture Capital and Seed Funds	Seed Capital and investment relations in return of equity	Formal	Startups; Business Angels; VC firms	Still et al., 2014; Powell et al, 1996; Oven- Smith and Powell, 2005
Spin-Offs	The creation of a separate company from part of an existing firm	Formal	Universities; Public Institutions; corporations	Capello and Faggian, 2005
Agreements for the access to infrastructure	Provide access to infrastructures in an innovative center to allow or facilitate the exercise of certain research activities for both companies and research groups often governed by contracts. Eg. Incubator: areas of services designed to accommodate new businesses	Formal	Large Chemical or Pharmaceutical Corporations, research institutes; university labs	Ter Wal, 2014
Co-patenting	Relationships established through the co-development and co-ownership of patents by universities and other organizations	Formal	DBFs; pharmaceutical corporations, research institutes; university labs	Capellari and De Stefano, 2016

Mobility of human resource between different organizations through formal or informal agreements	In the transition to a new organization a manager / researcher could maintain relations with the organization of origin subject Even in the absence of relationships, the subject brings with it knowledge and experience in another context	Informal/Formal	Corporations, research institutes;	Simoni and Schiavone, 2009; Capello and Faggian, 2005
Interlocking directorates	The presence of the same person in the respective Boards of Directors	Informal	Corporations, universities, research institutes;	Mizruchi 1992, Davis et al. 2003
Co-participation to thematic associations	The consortium brings together resources, direct research pathways and gather experts from the industry with the aim of enabling a specific research endeavor that could not be taken by a single organization alone.	Informal	Corporations, universities, research institutes;	Milne and Malins, 2012

Source: author's own elaboration

3.2.2 The Biopharma innovation system in Greater Boston Area

We decided to perform our empirical study in the case of the Greater Boston Area (GBA) Biopharma system. Due to its high ranking position among U.S. Biotech Cluster rankings (JJL U.S. Life Science, 2016), is considered a benchmark case for LIS successful performance. The Greater Boston Area (GBA) is renowned as the leading US Life Science cluster (JJL U.S. Life Science 2016) for the number of patent ownership per capita, venture capital funding and number of IPOs. The region is home to many of the leaders in tech and life science as well as world-class academic and research institutions as Harvard and the Massachusetts Institute of Technology (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 system has attracted a dynamic community of investors. More precisely, VC funding is of 2,580 million 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. Life Science industry in the area employs more than 86.000 individuals with an average employment growth rate of 1.3 % yearly (Table 3.2), including more than 30.000 scientists with an increasing, in the last decade only, of 22,000 jobs.

Table 3.2. The Biopharma LIS in Greater Boston Area – Economic scorecard

WORKFORCE	**Total life science**	**% life science to private employment**	**Year-over-year growth**
Employment	86,235	4.5%	1.3%
Establishments	2,136	4.3%	12.7%
FUNDING	**Total life science**	**% to total U.S.**	
VC funding	$2,580M	38.01%	
NIH funding	$2,057	18.72%	

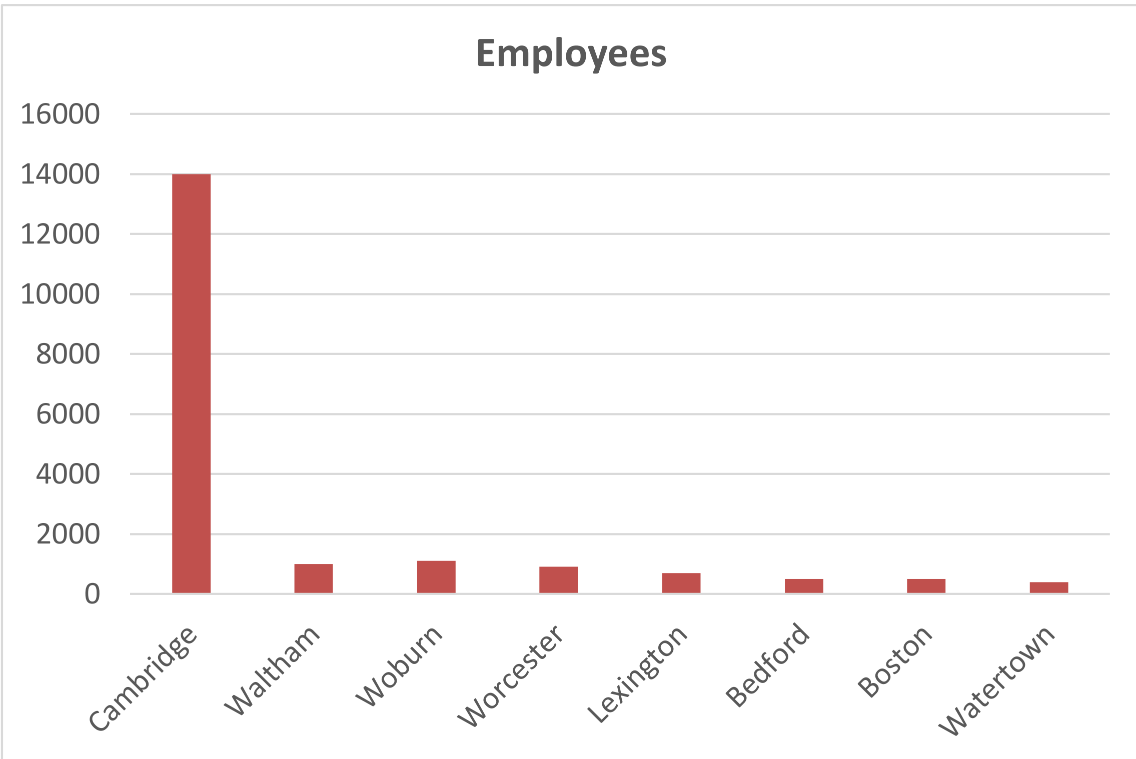
Source: author's own elaboration from JJL U.S. Life Science, 2016

The City of Cambridge is one of the most competitive global centers in the Life Science industry. East Cambridge alone is home to 87.4 percent of the city's lab space (JJL U.S. Life Science 2016) and hosts the 30% of the firms in GBA and 60% of the employment (Breznitz, 2015) (Figures 3.2 and 3.3).

Figure 3.2. The Biopharma LIS in Greater Boston Area - Biotechnology Firms by City

Source: author's own elaboration from Breznitz, 2015

Figure 3.3 The Biopharma LIS in Greater Boston Area - Biotechnology by Employment

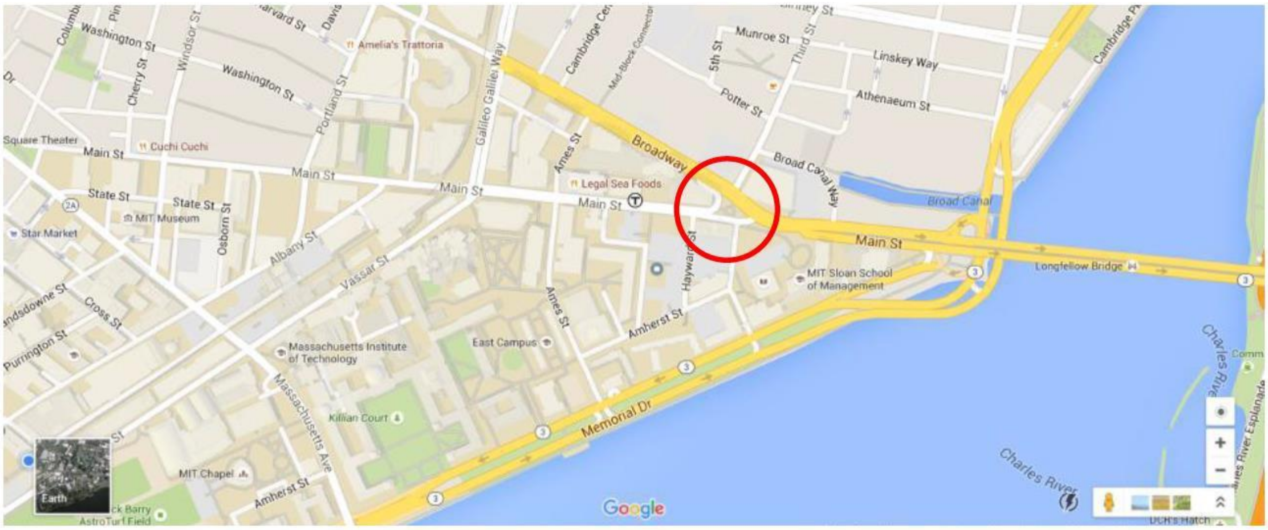


Source: author's own elaboration from Breznitz, 2015

Even in the City of Cambridge there is a high level of local clustering, with specific regard to Kendall

Square, a 10 acres area located in East Cambridge across the Charles River from Massachusetts General Hospital and adjacent to the MIT campus, which comprises a business district that hosts a number of global technology firms such as Amazon, Google, Facebook and Microsoft, as well as the biggest world players in Biopharma industry including Novartis, Genzyme, Lilly, Abbvie, Biogen, among others (Figure 3.4). Kendall Square in Cambridge has been defined as "the most innovative square mile on the planet", with regard to the high concentration of entrepreneurial start-ups and quality of innovation that emerged in proximity of the square since 2010. The rise of life science in Kendall Square was accompanied by the parallel decline in Boston's earlier innovation area district for tech known as Route 128. This refers to the area at the north of Boston that was competing with Silicon Valley as a technology center thanks to its booming minicomputers and mainframes industry, partly fueled by the military sector funds. As highlighted by Saxenian (1996), Route 128 proved to be unable to compete due to a vertical network structure dominated by a few large firms resulting in a closed model of innovation that failed to exploit the external sources of novelty as Silicon Valley did. In the early Twenty-first century, the MIT Investment Company (MITIMCo) focused its expansion plans toward Kendall Square Area. One of the emblematic outcomes of this strategy is represented by the One Broadway Center where a significant number of virtuous companies and organizations reside, including the popular Cambridge Innovation Center (CIC), a co-working space at the 14th floor of the building that provides start-ups (especially biotech) with a place to convene, work and grow. Similar to CIC, Lab Central, created in 1999, now represents another example of facility space for small biotech businesses that are offered with lab space and resources to scale and foster their innovative ideas. By 2010 Kendall Square has turned into the focal point of the GBA Innovation System. However, a few pitfalls followed its expansion. More specifically, the expensive real estate market makes it difficult for start- ups to survive in the area. As a consequence, many companies have started to relocate in different areas. The CBD Seaport District, and the core suburbs (Lexington, Waltham, Worcester and Bedford) have become attractive to mid-size tenants as well as more established companies due to their more affordable real estate market. By way of illustration, in 2014 Vertex Pharmaceutical has relocated from East Cambridge to the Seaport District.

Figure 3.4 Kendall Square, Cambridge, Massachusetts



Source: maps.google.com

3.3 Research Techniques

3.3.1 The Social Network Analysis

Social Network Analysis (SNA) has been widely implemented for the sociological study of individuals and organizations (Wasserman and Faust, 1994; Welser et al., 2007), as well as for the assessment of nested structures of inter-firm relationships (Moody and White 2003; Halinen et al. 2012). Networks' main components are actors (nodes or vertexes) and their ties (edges or links). Ties are either directed, in those case in which the arrows provide "from – to" information, or undirected. The complete set of nodes and ties is generally referred to as *social graph*, or simply the graph. In graph theory's basic terminology, the number of ties that a node has, is its degree, which can be distinguished in *in-degree* and *out-degree*. The sequence of ties and nodes between one another and another is a *path* and *path length* indicates the number of degrees between two nodes, often referred to as the *distance* between two nodes. Visual network analysis can serve as a tool for revealing the flow of information, know-how and financial resources among different actors (Russell et al. 2011). Relational metrics can allow for a deeper understanding of system's emergent structures, patterns and transformation dynamics (Freeman, 2002) and allow for a comparative analysis over time and across regions. As we analyzed in chapter 2, a number of authors have employed network metrics as indicators of relational capital to explore the structure of innovation ecosystems. The metrics for understanding the dynamics of an innovation system are distinguished based on the distinct but related levels of analysis: the network as the whole (ecosystem) and the node level (firm/individual) (Basole et al. 2013). Accordingly, network metrics can be divided in two broad groups:

- *Centrality Metrics*, which look at positions of individuals in the network, and
- *Structural Metrics*, which look at the whole network and its components.

At the *organizational and the individual level*, Centrality Metrics generally indicate the number of connections; the frequency of occurrence on paths between others and the diversity of connections. These indicators are usually used to identify those nodes that are well positioned to influence the network or to channel information. Some of the most common indicators are *Node degree* and *betweenness centrality*, which are calculated for understanding the functions of individual nodes or, in other words, of the actors in the ecosystem. *Node degree centrality* exemplifies the number of connections for a given vertex, providing information on its immediate connectivity and popularity and influence in the networks. A node's (in-) or (out-) degree is the number of links that lead into or out of the node and in an undirected graph they are obviously identical. The *Closeness centrality* calculates the mean length of all shortest paths from a vertex to all the other ones in the network. It is a measure of reach in the sense that it indicates the speed with which information can reach other nodes from a given starting vertex. *Betweeness centrality* indicates the number of times that a given node appears in the shortest path from all nodes in the network to all others. As a consequence, *betweenness centrality* shows the importance of a node in bridging the different parts or components of the network together. High *betwenness centrality* means that a node has a bridging role between different parts of the overall network. The *average betwenness centrality* shows the availability of bridging relationships across the system. Finally, a node's *eigenvector centrality* is proportional to the sum of the eigenvector centralities of all nodes directly connected to it. Put differently, a node with a high eigenvector centrality is linked to other nodes with high eigenvector centrality.

At the meso-structural level some of the most common indicators are *Modularity,* which is the fraction of links that fall within modules, minus the expected value of the same quantity if the links fall at random without regard for the modular structure and *Within-module degree* that indicates how the node is positioned, thus measuring how 'well connected' the node is to other nodes in the module.

At the *structural level*, most common indicators include the *density* of interactions; the *average degree* of separation and cross-group or cross-organization *connectivity*. These measures are particularly useful for comparing groups within networks or for gaining insights about changes in a network over time. The profile of the ecosystem is generally described through indicators of *size* and *composition* of the network. While the size is usually represented through the number of nodes and edges, the composition refers to the concept of *homophily*, which is the tendency to relate to nodes with similar characteristics that, in turn, leads to the formation of homogeneous groups (clusters) where establishing relations is deemed to be easier. Another aspect that can be measured through SNA structural indicators is the level of engagement of network's actors, usually indicated through the *ratio of edge-to-node* (i.e. the number of connections between nodes in the ecosystem).

Additionally, usually referred to as an indicator of vitality, a network's *density*, which is the ratio of the number of edges in the network over the total number of possible edges between all pairs of nodes (which is n(n-1)/2, where n is the number of vertices, for an undirected graph), is a common measure of how tightly connected a network is. A perfectly connected network is called a *clique* and has density equal to 1. Conversely, a directed graph will present half the density of its undirected equivalent, as there are twice as many possible edges, i.e. n (n-1). *Density* is particularly useful in comparing networks against each other, or in doing the same for different regions within a single network. Other two common indicators, which are often referred to as *small world properties* are *Average Clustering Coefficient* and *Average Path Length*. A node's clustering coefficient is the number of closed triplets in the node's neighborhood over the total number of triplets in the neighborhood, also known as *transitivity*. Clustering algorithms detect clusters or "groups" within networks on the basis of network structure and specific clustering criteria. While analyzing the structure of a network, the main indicator is the Average clustering coefficient that shows the ecosystem's overall connectivity based on local relationships. The average path length is the average graph-distance between all pairs of nodes. The longest shortest path (distance) between any two nodes is known as the *network's diameter*, which is a useful indicator of the reach of the network (instead of focusing only on the total number of nodes or edges). It also provides information about how long it will take at most to reach any vertex in the network (sparser networks usually present greater diameters). Additionally, the *Average Path Length* (average of all shortest paths) in a network is an interesting indicator of how far apart any two vertexes are expected to be on average (average distance). As further indicators of cohesion, it is possible to compute the *size of the major component,* i.e. the percentage of nodes belonging to the main component, which shows the cohesion to belonging to the largest group of the ecosystem. Similarly, the *ratio of the number of relations* in which there is an edge in both directions, over the total number of relations in the network. This is a useful indicator of the degree of mutuality and reciprocal exchange in a network, which relate to social cohesion but it only makes sense in directed graphs.

Table 3.3. The most common indicators in Social Network Analysis

		Snapshot indicator	Description
STRUCTURAL	Types of actors present	The similarity of actors present (homophily/heterophily)	The composition of the ecosystem
	Quantity of actors and ties	Number of nodes Number of edges	Ratio of edge - to - node: The number of connections between nodes in the ecosystem
	Diameter	The longest shortest path (distance) between any two nodes	Indicator of the reach of the network - (sparser networks usually present greater diameters).
	Density	Represents how tightly the network is connected	The actual interconnectedness in the ecosystem's overall connectivity based on local relationships – (the actual edges divided by the potential edges)
	Clustering co-efficient	The level of connectivity between the directly connected partners	Average clustering coefficient: showing the ecosystem's overall connectivity based on local relationships
	Average Path Length	Indicator of how far apart any two vertexes are expected to be on average (average distance)	The average graph-distance between all pairs of nodes
	Major component	Size of the main component Percentage of nodes belonging to the main component	% of nodes: showing the cohesion to belonging to the largest group of the ecosystem
	Degree of Reciprocity	Indicator of the degree of mutuality and reciprocal exchange in a network (only in directed graphs).	The ratio of the number of relations in which there is an edge in both directions, over the total number of relations in the network

MESO-STRUCTURAL	Modularity	Measures the strength of division of a network into modules (or groups, clusters or communities). Networks with high modularity have dense connections between the nodes within modules but sparse connections between nodes in different modules. It is used for detecting *community structure* in networks. l	The fraction of links that fall within modules, minus the expected value of the same quantity
	Within-module degree (z-score)	Indicates how the node is 'well connected' to other nodes in the module	intramodule z-scored within the node's module
ORGANIZATION AND INDIVIDUAL	Node Degree of Centrality	Provides information on node's immediate connectivity and popularity and influence in the networks.	The number of available connections Indegree (the number of incoming connections) Outdegree (the number of outgoing connections)
	Betweenness centrality	High betweenness centrality means that a node has a connecting role as a bridge between the different parts of the overall network	Average betweenness centrality: showing the availability of bridging relationships across the system
	Closeness centrality	It is a measure of reach as it indicates the speed with which information can reach other nodes from a given starting vertex	The mean length of all shortest paths from a vertex to all the other ones in the network
	Eigenvector centrality	A node with a high eigenvector centrality is linked to other nodes with high eigenvector centrality.	A node's eigenvector centrality is proportional to the sum of the eigenvector centralities of all nodes directly connected to it.

Source: author's own elaboration

3.3.2 Expert interviews

The expert interview is a consolidated methodology of qualitative empirical research, designed to explore expert knowledge, which has increased its popularity since the early 1990s. More specifically, expert interview has found increasing application in social science and its modes of implementation, from its role in individual research design to the methods used to decode and analyze its results, varies on a case basis. This method has been increasingly applied also for the study of innovation-driven networks (see e.g. Bianchi et al., 2011). However, it is widely accepted that the popularity gained by this methodology is due to the fact that, in relative terms, talking to experts during the exploratory phase of a research projects, turns out to be a more efficient and concentrated way to gather data compared to, for example, systematic quantitative surveys or participatory observation. Indeed, expert interviews can contribute to shorten the lengthy data gathering processes, especially in case of experts who are considered as "*crystallization points*" for achieving insider knowledge from practitioners and regarded as surrogates for a wider circle of stakeholders. One of the main methodological concerns that researchers are faced with is the identification of the "experts". Meuser and Nagel (1991) provide one of the most accredited definitions of expert, regarded as either a "*Person who is responsible for the development, implementation or control of solutions/strategies/policies*", or a "*Person who has privileged access to information about groups of persons or decision processes*". Expert interviews can be used for different purposes. In this regard, Boger and Menz (2002) provide a topology of expert interviews on the basis of the different purposes these are used for. Primarily, expert interviews can be used for exploring a new field of study to which conferring a thematic structure and for hypothesis generation. Secondly, this methodology can be implemented for collecting contextual information to complementary findings deriving from the application of other methodologies. Finally, expert interviews may be applied for theory building, by developing a framework as a result of knowledge reconstruction from various experts. For the development of this thesis' empirical study, the second typology of expert interview is implemented, i.e. the *systematizing expert interview,* to complement results deriving from the social network analysis. Interviews as qualitative research methodology may take different forms - namely, semi-structured, structured and unstructured interviews. This study adopts semi-structures in-depth interviews, differently from structured interviews that require the use of a set of standardized questions that the researcher creates in advance, are conducted with a fairly open framework that allow for focused, conversational, two-way communication where respondents have to answer openended questions for the duration of 30 minutes to more than an hour. More specifically, these are based on an interview guide, i.e. a schematic presentation of questions or topics to be explored by the interviewer. The interview guide consists of core questions as well as a number of associated questions that may improve further through pilot testing of the interview guide. The interview guide serves to exploration purposes in a more systematic and efficient way as it contributes to keep the conversation focused on the desired line of action. The main advantage of semi-structured in-depth interviews lies in the combination of both structure and flexibility, that allows respondents to interact with the investigator in terms of the issue under research, thus providing much more detailed information compared to other techniques to gather data, such as surveys, especially in those cases when an interviewee's answer to a preset question raises issues that the interview may further explore through follow-up questions. This specific format of interview is particularly appropriate in those cases in which you have a limited sample of key interviewees whose expertise and experience in the field under investigation may raise issues not previously covered by the researcher, allowing for s thicker understanding of the field (Corbin, and Strauss, 2008; Gray, 2009; Corbin and Morse, 2003).

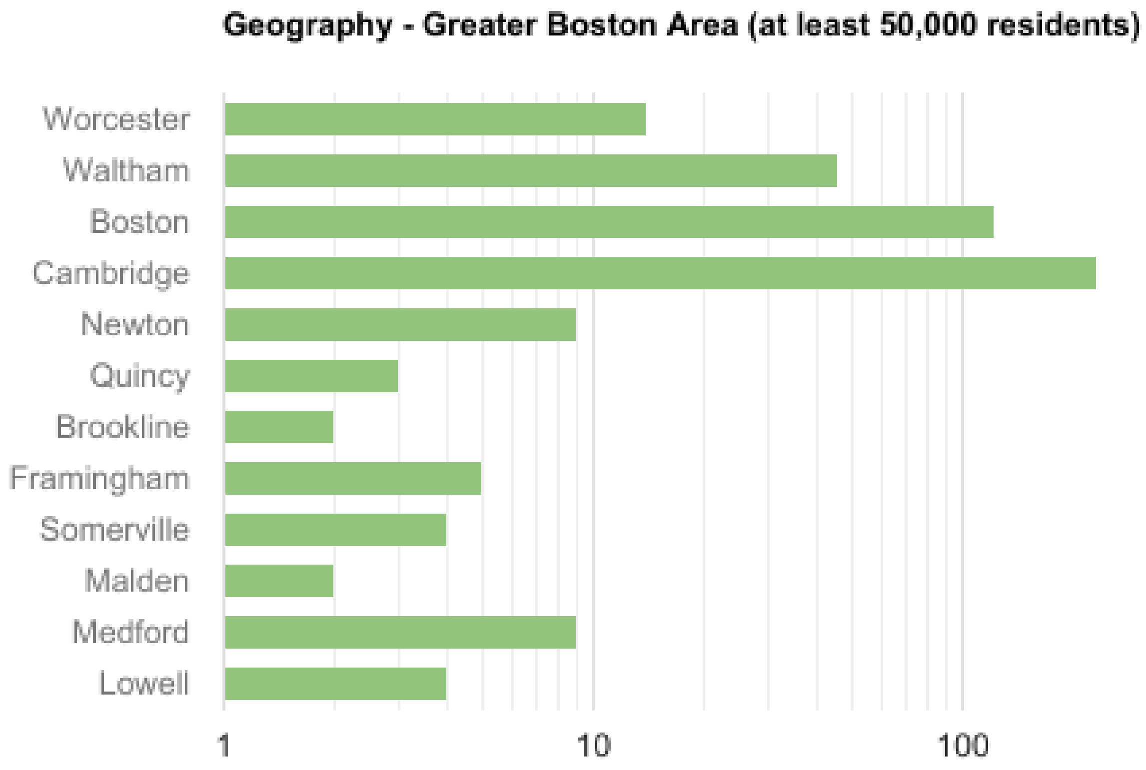
3.4 Data collection and analysis

3.4.1 Data collection for Social Network Analysis

3.4.1.1 Sample selection

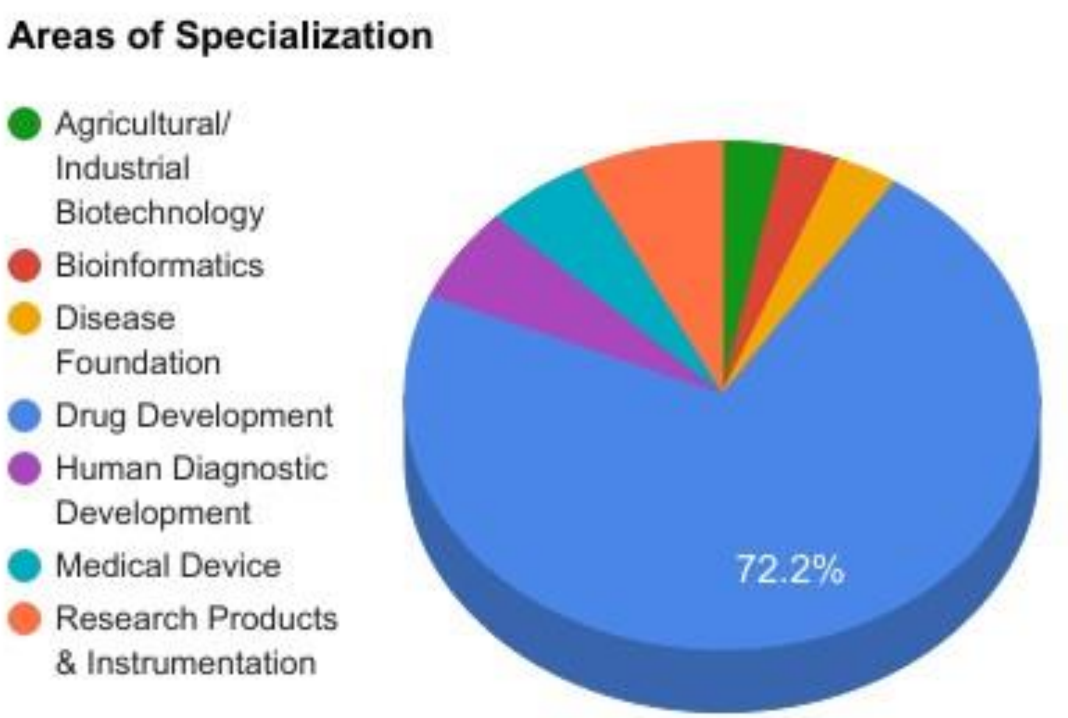
To explore data-driven network analytics by taking into account the diversity of the LIS' community, I selected the sample based on their memberships to MassBio, the freely available membership directory of the Massachusetts Biotechnology Council. MassBio counts more than 975 members dedicated to advancing cutting-edge research in life science industry in Massachusetts and provides information on their location, typology and area of specialization. Members range from Academic Hospitals & Non-Profit Organizations to Pharmaceutical Biotech companies and Capital Providers. I selected those organizations with headquarters or branch offices having mailing addresses in the metropolitan areas of Greater Boston. The spatial identification of each area included the suburban city names associated with identification of that metropolitan area with more than 50.000 inhabitants (U.S. Census Bureau, 2015) (Figure 3.5). Additionally, included in the sample are only those members belonging to the Biopharma industry that are specialized in drug development (Figure 3.6). The final sample counts 444 organizations distributed as follows: 85 Academic Hospitals & Non-Profit Organizations (Universities, Research Institutes, Hospitals, Government Agencies, Incubators); 55 Capital Risk Providers (VC, CVC, Hedge Funds, PE Firms); 304 Pharma-Biotech firms (Big Pharmas, DBFs, CROs, Start-up).

Figure 3.5 Geographical distribution – MassBio members in GBA (2012-2017)



Source: authors' own elaboration from MassBio

Figure 3.6. Areas of specialization- MassBio members in GBA (2012-2017)



Source: authors' own elaboration from MassBio

3.4.1.2 Data collection

To reveal insights about the overall innovation system's structure of Greater Boston metropolitan area, this paper regards two types of relationships: first, financial transactions represented by *venture deals*, i.e. Series A-E/Round 1-5; Grant; Seed; PIPE; Add-on; Venture Debt and second, *strategic alliances*, i.e. 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. To create the final dataset, I relied on two sources of relational data about relationships. To collect data on venture deals, I used 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. I selected deals 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 strategic alliances I collected data from the Strategic Transactions Database (Pharma & MedTech Business Intelligence) that summarizes deals by type, industry and sector from 1995 to date. I collected information on Strategic Alliances initiated or completed within 2012 – 2017-time frame including 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 and matched our sample. I integrated these two databases into a single dataset on networks consisting of 450 nodes and 289 links. The links are non-directed in order to measure small world properties (Kajikawata, 2010). I observed 148 Venture deals and 141 Strategic Alliances (Figure 3.7).

3.4.1.1 Data computation

To present the data and its metrics in a visual form I used Gephi, an interactive network analysis software that implements a set of key functionalities for visual network analytics and metrics computation (Still et al., 2015). I 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, 1992). I also provided complementary network visualization by using Kumu, a data visualization platform to organize complex information into interactive relationship maps (www.kumu.io). In the first visualization (Gephi), color-coding was added to provide information about the frequency of the tie (measured by counting the number of interaction in the timeframe). In the second case (Kumu) color-coding was included to differentiate the types of edges. Tie data allowed me to calculate measures of network structure that I used to evaluate the level of *embeddedness* of the network and to classify individual ties by their type: (i) R&D partnerships (i.e. R&D strategic alliances 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; (vi) Other Biotech Deals.

Figure 3.7. 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

Types of relationships	**Venture deals** (148) between firms and investors co-located in the GBA	**Strategic Alliances** (141) 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

3.4.2 Data collection for expert interviews

In order to gain insights about the most desirable network portfolio mix a round of expert interviews was organized and carried out with 9 key informants who have been chosen as representatives of the different categories of stakeholders in the Biopharma ecosystem of Greater Boston Area. The interviews have been conducted directly by the author. The list of participants who took part in each interview is reported in Table 3.4 and the profiles of the represented organizations are illustrated in Table 3.5. Assuming that the conditions that distinguish LISs from other forms of territorial aggregations (e.g. Industrial Districts) and a-spatial innovation systems (e.g. technological/sectorial systems of innovation) are:

- The existence of knowledge-intensive relationships for the combination of non-existing knowledge (analytic base of knowledge), and
- The embeddedness of the LIS' actors found in spatial proximity, which in turns allows easier access to information (Ferretti and Parmentola 2015)

Insights on the LIS successful network composition have been gained by exploring:

- which relationships have a greater impact on knowledge transfer, and

- for which relationships being in spatial proximity with the partners was more valuable.

The experts were asked to discuss those types of relationships that were more frequently implemented in their practices of innovation processes and provide insights on those that best contribute to knowledge transfer and about the importance of being in spatial proximity with the partners for each specific type of relationship.

Table 3.4. Expert interviews – Represented organizations

MIT Dept. of Chemical Engineering	Formally established as a separate department in 1920, MIT's Chemical Engineering department (ChemE) has not only set the standard for instruction and research in the field, it continues to redefine the discipline's frontiers. With one of three undergraduate programs focusing on chemical-biological engineering for students interested in the emerging biotech and life sciences industries, and two of three graduate programs providing an experiential course of study in chemical engineering practice in collaboration with MIT's Sloan School of Management, ChemE at MIT is quite unlike chemical engineering anywhere else. In 2017, for the 29th consecutive year, US News & World Report gave its top rankings to both our graduate and undergraduate programs among the nation's chemical engineering departments. In 2017, for the 7th straight year, MIT Chemical Engineering has been ranked first in the world by QS World University Rankings. More than 10% of our alumni are senior executives of industrial companies. Nearly 25% of the recipients of major awards presented by the American Institute of Chemical Engineers and the American Chemical Society's Murphree Award have been alumni or faculty of MIT. Source**: https://cheme.mit.edu**
Massachusetts Life Science Center (MLSC)	The Massachusetts Life Sciences Center (MLSC) is an investment agency that supports life sciences innovation, education, research & development, and commercialization. The MLSC is charged with implementing a $1-billion, state-funded investment initiative to create jobs and support advances that improve health and well-being. The MLSC offers the nation's most comprehensive set of incentives and collaborative programs targeted to the
	life sciences ecosystem. These programs propel the growth that has made Massachusetts the global leader in life sciences. The MLSC creates new models for collaboration and partners with organizations, both public and private, around the world to promote innovation in the life sciences. Source: http://www.masslifesciences.com
Novartis	Novartis is a Swiss multinational pharmaceutical company based in Basel, Switzerland. It is one of the largest pharmaceutical companies by both market cap and sales. Novartis manufactures the drugs clozapine (Clozaril), diclofenac (Voltaren), carbamazepine (Tegretol), valsartan (Diovan) and imatinib mesylate (Gleevec/Glivec). Additional agents include ciclosporin (Neoral/Sandimmun), letrozole (Femara), methylphenidate (Ritalin), terbinafine (Lamisil), and others. Source: https://www.novartis.com
Ironwood Pharmaceuticals, Inc.	Ironwood Pharmaceuticals, Inc. is a biotechnology company. The Company is advancing product opportunities in areas of unmet need, including irritable bowel syndrome with constipation (IBS C), and chronic idiopathic constipation (CIC), hyperuricemia associated with uncontrolled gout, uncontrolled gastroesophageal reflux disease (uncontrolled GERD), and vascular and fibrotic diseases. It operates in human therapeutics business segment. Its product, linaclotide, is available to adult men and women suffering from IBS C or CIC in the United States under the trademarked name LINZESS, and is available to adult men and women suffering from IBS C in certain European countries under the trademarked name CONSTELLA. It is also advancing IW-3718, a gastric retentive formulation of a bile acid sequestrant with the potential to provide symptomatic relief in patients with uncontrolled GERD. Its vascular/fibrotic programs include IW-1973 and IW-1701, which targets soluble guanylate cyclase (sGC). Source: https://www.ironwoodpharma.com

Alnylam	Alnylam is leading the translation of RNA interference (RNAi) into a whole new class of innovative medicines with the potential to transform the lives of patients who have limited or inadequate treatment options. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of debilitating diseases with high unmet medical need. Alnylam was founded in 2002 on a bold vision to turn scientific possibility into reality, which is now marked by its robust discovery platform and deep pipeline of investigational medicines, including 4 programs in late-stage clinical development. Source:
Obsidian Therapeutics	Obsidian Therapeutics, founded by Atlas Venture in 2016, is a biotech firm based in Cambridge, which develops next-generation cell and gene therapeutics that employ precise exogenous control of transgenes for improved safety and efficacy. Source:
Angiex	Angiex was founded is a start-up biotech firm that develops vascular-targeted biotherapeutics. Angiex targets fundamental aspects of endothelial biology with a focus on angiogenesis; its lead product is an antibody-drug conjugate therapy for cancer. Angiex was launched with IP from Beth Israel Deaconess Medical Center, is resident at LabCentral in Cambridge, and recently closed a $3 million Series A round. Angiex founders discovered VEGF-A, have been recognized as the world's leading experts in tumor blood vessel biology, developed new methods for per cell mRNA quantification, founded four companies, and wrote a best-selling diet book. Source: http://www.alnylam.com
Kymera Therapeutics	Kymera Therapeutics is a seed-stage therapeutics company focused on targeting the traditionally undruggable proteome within key pathways involved in inflammation, immunity, and oncology. Its approach combines the power of effective genetic silencing with the flexibility and drug-like properties of small molecules to harness the body's innate protein regulation machinery. Source: https://labcentral.org/resident-companies/kymera/
ReviveMed	ReviveMed is a precision-medicine platform that leverages the data from small molecules or metabolites. Metabolomics (which is the study of small molecules such as glucose or cholesterol) is essential for developing the right therapeutics for the right patients. However, because identifying a large set of metabolites for each patient is costly and slow, metabolomic data has been under-utilized – and the firm aim at filling this gap. ReviveMed technology, which was developed at MIT and published in Nature Methods, uniquely overcomes the difficulty of using a large set of metabolomic data, and transform these data into actionable insight. Currently, we are working with a few strategic partners from leading pharma/biotech companies, while developing our own metabolomics based therapeutics. Source: http://www.revive-med.com

Source: authors' own elaboration

Table 3.5. Expert interviews – List of participants

Position	Organization	Stakeholder
Full Professor	*MIT Dept. of Chemical Engineering*	University and Research institutes
General Counsel and Vice-President for Academic and Workforce Program	*Massachusetts Life Science Center*	Government
Chief Executive Officer	*Obsidian*	Entrepreneurship - Biotech
Chief Executive Officer	*Angiex*	Entrepreneurship – Start-up
Chief Executive Officer	*Kymera Therapeutics*	Entrepreneurship – Start-up
Chief Executive Officer	*Revive-med*	Entrepreneurship – Spin-off
Alliance Manager	*Alnylam*	Entrepreneurship – Start-up
Research Associate	*Novartis*	Corporate
Senior Vice President, R&D Strategy and External Innovation	*Ironwood Pharmaceuticals, Inc.*	Corporate

Source: authors' own elaboration

3.5 Summary

This chapter has illustrated the methodological approach and the research design selected for the exploration of the relation dimension of LIS. The insights on the Biopharma industry main features in both terms of R&D dynamics and forms of inter-organizational cooperation served to prove the suitability of the industry for the empirical purposes of this study. Indeed, the high level of specialization of the activities and the high risks and costs associated to the drug development process, make cooperation particularly crucial to actors' competitiveness. The description of the Greater Boston Biopharma System, through the provision of its historical background and metrics of performance, served to depict this system as a benchmark of success in the field whose implication in terms of network structure and portfolio are of particular importance for emerging systems. Finally, the discussion about the two selected research techniques and the emphasis on their points of strength and weaknesses, allowed appreciating the advantages deriving from a combined approach to broaden the reach of the analytic framework. The next chapter will discuss main findings derived from data analysis and provide a theoretical framework for the study of LIS relational dimension.

CHAPTER 4 – RESULTS FROM THE EMPIRICAL STUDY

This chapter aims to discuss the main findings deriving from data analysis and proposes a theoretical framework for the study of LIS relational dimension. The first section illustrates main results emerging from the social network analysis conducted on a sample of organizations in Biopharma sector localized in the Greater Boston Area to provide a snapshot of the network structural configuration and to identify the central nodes. Section 4.2 illustrates and critically discusses the results of the round of interviews conducted with representatives of different organizations in Biopharma with the specific purpose of gaining insights about the preferable network portfolio combination along two specific dimensions, i.e. the impact on knowledge transfer and the importance of spatial proximity. Section 4.3 provides an in-depth discussion of results from both analyses and combine them to achieve a more complete overview about the whole system's functioning and proposes an analytical framework for future studies. A set of propositions for practitioners are presented in the conclusive section, together with main limitations of the study and suggestion for future research.

4.1 Results from the Social Network Analysis

The network resulting from the sample of organizations consists of 281 connected nodes and 381 edges, with a diameter of 13. From the analysis of network composition, it emerges that venture deals represent the most frequent type of tie in our sample (58.1%), followed by IP transfer (20.8%). R&D Partnerships and other biotech deals account for the 9% each and finally, joint ventures and academic spin-offs / corporate spinouts represent only 2.2% and 0.9% of the network portfolio, respectively (Figure 4.1). Table 3 reports findings from the social network analysis conducted on relational data available for the Greater Boston Biopharma system and network metrics have been interpreted as indicators of LIS relational capital.

At the micro-level, the computation of *betweenness centrality* served to identify the top 20 actors in terms of centrality position in the network. Indeed, high *betweenness centrality* values indicate that a node has a connecting role between the different parts of the overall network and contributes to identify key stakeholders within the innovation systems.

Top positions are occupied mainly by large venture capital firms (e.g. New Entreprises Associates; Third Rock Ventures; Polaris Partners) and pharmaceutical companies with a venture arms (CRISPR; Pfizer, Inc.; Celgene; Novartis Venture funds; Astrazeneca Pharmaceutical, LP.) (Table 4.1).

At the structural level, metrics of density, average degree, modularity and small worlds properties have been computed to gain insights about the overall configuration of the network (Table 4.2). More specifically, the *ratio of edge-to-node* has been calculated to show the number of connections between nodes in the system, which indicates a high level of engagement of the network and density, which in turn, expresses the number of actual linkages divided by the maximum number of possible linkages, has been calculated to provide indication of network *vitality* (Russell et al., 2015). Values of density close to 0 indicate that the network is *poorly connected*, and conversely, when these are proximate to 1, they exemplify a high level of connectivity in the network. In the case of

GBA Biopharma LIS, the graph shows a relatively low value of density (0.008), suggesting that the network is relatively sparse (Balland et al., 2012) and characterized by the presence of structural holes (Ahuja, 2000).

The *Average Degree*, i.e. the average number of available connections per entity, reveals insights about the relational potential and expresses, on average, the number of organizations' partners. In the case of GBA Biopharma LIS, the *average degree* and the *average weighted degree* (interactions weighted according to their frequency) show values that indicate an average level of engagement by the network's actors with partners in spatial propinquity (Kajikawata et al., 2010; Still et al., 2010 and Salavisa et al., 2012). At the meso-structural level, *modularity* scores (0.626) and the high number of *connected components* (120) suggest a high tendency of network's actors to form sub-groups where interactions occur more easily. In fact, a connected component of an undirected graph is a maximal set of nodes, in a way that a path connects each pair of nodes. Connected components constitute a partition of the set of graph nodes, which means that connected components are non-empty, but rather pairwise disjoints, and the union of connected components constitutes the set of all nodes. Additionally, we analyzed the network from a *small world* perspective, by calculating the *average path length* and the *average clustering coefficient* (Watts and Strogatz, 1998). Following Kajikawata (2010), the *Average Path Length*, i.e. the average graph- distance between all pairs of nodes, is fundamental for the assessment of the network performance as it indicates that a node can have an easier and quicker access to other actors with less efforts, thus accessing to a larger amount of knowledge or information. Generally speaking, a small value of average path length indicates a small diameter of the network, which in turns suggests that organizations in the network can pool resources through a smaller number of paths and structural holes are buried. *Clustering coefficient* represents the extent to which nodes connected to *i* are also linked to each other and the *average cluster coefficient* shows the system's overall connectivity based on local relationships, suggesting a greater accumulation of social capital.

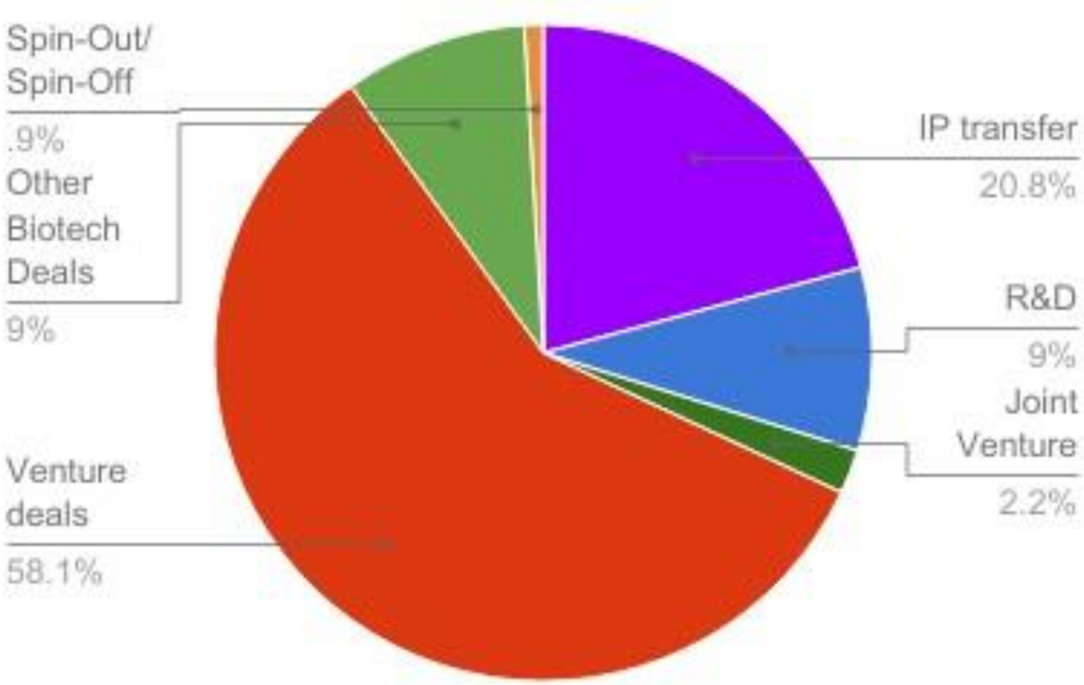
It is argued that small world configuration allows achieving both advantages of closed and open networks. In fact, while, a network with a small path length sustains network closure (as it allows information to circulate more easily and quickly through a less number of paths and structural holes) a network with high clustering coefficient suggests that larger social capital is accumulated, which is a benefit of open and sparser networks.

The GBA innovation system presents relatively high values for both the first small world property, i.e. *average path length* (4.458), and the second one, i.e. *clustering coefficient score* (Kajikawa et al., 2010) (0.058), thus confirming its structural tendency toward a more open configuration, with specific implications in terms of a more diversified relational capital through less redundant and weaker ties. Visualisations of the GBA network are provided in Figure 4.2 and Figure 4.3. While the former highlights the tendency of forming dyadic and triplets forms of interactions as well as visual information about their frequency, the latter presents the distribution of the different types of relationships composing the relational dataset.

In conclusion, the GBA Biopharma LIS appears to be characterized by an open structure with structural holes and the tendency of vertices to form small groups where interactions are more frequent. Finally, bridging functions appear to be mostly undertaken by large venture capital firms and pharmaceutical companies with venture arms.

However, due to the lack of exact benchmark parameters for network structural metrics in the network literature, these results should be taken as a reference for future comparative analysis.

Figure 8.1. Network Portfolio composition - Greater Boston Area (2012-2017)



Source: author's own elaboration from Preqin Ltd. 2017 and Pharma & MedTech Business Intelligence, 2017

Table 4.1. Top 20 Actors - Betweenness centrality Greater Boston Area (2012-2017)

Rank	Organization	Value
1	Rhythm Pharmaceuticals, Inc.	0.225
2	New Entreprise Associates	0.176
3	Third Rock Ventures	0.155
4	CRISPR	0.154
5	Polaris Partners	0.107
6	Pfizer, Inc.	0.105
7	SR One (GSK)	0.103
8	Ra Pharma	0.102
9	Celgene	0.094
10	MPM Capital	0.087
11	Kala Pharmaceuticals, Inc.	0.084
12	Moderna	0.084
13	Novartis Venture Funds	0-081
14	Navitor	0.081
15	Aileron Therapeutics, Inc.	0.077
16	Lightstones Ventures	0.076
17	Atlas Venture	0.071
18	Syros Pharmaceuticals, Inc.	0.069

19	Ctabasis Pharmaceuticals	0.066
20	AstraZeneca Pharmaceuticals	0.065

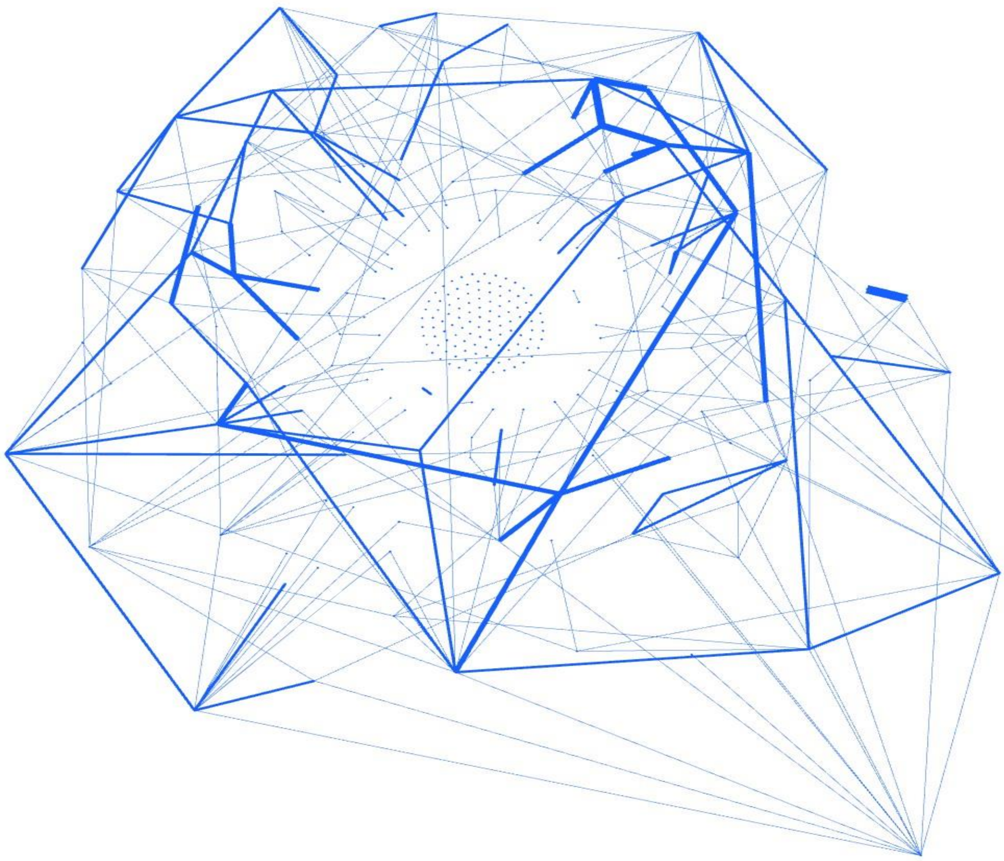
Source: author's own elaboration

Table 4.2. Social Network Analysis Metrics - Greater Boston Area (2012-2017)

# nodes	281
# edges	323
Ratio edge-to-node	1,15
Network Diameter	13
Average Degree	2,299
Avg. Weighted Degree	3,039
Graph Density	0,008
Modularity	0,626
Connected components	120
Avg. Clustering Coefficient	0,059
Avg. Path Length	4,458

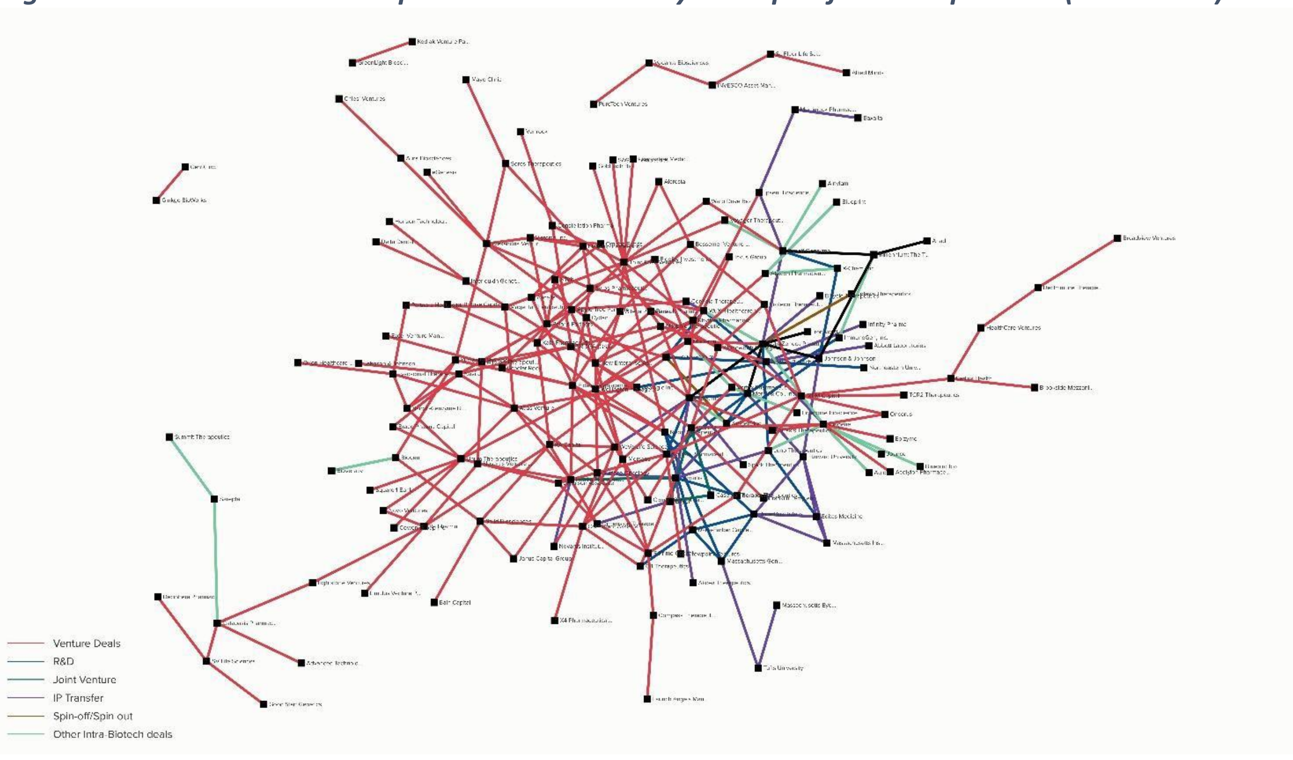
Source: author's own elaboration

Figure 4.2. Greater Boston Biopharma Innovation System: network structure (2012-2017)



Source: author's own elaboration

Figure 4.3. Greater Boston Biopharma Innovation System: portfolio composition (2012-2017)



Source: author's own elaboration

4.2 Results from the expert interviews

4.2.1. The most common practices of innovation-driven interactions within the LIS

From the results of expert interviews, it emerged that the most frequent practices of innovation-driven interactions with the actors in the area are:

1. Value Added Supply agreements
2. Venture Capital and Seed investments
3. Agreements for the access and use of infrastructure
4. Co-participation in thematic associations and symposia
5. Board interlocks
6. Formal and informal industry-university agreements for the mobility of human resources
7. Sponsored research
8. Intellectual Property transfer
9. R&D strategic alliances

In general terms, it emerged that partnerships that promote connectivity among different disciplines are more likely to bring potential for innovation and that these should be incentivized through, for example, thematic initiatives (e.g. student clubs), which are able to pool talents with a diverse set of capabilities and knowledge. There is a common agreement that cross-disciplinary interaction contributes to bring complementary skills and smooth the c.d. *knowledge disabilities*. Additionally, there is a large consensus that informal relations, compared to more structured and institutionalized alliances, represent an easier way of *know-how trading* (cit. *"the more formal the relationship the lower opportunity for transfer of information"*) due to the potential of learning through face-to face conversation, facilitated by embeddedness. The physical proximity of different ecosystem's actors turns out to be very important as it stimulates mechanisms of trust through the building of social relations (cit. "*relationships are important because relationships between people* *are important"*) and that the emergence of a "culture of trust" is vital for the ecosystem performance.

4.2.2. Types of relationships that contribute to knowledge transfer

More specifically, it emerged that knowledge transfer is particularly enhanced in:

1. Co-participation in thematic associations and symposia;
2. Agreements for the access and use of infrastructure;
3. Venture Capital and Seed investments;
4. Formal and informal industry-university agreements for the mobility of human resources;

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, thus avoiding redundancy of information and enhancing innovation potential. 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, as the consortium gathers all major academic centers in the area 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. Similarly, but to a much lower extent of formalization, the Alliance Manager from Ironwood, reported his experience in arranging periodical target specific symposia for sharing pre-competitive knowledge with competitors and major research actors in the area (e.g. Novartis, MIT, Harvard and Tufts) for the development of a specific molecule. These meetings, which have a grassroots origin (from company scientists' initiative), take place in an informal way *"It's a mix of social and science" (cit.)*: mostly during a poster session, with five to seven participants and a couple of speakers. One interesting point is that, despite the high confidentiality of the information exchanged, there is no need of non-disclosure formal agreements due to the level of trust and mutual understanding that naturally emerges among the participants.

Secondly, *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 regarding 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.

As for the *Agreements for the access and use of infrastructure*, the advantages in terms of knowledge transfer are a spillover effect of the environment provided by hosting organizations. From the experience of Obsidian, 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 in this case. Also, incubators and accelerators generally offer services of business consultancy to scientists and engineers that lack capabilities in this field.

Finally, *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.

With regards to *Board interlocks*; *Sponsored Research* and *IP transfer* the process of knowledge transfer is less accentuated. More specifically, interlocking directorates are considered to be more useful for establishing new partnerships as a direct consequence of the exploitation of board members' diverse networks. Most interviewees agreed on the fact that knowledge transfer efficacy really depends on the board composition. As a way of illustration, Ironwood's CEO reported the advantages of having the CEO of Blue Cross and Blue Shield of Massachusetts, Inc. on their board of directors, as he gave them "*the perspective of what it means to deliver products to patients to deliver healthcare*". Also, the interviewees reported that knowledge transfer manifests more explicitly through the establishment of *ad hoc* scientific advisory committees where the composition of members (often from academia) is more flexible, according to the innovation's specific issues under discussion.

Sponsored Research and more in general relationships with academia contribute to knowledge transfer depending on the stage of the innovation process. Experts from the Industry agreed on the fact that, in general terms, academic investigators are really good at idea generation - "*to think outside the box*" - while they tend to lack competencies concerning the product development cycle. Partnering with academic centers of excellence may give access to the newest thinking and potential disruptive ideas as well as very specific expertise. In the second case, sponsored research may take the form of a *fee-for-service* as in the case the company is willing to use a specific model system to understand how their compound behaves with a specific disease.

IP transfer is traditionally renowned as a practice of knowledge transfer despite many of the experts reported that the tendency towards a more *hands-off approach* limits the amount of information exchanged to the operative phases and not to the innovation process itself. As claimed by the CEO of Angiex, while discussing his experience with the Beth Israel Deaconess Medical Center where the company in-licensed some IP: "*It's very difficult to transfer knowledge and the IP transfer process is different from knowledge transfer process. IP transfer process is essentially work for lawyers and technology venture offices who are trying to find a home for patents and that do not necessarily know that much about the science behind things*". The IP is generally developed by academics, therefore in typical companies where the academics who developed the IP did not leave the hospital, they typically become advisors to the company (sitting in the advisory board) and receive stocks in exchange of taking care of that knowledge transfer. In these cases, the IP developers are able to give company's employees some background about the technology and the work that was done in their academic institution.

4.2.3 The role of Spatial Proximity for the different types of relationships

While asking for which specific types of relationship being in spatial proximity with the partners was more valuable, the experts refer to:

- Agreements for the access and use of infrastructure;

- Venture Capital and Seed investments;
- Co-participation in thematic associations;
- Strategic alliance

More precisely, proximity is at the core of the *innovation centers* concept, some of the experts that we interviewed have operations in different of these centers, as in the case of Obsidian, which used to have operations distributed in three different facilities in Cambridge (LabCentral, Cambridge Biolabs and Broad Institute). Therefore, it is clear that in case of *Agreements for the access and use of infrastructure*, operating in the same area of the hosting structure is fundamental. According to the experts, 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*, as in the case of the Koch Center where engineers and scientists are located in the same floor.

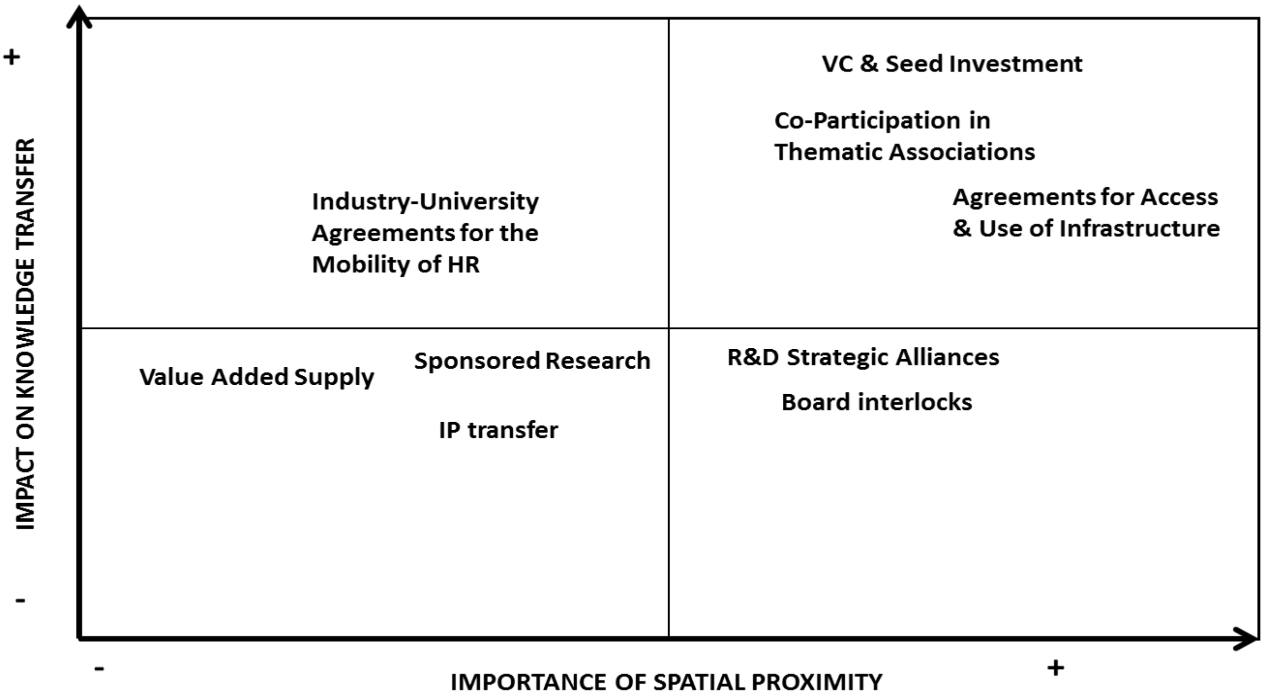
As for *Venture Capital and Seed investments* the importance of spatial proximity is mainly explained by the frequency of interactions required –especially at the seed stage - and the need of establishing trust mechanisms with the partners. As affirmed by Kymera's CEO, "*personal ties play a key role in fostering relationships with investors and living in the same place makes a difference*". Proximity allows to have more frequent interactions with a network of operators in the area that may eventually function as a *talent validation* device, which turns out to be particularly useful for risky operations as in the case of VC and seed funds. While exploring the relationship between Kymera and Atlas Venture – a VC company headquartered in Kendall Square (Cambridge, MA) - it emerged that it is not uncommon for VC 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.

Proximity is particularly important also in the case of *co-participation in thematic associations* between more organizations as it enables to enhance interactions outside the association's meetings and building trust mechanisms, which are particularly important if we consider that many of the members are competitors and their frequent interactions contribute to align their vision, as reported by MLS.

Finally, while exploring the 10-years *strategic alliance* between Novartis and the MIT Department. of Chemical Engineering, the former Dean highlighted how R&D Partnerships between Industry and University have evolved over time from covering a less significant share of funds and following a more *hands-off approach* to becoming more strategic. In his view, nowadays the company has a clear understanding of its long-term goals and presents a higher level of engagement in university activities, which requires more frequent interaction between the company and the academic department. Also, in the case of *Strategic Alliances* geographic proximity would decrease the c.d. *collaboration risk* (*e.g.* project orphaning; divergence of missions and goals).

Conversely, spatial proximity with partners within *value added supply relationships*, especially with CROs, does not seem to play a key role. As frequently reported by interviewees, "CROs can be anywhere", and this is partly explained by the high degree of standardization of many of the outsourced services in the drug development industry and the stage of the Life Science R&D cycle when these interactions happen, i.e. *target validation*. Only in those cases where contract manufacturing requires a high degree of customization, geographic proximity may play a more significant role.

Figure 4.4. Network portfolio in Biopharma LIS in Greater Boston Area



Source: author's own elaboration

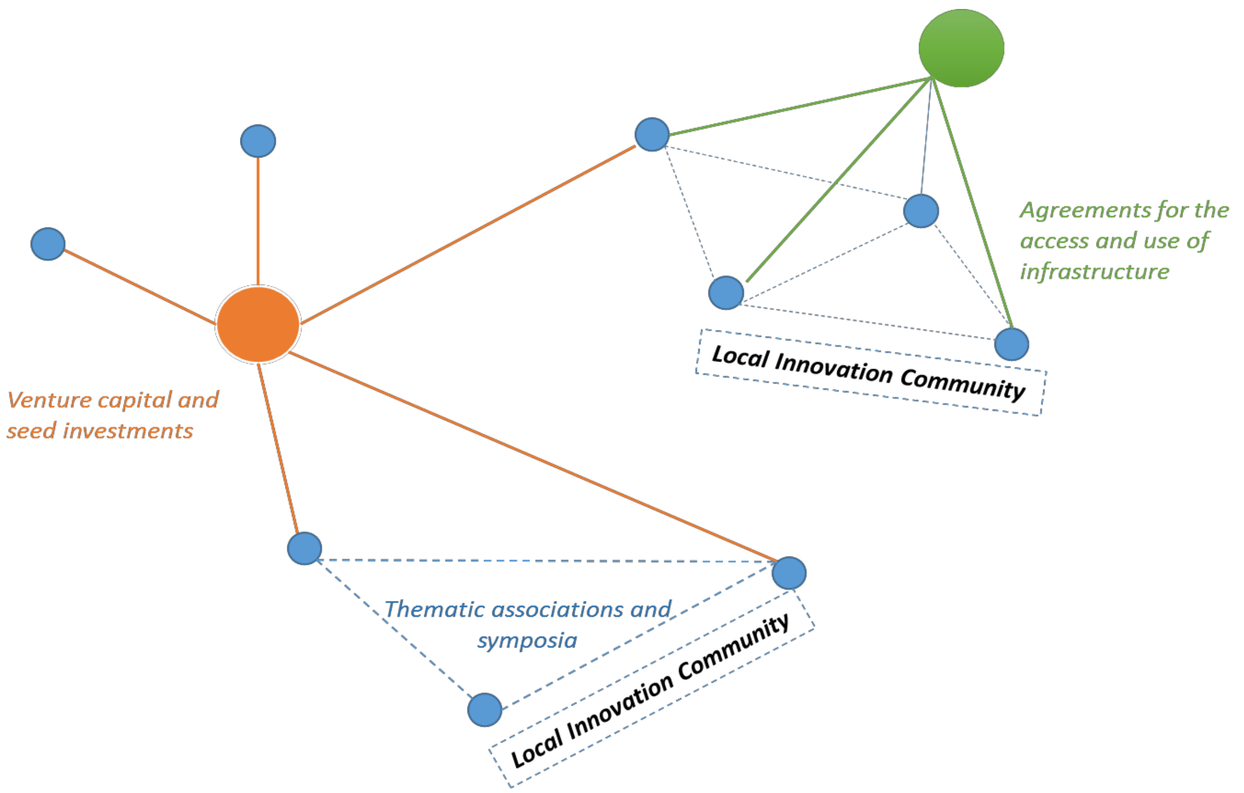
4.3 Discussion

From the results of the analyses reported in section 4.1 and 4.2, it emerges that the GBA Biopharma LIS is an open network with structural holes where bridging functions are mostly undertaken by large venture capital firms and pharmaceutical companies with a venture arm, and in which vertices tend to form small groups where interactions are more frequent. Also, the network portfolio of relationships that enhance knowledge transfer and for which spatial proximity is more important are traceable to those that foster cross-disciplinary interaction and match complementary resources (financial and technical) and skills (business support and scientific capabilities), i.e. *Co-participation in thematic associations and symposia*; *Agreements for The Access and Use of Infrastructure* and *Venture Capital and Seed investments* (Figure 4.4). It is worth mentioning how the closed network structure was appointed by Saxenian (1996) as one of the determining causes of the decline of the

Boston innovation system on semiconductor industry - known as Route 128 – in favor of the more open and horizontal network of Silicon Valley. Results from social network analysis 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, the *co-participation in thematic associations and symposia* contributes to the level of efficiency of the innovation system as a whole, as it improves information exchange between actors in the same field with implications in terms of avoiding the replication of failures in the pre-commercial phase, of aligning the vision and missions, thus leading to a collective resolution of R&D problems, as well as cutting the costs and times of partnership seeking and identifying the gaps in research areas. The *agreements for the access and use of infrastructure*, which are reflected in the proliferation of innovation centers in the area (co-working spaces, accelerators and incubators) positively affect the innovation system performance by exerting a knowledge spillover effect deriving by the environment they provide for their residents; by enhancing those *casual encounters* and visibility with target-oriented partners and providing resources in terms of both business support and facilities. As a consequence, the initial costs for developing an innovation are reduced and the market barriers for start-ups with a limited experience in business know-how can be smoothened by those benefits deriving from the knowledge production output for the whole system. Similarly, *Venture Capital and Seed investments* represent an important vehicle for the transfer of complementary assets and represent a key player for the development of innovative products along the whole innovation process. In general terms, it is possible to argue that the innovation system performance is enhanced by those types of partnerships that promote connectivity among different disciplines and sectors as these contribute to smooth *knowledge disabilities* and the *know-how trading.* 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 LIS. These *local innovation communities* are therefore characterized by a high intensity knowledge transfer through organizations of different nature and a high frequency of interactions, yet with a low degree of formalization, co-localized in the same geographical area (Figure 4.5)

Figure 4.5. Local Innovation Communities and their role in open networks



Source: author's own elaboration

4.4 Conclusions

The goal of this work is to explore the relational dimension of LIS by deriving evidence from the study of a successful case and derive propositions to be tested in future studies. More specifically, two research questions have been formulated for this purpose: (RQ1) Which is the configuration of the network structure in a successful Local Innovation System? And secondly, (RQ2) Which portfolio of relationships is implemented in a successful Local Innovation System? These research questions have been formulated in order to capture both aspects of LIS's relational dimension (Network structure and Network Portfolio composition). From the results of the study conducted on the GBA Biopharma LIS it is possible to derive a set of propositions, which are intended to be tested in future studies and to develop practical implications for those regions whose innovation system is at its early stage of development. More specifically, with regards to the network structure, it emerged that:

P1. *LIS performance is impacted by its network structure*

Indeed, the positional and structural indicators computed through the social network analysis suggest that the performance of LIS is positively impacted by a sparse network where bridging roles are mostly undertaken by venture firms or large biopharmaceutical companies with a venture arm. Therefore, a sub-proposition may be derived:

P1.1 *A highly performant LIS is characterized by an open network structure with structural holes*

Also, indicators at the meso-structural level suggest that the performance of LIS is positively impacted by the level of network's division 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. Therefore,

P1.2 *A highly performant LIS is characterized by a high level of division of a network into modules*

As a second step, network portfolio composition has been analyzed according two dimensions, namely the impact for knowledge transfer, considered as a precondition of innovation creation and secondly, the importance of spatial proximity which, in turn, is a precondition for the frequency of the interactions and for the emergence of trust mechanisms (Granovetter, 1984). Weak ties result from the embeddedness of actors within a certain spatial configuration. Figure 4.4 shows the relationships with high scores for both dimensions, i.e. *venture capital and seed investments, co-*

participation in thematic associations and symposia and *agreements for the access and use of infrastructure*. With reference to *VC and seed investment*, despite the formalization that characterize this form of tie, 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, that play a major role. The relationships that are established between VC and start-ups allow the latter to access to VC's network with large pharmaceutical companies and give them credibility and talent validation for further partnerships and future growth. The way through which these relationships emerge and grow is considered to be highly enhanced by the spatial proximity that multiply the chances of casual encounters and visibility for those start-ups willing to receive funds. Additionally, the spatial propinquity allows VC to achieve a more effective monitoring and continuous support to their start-up partners. With regards to *co-participation in thematic associations and symposia*, spatial proximity of the partners ensures the frequency of the interaction between members, who can establish relationships outside the periodical meetings and form further partnerships based on trust mechanisms resulting from the common affiliation and mission toward specific target research areas. Also, these relationships promote the convening of actors of different nature and disciplines, which ensures the non-redundancy of the exchanged information and the transfer of different (and complementary) practices to tackle with specific research challenges. Finally, the agreements for the access and use of infrastructure are deemed to provide knowledge spillovers for the actors who physically locate in innovation centers and foster an environment of informal cooperation deriving from their daily interaction, which contribute to the emergence of mechanisms of trust that are key for potential cooperation in specific target areas on the basis of weak ties.

Therefore, from what observed it is possible to suggest that:

P2. *LIS performance is impacted by its network portfolio composition*

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 and reputation effects without the necessity of contractual bounds (informal ties) whose existence is stimulated by spatial proximity. This, in turn, suggests that the composition of a network portfolio is predominated by the presence of weak ties. Therefore:

P2.1 *A highly performant LIS is characterized by a network portfolio dominated by weak ties*

Additionally, the content of the observed types of relationships, with specific reference to the diversity of the nature of engaged partners and the complementarity of the resource exchanged, suggests that:

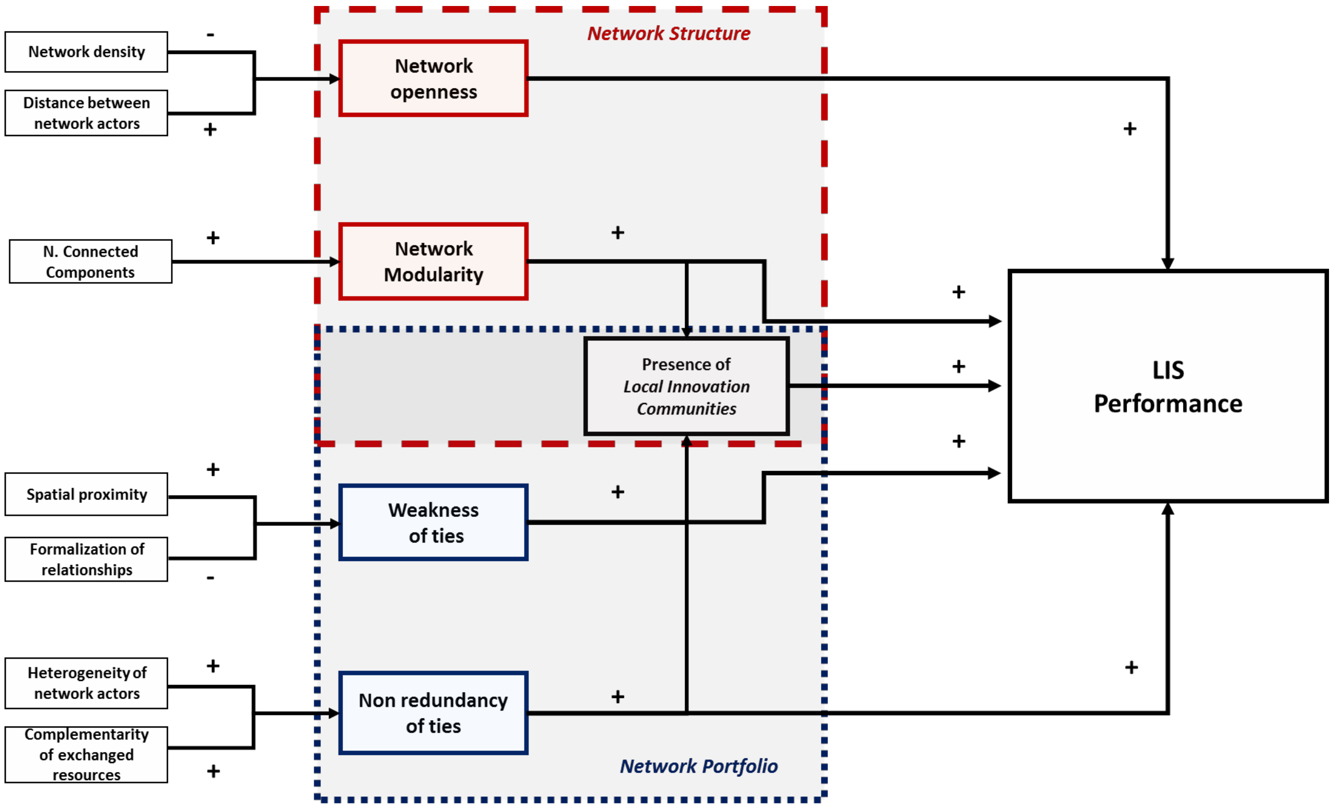
P2.2 *A highly performant LIS is characterized by a network portfolio dominated by non-redundant ties*

Finally, by combining the results deriving from both the analysis of the structure and the portfolio of the network, it is possible to observe 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, that are able to span the structural holes typical of the open structure of the network, i.e. *local innovation communities*. Therefore,

P3. *A highly performant LIS is characterized by the presence of local innovation communities*

Conclusively, this work suggests that the performance of a Local Innovation System is positively affected by the openness of its network structure, the weakness of the relationships between its actors and the tendency of the actors to form local innovation communities (Figure 4.6).

Figure 4.6. Analytical framework for the study of LIS performance from a relational perspective



Source: author's own elaboration

4.4.1 Main contribution and limitations of the study

This study contributes to the debate about the optimal configuration of network structure (e.g. Closure network vs. Structural Holes) suggesting that an open structure is preferable for determining the successful performance of a LIS. Additionally, from a methodological perspective it contributes to meet the challenges related to the adoption of a holistic approach, by capturing the heterogeneous nature of LIS 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 LIS literature, allowing for the identification of those relationships considered more fruitful for fostering the innovation processes from a local perspective.

In particular, this last aspect of the study's contribution has practical implications for policy makers and those actors willing to undertake an active role in the development of a LIS in their own regions. However, this study is not free from limitations. As a start, the sample could be expanded to include a greater number of organizations in the expert interviews. Also, new databases could be included in the social network analysis for extending the analysis on a greater number of typologies of partnerships and in order to achieve less biased results regarding the nature of bridging actors deriving from their centrality score. Finally, a comparative study with other LIS in different stages of development would contribute to a greater extent of validation of the propositions. Therefore, future scholars are invited to fill these limitations and test the propositions in different geographical and industrial contexts and to operationalize the dimensions along with measuring the LIS performance from a relational perspective.

References

Abramovsky, L., & Simpson, H. (2011). Geographic proximity and firm–university innovation linkages: evidence from Great Britain. Journal of economic geography, 11(6), 949-977.

Acs, Z. J., Anselin, L., & Varga, A. (2002). Patents and innovation counts as measures of regional production of new knowledge. Research policy, 31(7), 1069-1085.

Agrawal, A., Cockburn, I., & McHale, J. (2006). Gone but not forgotten: knowledge flows, labor mobility, and enduring social relationships. Journal of Economic Geography, 6(5), 571-591.

Ahuja, G. (2000). Collaboration networks, structural holes, and innovation: A longitudinal study. Administrative science quarterly, 45(3), 425-455.

Aldrich, H., Zimmer, C., & Jones, T. (1986). Small business still speaks with the same voice: a replication of 'the voice of small business and the politics of survival'. The Sociological Review, 34(2), 335-356.

Allen, T. J. (1977). Managing the flow of technology: technology transfer and the dissemination of technological information within the R and D organization.

Archibugi, D., & Coco, A. (2004). A new indicator of technological capabilities for developed and developing countries (ArCo). World development, 32(4), 629-654.

Archibugi, D., & Coco, A. (2005). Measuring technological capabilities at the country level: A survey and a menu for choice. Research policy, 34(2), 175-194.

Arenius, P., & De Clercq, D. (2005). A network-based approach on opportunity recognition. Small business economics, 24(3), 249-265.

Arora, R. (2002). Implementing KM–a balanced score card approach. Journal of knowledge management, 6(3), 240-249.

Asheim, B. R. T. (1996). Industrial districts as 'learning regions': a condition for prosperity. European planning studies, 4(4), 379-400.

Asheim, B. T., & Coenen, L. (2005). Knowledge bases and regional innovation systems: Comparing Nordic clusters. Research policy, 34(8), 1173-1190.

Asheim, B. T., & Gertler, M. S. (2005). The geography of innovation: regional innovation systems. In The Oxford handbook of innovation.

Asheim, B. T., & Gertler, M. S. (2005). The geography of innovation: regional innovation systems. In The Oxford handbook of innovation.

Asheim, B. T., & Isaksen, A. (1997). Location, agglomeration and innovation: towards regional innovation systems in Norway?. European planning studies, 5(3), 299-330.

Asheim, B. T., Isaksen, A., Nauwelaers, C., & Tödtling, F. (Eds.). (2003). Regional Innovation Policy for Small+ Medium Enterprises. Edward Elgar Publishing.

Audretsch, D. B. (2004). Sustaining innovation and growth: Public policy support for entrepreneurship. Industry and innovation, 11(3), 167-191.

Audretsch, D. B., & Feldman, M. P. (1996). R&D spillovers and the geography of innovation and production. The American economic review, 86(3), 630-640.

Bajmócy, Z. (2013). Constructing a Local Innovation Index: Methodological Challenges Versus Statistical Data Availability. Applied Spatial Analysis and Policy, 6(1), 69-84.

Balland, P. A., De Vaan, M., & Boschma, R. (2012). The dynamics of interfirm networks along the industry life cycle: The case of the global video game industry, 1987–2007. Journal of Economic Geography, 13(5), 741-765.

Balland, P. A., Suire, R., & Vicente, J. (2013). Structural and geographical patterns of knowledge networks in emerging technological standards: evidence from the European GNSS industry. Economics of Innovation and New Technology, 22(1), 47-72.

Barabási, A. L., & Albert, R. (1999). Emergence of scaling in random networks. science, 286(5439), 509-512.

Basole, R. C., & Rouse, W. B. (2008). Complexity of service value networks: Conceptualization and empirical investigation. IBM systems journal, 47(1), 53-70.

Basole, R. C., Clear, T., Hu, M., Mehrotra, H., & Stasko, J. (2013). Understanding interfirm relationships in business ecosystems with interactive visualization. IEEE Transactions on visualization and computer graphics, 19(12), 2526-2535.

Basole, R. C., Park, H., & Barnett, B. C. (2015). Coopetition and convergence in the ICT ecosystem. Telecommunications Policy, 39(7), 537-552.

Bathelt, H., & Glückler, J. (2003). Toward a relational economic geography. Journal of economic geography, 3(2), 117-144.

Bathelt, H., Malmberg, A., & Maskell, P. (2004). Clusters and knowledge: local buzz, global pipelines and the process of knowledge creation. Progress in human geography, 28(1), 31-56.

Baum, J. A., Calabrese, T., & Silverman, B. S. (2000). Don't go it alone: Alliance network composition and startups' performance in Canadian biotechnology. Strategic management journal, 267-294.

Baxter, P., & Jack, S. (2008). Qualitative case study methodology: Study design and implementation for novice researchers. The qualitative report, 13(4), 544-559.

Becattini, G., Bellandi, M., & De Propris, L. (Eds.). (2014). *A handbook of industrial districts*. Edward Elgar Publishing.

Becheikh, N., Landry, R., & Amara, N. (2006). Lessons from innovation empirical studies in the manufacturing sector: A systematic review of the literature from 1993–2003. Technovation, 26(5), 644-664.

Beckman, C. M., Haunschild, P. R., & Phillips, D. J. (2004). Friends or strangers? Firm-specific uncertainty, market uncertainty, and network partner selection. Organization science, 15(3), 259-275.

Bell, G. G. (2005). Clusters, networks, and firm innovativeness. Strategic management journal, 26(3), 287-295.

Bell, G. G., & Zaheer, A. (2007). Geography, networks, and knowledge flow Organization Science, 18(6), 955-972.

Ben Lataifa, S., & Rabeau, Y. (2013). Too close too collaborate? How geographical proximity could impede entrepreneurship and innovation. Journal of Business Research, http://dx. doi. org/10.1016/j. jburses, 33.

Bergek, A., Jacobsson, S., Carlsson, B., Lindmark, S., & Rickne, A. (2008). Analyzing the functional dynamics of technological innovation systems: A scheme of analysis. Research policy, 37(3), 407-429.

Bergman, E. M. (2009). Embedding network analysis in spatial studies of innovation. The Annals of Regional Science, 43(3), 559-565.

Bianchi, M., Cavaliere, A., Chiaroni, D., Frattini, F., & Chiesa, V. (2011). Organisational modes for Open Innovation in the bio-pharmaceutical industry: An exploratory analysis. Technovation, 31(1), 22-33.

Bogner, A., & Menz, W. (2002). Das theoriegenerierende Experteninterview. In Das Experteninterview (pp. 33-70). VS Verlag für Sozialwissenschaften.

Boschma, R. (2005). Proximity and innovation: a critical assessment. Regional studies, 39(1), 61-74.

Boschma, R. A., Lambooy, J. G., & Schutjens, V. A. J. M. (2002). Embeddedness and innovation.

Breschi, S., & Catalini, C. (2010). Tracing the links between science and technology: An exploratory analysis of scientists' and inventors' networks. Research Policy, 39(1), 14-26.

Breschi, S., Lenzi, C., Lissoni, F., & Vezzulli, A. (2010). The geography of knowledge spillovers: the role of inventors' mobility across firms and in space. The Handbook of Evolutionary Economic Geography, Cheltenham: Edward Elgar, 353-369.

Breznitz, S. M. (2015). Invention & Reinvention: The Evolution of San Diego's Innovation Economy By Mary Lindenstein Walshok and Abraham J. Shragge Stanford, CA: Stanford University Press, 2014. Economic Geography, 91(1), 117-118.

Broekel, T., & Boschma, R. (2011). Knowledge networks in the Dutch aviation industry: the proximity paradox. Journal of Economic Geography, 12(2), 409-433.

Broekel, T., & Mueller, W. (2017). Critical links in knowledge networks–What about proximities and gatekeeper organizations?.

Budden, P. & Murray, F. (2015). Case study. Kendall Square & MIT: Innovation Ecosystems and the University. MIT Lab for Innovation Science and Policy.

Bunnell, T. G., & Coe, N. M. (2001). Spaces and scales of innovation. Progress in Human geography, 25(4), 569-589.

Burt, R. S. (1992). Structural holes: the structure of social capital competition. MA: Harvard University Press, Cambridge.

Burt, R. S. (2000). The network structure of social capital. Research in organizational behavior, 22, 345-423.

Burt, R. S. (2002). Bridge decay. Social networks, 24(4), 333-363.

Buskens, V. (2002). Social networks and trust (Vol. 30). Springer Science & Business Media.

Cainelli, G., Mancinelli, S., & Mazzanti, M. (2007). Social capital and innovation dynamics in district-based local systems. The Journal of Socio-Economics, 36(6), 932-948.

Campanella, F., Rosaria Della Peruta, M., & Del Giudice, M. (2014). Creating conditions for innovative performance of science parks in Europe. How manage the intellectual capital for converting knowledge into organizational action. Journal of Intellectual Capital, 15(4), 576-596.

Cantner, U., & Graf, H. (2006). The network of innovators in Jena: An application of social network analysis. Research Policy, 35(4), 463-480.

Cantner, U., Meder, A., & Ter Wal, A. L. (2010). Innovator networks and regional knowledge base. Technovation, 30(9), 496-507.

Canzanelli, G., & Loffredo, L. (2008). Territorial systems for innovation. Evolution, 1,1.

Capaldo, A. (2004). Strategia, reti di imprese e capacità relazionali. Cedam.

Capaldo, A. (2007). Network structure and innovation: The leveraging of a dual network as a distinctive relational capability. Strategic management journal, 28(6), 585-608.

Capellari, S., Chies, L., De Stefano, D., & Puggioni, A. (2016). L'analisi di rete per capire il mercato del lavoro. I flussi di assunzione di laureati e dottori di ricerca nel Friuli Venezia Giulia nel periodo 2005-2014.

Capello, R., & Faggian, A. (2005). Collective learning and relational capital in local innovation processes. Regional studies, 39(1), 75-87.

Carayannis, E. G., & Campbell, D. F. (2009). 'Mode 3'and'Quadruple Helix': toward a 21st century fractal innovation ecosystem. International journal of technology management, 46(3-4), 201-234.

Carayannis, E. G., & Campbell, D. F. (2012). Mode 3 knowledge production in quadruple helix innovation systems. In Mode 3 Knowledge Production in Quadruple Helix Innovation Systems (pp. 1-63). Springer New York.

Carayannis, E. G., & Turner, E. (2006). Innovation diffusion and technology acceptance: The case of PKI technology. Technovation, 26(7), 847-855.

Carayannis, E. G., Grigoroudis, E., & Goletsis, Y. (2016). A multilevel and multistage efficiency evaluation of innovation systems: A multiobjective DEA approach. Expert Systems with Applications, 62, 63-80.

Carlsson, B., & Stankiewicz, R. (1991). On the nature, function and composition of technological systems. Journal of evolutionary economics, 1(2), 93-118.

Carlsson, B., Jacobsson, S., Holmén, M., & Rickne, A. (2002). Innovation systems: analytical and methodological issues. Research policy, 31(2), 233-245.

Carrincazeaux, C., Grossetti, M., & Talbot, D. (2008). Clusters, proximities and networks. European Planning Studies, 16(5), 613-616.

Casanueva, C., Castro, I., & Galán, J. L. (2013). Informational networks and innovation in mature industrial clusters. Journal of Business Research, 66(5), 603-613.

Cassi, L., & Plunket, A. (2014). Proximity, network formation and inventive performance: in search of the proximity paradox. The Annals of Regional Science, 53(2), 395-422.

Cassi, L., Morrison, A., & Ter Wal, A. L. (2012). The evolution of trade and scientific collaboration networks in the global wine sector: a longitudinal study using network analysis. Economic geography, 88(3), 311-334.

Castilla, E. J., Hwang, H., Granovetter, E., & Granovetter, M. (2000). Social networks in Silicon Valley. The Silicon Valley edge: A habitat for innovation and entrepreneurship, 218-247.

Chesbrough, H. (2003). Open innovation.

Chesbrough, H. W., & Appleyard, M. M. (2007). Open innovation and strategy. California management review, 50(1), 57-76.

Chesbrough, H., & Crowther, A. K. (2006). Beyond high tech: early adopters of open innovation in other industries. R&d Management, 36(3), 229-236.

Chiaroni, D., Chiesa, V., & Frattini, F. (2010). Unravelling the process from Closed to Open Innovation: evidence from mature, asset-intensive industries. R&d Management, 40(3), 222-245.

Chiu, Y. (2008). How network competence and network location influence innovation performance. *Journal of Business & Industrial Marketing*, *24*(1), 46-55.

Cloodt, M., Hagedoorn, J., & Roijakkers, N. (2010). Inter-firm R&D networks in the global software industry: An overview of major trends and patterns. Business History, 52(1), 120-149.

Cloodt, M., Hagedoorn, J., & Roijakkers, N. (2010). Inter-firm R&D networks in the global software industry: An overview of major trends and patterns. Business History, 52(1), 120-149.

Coenen, L., Moodysson, J., & Asheim, B. T. (2004). Nodes, networks and proximities: on the knowledge dynamics of the Medicon Valley biotech cluster. European Planning Studies, 12(7), 1003-1018.

Cohen, W. M., & Levinthal, D. A. (1990). Absorptive capacity: A new perspective on learning and innovation. Administrative science quarterly, 128-152.

Coleman, J. (1990). Foundations of Social Theory. Cambridge, Mass.: Belknap Press of Harvard University Press.

Coleman, J. S. (1988). Social capital in the creation of human capital. American journal of sociology, 94, S95-S120.

Cooke, P. (1992). Regional innovation systems: competitive regulation in the new Europe. Geoforum, 23(3), 365-382.

Cooke, P. (2001). Regional innovation systems, clusters, and the knowledge economy. Industrial and corporate change, 10(4), 945-974.

Cooke, P. (2004). Regional innovation systems: an evolutionary approach. Regional innovation systems: the role of governance in a globalized world, 1-20.

Cooke, P., Uranga, M. G., & Etxebarria, G. (1997). Regional innovation systems: Institutional and organisational dimensions. Research policy, 26(4-5), 475-491.

Corbin J, Morse JM. (2003), The unstructured interactive interview: Issues of reciprocity and risks when dealing with sensitive topics. Qual Inq. 9:335–54.

Corbin J, Strauss A. (2008) Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory.3rd ed. Thousand Oaks, California: Sage Publications;.

Cowan, R., & Jonard, N. (2004). Network structure and the diffusion of knowledge. Journal of economic Dynamics and Control, 28(8), 1557-1575.

D'Este, P., Iammarino, S., Savona, M., & von Tunzelmann, N. (2012). What hampers innovation? Revealed barriers versus deterring barriers. Research policy, 41(2), 482-488.

Dahl, M. S., & Pedersen, C. Ø. (2004). Knowledge flows through informal contacts in industrial clusters: myth or reality?. Research policy, 33(10), 1673-1686.

Davis, D., Davis, M. E., Jadad, A., Perrier, L., Rath, D., Ryan, D., ... & Zwarenstein, M. (2003). The case for knowledge translation: shortening the journey from evidence to effect. Bmj, 327(7405), 33-35. Davis, G. F., Yoo, M., & Baker, W. E. (2003). The small world of the American corporate elite, 1982-2001. *Strategic organization*, *1*(3), 301-326.

Davis, S. (1970). Building talented teams. Innovation, (15), 1-20.

de Andrade, 2013

De la Mothe, J., & Paquet, G. (1998). Local and regional systems of innovation as learning socio-economies. ECONOMICS OF SCIENCE TECHNOLOGY AND INNOVATION, 14, 1-18.

DeBresson, C., & Amesse, F. (1991). Networks of innovators: A review and introduction to the issue. Research policy, 20(5), 363-379.

Dicken, P., Kelly, P. F., Olds, K., & Wai-Chung Yeung, H. (2001). Chains and networks, territories and scales: towards a relational framework for analysing the global economy. Global networks, 1(2), 89-112.

Doloreux, D. (2002). What we should know about regional systems of innovation. Technology in society, 24(3), 243-263.

Doloreux, D., & Parto, S. (2005). Regional innovation systems: Current discourse and unresolved issues. Technology in society, 27(2), 133-153.

Durst, S., & Poutanen, P. (2013). Success factors of innovation ecosystems-Initial insights from a literature review. Pros. Co-Create.

Dyer, J. H., & Singh, H. (1998). The relational view: Cooperative strategy and sources of interorganizational competitive advantage. Academy of management review, 23(4), 660-679.

Edquist, C. (2011). Design of innovation policy through diagnostic analysis: identification of systemic problems (or failures). Industrial and Corporate Change, 20(6), 1725-1753.

Edquist, C. (Ed.). (1997). Systems of innovation: technologies, institutions, and organizations. Psychology Press.

Edquist, C., & Johnson, B. (1997). System of innovation: overview and basic concepts. Systems of innovation: technologies, institutions and organizations. Abigdon, OX: Routledge Press from http://books. google. com/books.

Edquist, C., & Zabala, J. M. (2009, October). Outputs of innovation systems:

accounting what comes out of the system. Georgia Institute of Technology.

Eggink, M. E. (2012). Innovation system performance: How to address the measurement of a system's performance. Journal of Innovation and Business Best Practices, 2012, 1.

Eisenhardt, K. M., & Schoonhoven, C. B. (1996). Resource-based view of strategic alliance formation: Strategic and social effects in entrepreneurial firms. organization Science, 7(2), 136-150.

Elfring, T., & Hulsink, W. (2003). Networks in entrepreneurship: The case of high-technology firms. Small business economics, 21(4), 409-422.

Emden, Z., Calantone, R. J., & Droge, C. (2006). Collaborating for new product development: selecting the partner with maximum potential to create value. Journal of product innovation management, 23(4), 330-341.

Ensing, E. (2017). Biopharma R&D Partnerships: From David & Goliath to Networked R&D. By Robert Thong, Phizz Rx Publishing: London, 2016, pp. 272. R&D Management, 47(2), 330-331.

Etzkowitz, H. (1993). Academic-industry relations: a new mode of production. In Workshop on academic-industry relations. Memoria. México. Enero.-Etzkowitz H y Webster A.(1991). Academy and industry relations. The second academia revolution.

Etzkowitz, H. (1996). From knowledge flows to the triple helix: the transformation of academic–industry relations in the USA. Industry and Higher education, 10(6), 337-342.

Etzkowitz, H., & Leydesdorff, L. A. (1995). Universities and the global knowledge economy: a triple helix of university-industry-government relations.

Fagerberg, J. (2005). Innovation and competitiveness. Georgia Institute of Technology.

Fagerberg, J., & Srholec, M. (2009). Innovation systems, technology and development: unpacking the relationships. Handbook of Innovation Systems and Developing Countries: Building Domestic Capabilities in a Global Setting, 83-115.

Fagerberg, J., Martin, B. R., & Andersen, E. S. (Eds.). (2013). Innovation studies: evolution and future challenges. OUP Oxford.

Ferretti, M., & Parmentola, A. (2015). Local Innovation Systems in Emerging Countries. In The Creation of Local Innovation Systems in Emerging Countries (pp. 7- 36). Springer International Publishing.

Fitjar, R. D., Huber, F., & Rodríguez-Pose, A. (2016). Not too close, not too far: testing the Goldilocks principle of 'optimal'distance in innovation networks. Industry and Innovation, 23(6), 465-487.

Fombrun, C. J. (1982). Strategies for network research in organizations. Academy of Management Review, 7(2), 280-291.

Fontes, M. (2005). Distant networking: The knowledge acquisition strategies of'out-cluster'biotechnology firms. European Planning Studies, 13(6), 899-920.

Freeman, C. (1989). Technology policy and economic performance (p. 34). Great Britain: Pinter Publishers.

Freeman, C. (2002). Continental, national and sub-national innovation systems—complementarity and economic growth. Research policy, 31(2), 191-211.

Fuller-Love, N. (2009). Formal and informal networks in small businesses in the media industry. International Entrepreneurship and Management Journal, 5(3), 271-284.

Gambardella A., L'impresa e la struttura di impresa, GIAPPICHELLI, Torino 1993

Gambardella, A. (1995). *Science and innovation: The US pharmaceutical industry during the 1980s*. Cambridge University Press.

Gargiulo, M., & Benassi, M. (2000). Trapped in your own net? Network cohesion, structural holes, and the adaptation of social capital. Organization science, 11(2), 183-196.

Gebauer, A., Nam, C. W., & Parsche, R. (2005). Regional technology policy and factors shaping local innovation networks in small German cities. *European Planning Studies*, *13*(5), 661-683.

Geenhuizen, M. V. (2008). Knowledge networks of young innovators in the urban economy: biotechnology as a case study. Entrepreneurship and Regional Development, 20(2), 161-183.

Geldes, C., Felzensztein, C., Turkina, E., & Durand, A. (2015). How does proximity affect interfirm marketing cooperation? A study of an agribusiness cluster. Journal of Business Research, 68(2), 263-272.

Gertler, M. (1997). The invention of regional culture. Geographies of economies, 47-58.

Gilly, J. P., & Torre, A. (2000). Proximity relations. Elements for an analytical framework. Industrial networks and proximity, 1-16.

Gilsing, V. A., & Duysters, G. M. (2008). Understanding novelty creation in exploration networks—structural and relational embeddedness jointly considered. Technovation, 28(10), 693-708.

Giuliani, E. (2013). Network dynamics in regional clusters: Evidence from Chile. *Research Policy*, *42*(8), 1406-1419.

Giuliani, E., & Bell, M. (2005). The micro-determinants of meso-level learning and innovation: evidence from a Chilean wine cluster. Research policy, 34(1), 47-68.

Glückler, J. (2007). Economic geography and the evolution of networks. Journal of Economic Geography, 7(5), 619-634.

Gould, R. V., & Fernandez, R. M. (1989). Structures of mediation: A formal approach to brokerage in transaction networks. Sociological methodology, 89-126.

Grabher, G. (2006). Trading routes, bypasses, and risky intersections: mapping the travels ofnetworks' between economic sociology and economic geography. Progress in human geography, 30(2), 163-189.

Grabher, G., & Ibert, O. (2006). 2006: Bad company? The ambiguity of personal knowledge networks, Journal of Economic Geography 6, 251-71.

Graf, H., & Krüger, J. J. (2011). The performance of gatekeepers in innovator networks. Industry and Innovation, 18(1), 69-88.

Granovetter, M. (1985). Economic action and social structure: The problem of embeddedness. American journal of sociology, 91(3), 481-510.

Granovetter, M. S. (1973). The strength of weak ties. American journal of sociology, 78(6), 1360-1380.

Greenhalgh, C., & Rogers, M. (2010). Innovation, intellectual property, and economic growth. Princeton University Press.

Gray DE. (2009). Doing Research in the Real World. 2nd ed. Thousand Oaks, California: Sage Publications;

Guan, J., & Chen, K. (2010). Measuring the innovation production process: A cross-region empirical study of China’s high-tech innovations. Technovation, 30(5), 348-358.

Gulati, R. (1995). Social structure and alliance formation patterns: A longitudinal analysis. Administrative science quarterly, 619-652.

Gulati, R. (1999). Network location and learning: The influence of network resources and firm capabilities on alliance formation. Strategic management journal, 20(5), 397-

420.

Gulati, R., & Gargiulo, M. (1999). Where do interorganizational networks come from?. American journal of sociology, 104(5), 1439-1493.

Hagedoorn, J. (1993). Understanding the rationale of strategic technology partnering: Nterorganizational modes of cooperation and sectoral differences. Strategic management journal, 14(5), 371-385.

Halinen, A. (2012). Relationship marketing in professional services: a study of agency-client dynamics in the advertising sector. Routledge.

Hamaguchi (2008). High-tech Brazil: Challenge of Local Innovation Systems.

Hanaki, N., Nakajima, R., & Ogura, Y. (2010). The dynamics of R&D network in the IT industry. Research policy, 39(3), 386-399.

Hargadon, A. B. (1998). Firms as knowledge brokers: Lessons in pursuing continuous innovation. California management review, 40(3), 209-227.

Hargadon, A., & Sutton, R. I. (1997). Technology brokering and innovation in a product development firm. Administrative science quarterly, 716-749.

Hartley, R. F. (1994). Management mistakes & successes. John Wiley & Sons.

Hekkert, M. P., Suurs, R. A., Negro, S. O., Kuhlmann, S., & Smits, R. E. (2007). Functions of innovation systems: A new approach for analysing technological change. Technological forecasting and social change, 74(4), 413-432.

Hoang, H., & Rothaermel, F. T. (2005). The effect of general and partner-specific alliance experience on joint R&D project performance. Academy of Management Journal, 48(2), 332-345.

Holland, P. W., & Leinhardt, S. (1971). Transitivity in structural models of small groups. Comparative Group Studies, 2(2), 107-124.

Howells, J. R. (2002). Tacit knowledge, innovation and economic geography. Urban studies, 39(5-6), 871-884.

Huang, H. C., Lai, M. C., & Lo, K. W. (2012). Do founders' own resources matter? The influence of business networks on start-up innovation and performance. Technovation, 32(5), 316-327.

Huber, F. (2012). On the role and interrelationship of spatial, social and cognitive proximity: personal knowledge relationships of R&D workers in the Cambridge information technology cluster. Regional Studies, 46(9), 1169-1182.

Huston, L., & Sakkab, N. (2006). Connect and develop. Harvard business review, 84(3), 58-66.

Hwang, V. W., & Horowitt, G. (2012). The rainforest: The secret to building the next Silicon Valley (p. 304). Los Altos Hills, CA: Regenwald.

Iansiti, M., & Levien, R. (2004). The keystone advantage: what the new dynamics of business ecosystems mean for strategy, innovation, and sustainability. Harvard Business Press.

Isaksen, A., & Nilsson, M. (2011). Linking scientific and practical knowledge in innovation systems. Papers in Innovation Studies 2011, 12.

Jensen, M. B., Johnson, B., Lorenz, E., & Lundvall, B. Å. (2007). Forms of knowledge and modes of innovation. The Learning Economy and the Economics of Hope, 155.

JJL U.S. Life Science 2016

Johannisson, B., & Ramirez-Pasillas, M. (2001). Networking for entrepreneurship: building a topography model of human, social and cultural capital. Frontiers of Entrepreneurship Research.

Johansson, 2005

Johansson, P. (2003, September). Madfilm-a multimodal approach to handle search and organization in a movie recommendation system. In Proceedings of the 1st Nordic Symposium on Multimodal Communication (pp. 53-65).

Johnson (1992) introduced the notion of *learning – by – interacting*

Johnson, B., & Andersen, A. D. (2012). *Learning, Innovation and Inclusive Development: New perspectives on economic development strategy and development aid*. Aalborg Universitetsforlag.

Kajikawa, Y., Takeda, Y., Sakata, I., & Matsushima, K. (2010). Multiscale analysis of interfirm networks in regional clusters. Technovation, 30(3), 168-180.

Kirat, T., & Lung, Y. (1999). Innovation and proximity: territories as loci of collective learning processes. European urban and regional studies, 6(1), 27-38.

Kirschbaum, R. (2005). Open innovation in practice. Research-Technology Management, 48(4), 24-28.

Knoben, J., & Oerlemans, L. A. (2006). Proximity and inter-organizational collaboration: A literature review. International Journal of Management Reviews, 8(2), 71-89.

Kogut, B. (1989). The stability of joint ventures: Reciprocity and competitive rivalry. The Journal of Industrial Economics, 183-198.;

Kohlbacher, F. (2006, January). The use of qualitative content analysis in case study research. In Forum Qualitative

Kohn, A. (1997). How not to teach values: A critical look at character education. Phi Delta Kappan, 78(6), 429-439.

Kreiner, K., & Schultz, M. (1993). Informal collaboration in R & D. The formation of networks across organizations. Organization studies, 14(2), 189-209.

Laursen, K., & Salter, A. (2006). Open for innovation: the role of openness in explaining innovation performance among UK manufacturing firms. Strategic management journal, 27(2), 131-150.

Lawson, C., & Lorenz, E. (1999). Collective learning, tacit knowledge and regional innovative capacity. Regional studies, 33(4), 305-317.

LeBel, P. (2008). The role of creative innovation in economic growth: Some international comparisons. Journal of Asian Economics, 19(4), 334-347.

Lerro, A., & Schiuma, G. (2015). Assessing performance and impact of the Technological Districts (TDs): general modelling and measurement system. Measuring Business Excellence, 19(3), 58-75.

Lundvall, B. Å. (1985). Product innovation and user-producer interaction. The Learning Economy and the Economics of Hope, 19.

Lundvall, B. A. (1992). National systems of innovation: An analytical framework. London: Pinter.

Lundvall, B. Å. (Ed.). (2010). National systems of innovation: Toward a theory of innovation and interactive learning (Vol. 2). Anthem Press.
Lundvall, B. A., & Johnson, B. (1994). The learning economy. The Learning Economy and the Economics of Hope, 107.

Lundvall, B. A., & Johnson, B. (1994). The learning economy. The Learning Economy and the Economics of Hope, 107.

Lundvall, B. A., Dosi, G., & Freeman, C. (1988). Innovation as an interactive process: from user-producer interaction to the national system of innovation. 1988, 349-369.

Lyon, F. (2000). Trust, networks and norms: the creation of social capital in agricultural economies in Ghana. World Development, 28(4), 663-681.

Maggioni, M. A., Nosvelli, M., & Uberti, T. E. (2007). Space versus networks in the geography of innovation: A European analysis. Papers in Regional Science, 86(3), 471-493.

Malerba, F. (2002). Sectoral systems of innovation and production. Research policy, 31(2), 247-264.

Mars, R. B., Neubert, F. X., Noonan, M. P., Sallet, J., Toni, I., & Rushworth, M. F. (2012). On the relationship between the “default mode network” and the “social brain”. Frontiers in human neuroscience, 6.

Marshak, R. J. (1993). Lewin meets Confucius: a review of the OD model of change. The Journal of applied behavioral science, 29(4), 393-415.

Martin, R., & Simmie, J. (2008). Path dependence and local innovation systems in city-regions. Innovation, 10(2-3), 183-196.

McEvily, B., & Zaheer, A. (1999). Bridging ties: A source of firm heterogeneity in competitive capabilities. Strategic management journal, 1133-1156.

McEvily, B., Perrone, V., & Zaheer, A. (2003). Trust as an organizing principle. Organization science, 14(1), 91-103.

McPherson, M., Smith-Lovin, L., & Cook, J. M. (2001). Birds of a feather: Homophily in social networks. Annual review of sociology, 27(1), 415-444.

Meuser, M., & Nagel, U. (1991). Expertlnneninterviews—vielfach erprobt, wenig bedacht. In Qualitativ-empirische sozialforschung (pp. 441-471). VS Verlag für Sozialwissenschaften. Sozialforschung/Forum: Qualitative Social Research (Vol. 7, No. 1).
Milne, C. P., & Malins, A. (2012). Academic-industry partnerships for biopharmaceutical research & development: Advancing medical science in the US. *Tuft Center for the Study of Drug Development*.

U.S. Census Bureau, 2015

MIT Regional Entrepreneurship Acceleration Program, 2015. http://reap.mit.edu/.

Mizruchi, M. S. (1992). The structure of corporate political action: Interfirm relations and their consequences. Harvard University Press.

Moensted, M. (2007). Strategic networking in small high tech firms. International Entrepreneurship and Management Journal, 3(1), 15-27.

Molina-Morales, F. X., Belso-Martínez, J. A., Más-Verdú, F., & Martínez-Cháfer, L. (2015). Formation and dissolution of inter-firm linkages in lengthy and stable networks in clusters. Journal of Business Research, 68(7), 1557-1562.

Molina-Morales, F. X., García-Villaverde, P. M., & Parra-Requena, G. (2014). Geographical and cognitive proximity effects on innovation performance in SMEs: a way through knowledge acquisition. International Entrepreneurship and Management Journal, 10(2), 231-251.

Moody, J., & White, D. R. (2003). Structural cohesion and embeddedness: A hierarchical concept of social groups. American Sociological Review, 103-127.

Moore, B. (1996). Sources of innovation, technology transfer and diffusion. The changing state of British enterprise, ESRC Centre for Business Research, Cambridge.

Morgan, K. (2004). The exaggerated death of geography: learning, proximity and territorial innovation systems. Journal of economic geography, 4(1), 3-21.

Morrison, A. (2003). Local Systems of Innovation in Developing Countries: Evidence from a Brazilian Furniture Cluster. Università del Piemonte Orientale, Novara.

Morrison, A. (2008). Gatekeepers of knowledge within industrial districts: who they are, how they interact. Regional Studies, 42(6), 817-835.

Moulaert, F., & Sekia, F. (2003). Territorial innovation models: a critical survey. Regional studies, 37(3), 289-302.

Mowery, D. C., & Teece, D. J. (1993). Japan's growing capabilities in industrial technology: Implications for US managers and policymakers. California Management Review, 35(2), 9-34.

Murdoch, J. (2000). Networks—a new paradigm of rural development?. Journal of rural studies, 16(4), 407-419.

Muscio, A. (2006). Patterns of innovation in industrial districts: an empirical analysis. Industry and Innovation, 13(3), 291-312.

Mustilli, M., Campanella, F., & Sorrentino, F. (2012). La valutazione delle performance innovative dei sistemi locali di innovazione: il caso dell'aerospazio e dei nuovi materiali in Campania. Sinergie rivista di studi e ricerche, (84).

Nonaka, L., Takeuchi, H., & Umemoto, K. (1996). A theory of organizational knowledge creation. International Journal of Technology Management, 11(7-8), 833-845.

Nooteboom, B. (1999). Innovation and inter-firm linkages: new implications for policy. Research policy, 28(8), 793-805.

Nooteboom, B. (2000). Learning by interaction: absorptive capacity, cognitive distance and governance. Journal of management and governance, 4(1-2), 69-92.

Norton, M. G. (2007, July). Japan's Eco-towns-Industrial clusters or Local Innovation Systems?. In *Proceedings of the 51st Annual Meeting of the ISSS-2007, Tokyo, Japan* (Vol. 51, No. 2).

OECD. (1997). National Accounts, 1983–1995, OECD.

Oerlemans, L., & Meeus, M. (2005). Do organizational and spatial proximity impact on firm performance? Regional studies, 39(1), 89-104.

Osborn, R. N., & Hagedoorn, J. (1997). The institutionalization and evolutionary dynamics of interorganizational alliances and networks. Academy of Management Journal, 40(2), 261-278.

Østergaard, C. R. (2009). Knowledge flows through social networks in a cluster: Comparing university and industry links. Structural Change and Economic Dynamics, 20(3), 196-210.

Owen-Smith, J., & Powell, W. W. (2004). Knowledge networks as channels and conduits: The effects of spillovers in the Boston biotechnology community. Organization science, 15(1), 5-21.

Ozman, M. (2009). Inter-firm networks and innovation: a survey of literature. Economic of Innovation and New Technology, 18(1), 39-67. Perkmann, M., & Walsh, K. (2007). University–industry relationships and open innovation: Towards a research agenda. International Journal of Management Reviews, 9(4), 259-280.

Piller, F. T., & Walcher, D. (2006). Toolkits for idea competitions: a novel method to integrate users in new product development. R&d Management, 36(3), 307-318.

Polanyi, K. (1944). The great transformation: Economic and political origins of our time. Rinehart, New York.

Ponds, R., Van Oort, F., & Frenken, K. (2007). The geographical and institutional proximity of research collaboration. Papers in regional science, 86(3), 423-443.

Porter, M. E. (1998). Clusters and the new economics of competition (Vol. 76, No. 6, pp. 77-90). Boston: Harvard Business Review.

Powell, W. Koput, & Owen-Smith (2005) Powell, WW, White, DR, Koput, KW, & Owen-Smith, J.(2005). Network dynamics and field evolution: The growth of interorganizational collaboration in the life sciences. American Journal of Sociology, 110(4), 1132-1205.

Powell, W. W., Koput, K. W., & Smith-Doerr, L. (1996). Interorganizational collaboration and the locus of innovation: Networks of learning in biotechnology. Administrative science quarterly, 116-145.

Powell, W. W., Koput, K. W., Smith-Doerr, L., & Owen-Smith, J. (1999). Network position and firm performance: Organizational returns to collaboration in the biotechnology industry. Research in the Sociology of Organizations, 16(1), 129-159.

Presutti, M., Boari, C., & Majocchi, A. (2013). Inter-organizational geographical proximity and local start-ups' knowledge acquisition: a contingency approach. Entrepreneurship & Regional Development, 25(5-6), 446-467.

Rahayu, S., & Zulhamdani, M. (2014). Understanding Local Innovation System as an Intelligent Organism Using the Viable System Model Case Study of Palm Oil Industry in North Sumatra Province. Procedia-Social and Behavioral Sciences, 115, 68-78.

Rantisi, N. M. (2002). The local innovation system as a source of'variety': openness and adaptability in New York City's garment district. Regional Studies, 36(6), 587-602.

Reagans, R., & McEvily, B. (2003). Network structure and knowledge transfer: The effects of cohesion and range. Administrative science quarterly, 48(2), 240-267.

Revutska, N. (2014). Open innovation as a strategic model of modern business. European Scientific Journal, ESJ, 9(10).

Reynolds, E. B., & Uygun, Y. (2017). Strengthening advanced manufacturing innovation ecosystems: The case of Massachusetts. *Technological Forecasting and Social Change*

Rickne, A. (2001). Assessing the functionality of an innovation system. Goteborg, Chalmers University of Technology.

Ritter, T., & Gemünden, H. G. (2003). Network competence: Its impact on innovation success and its antecedents. Journal of business research, 56(9), 745-755.

Rosenthal, S. S., & Strange, W. C. (2001). The determinants of agglomeration. Journal of urban economics, 50(2), 191-229.

Rowley, T., Behrens, D., & Krackhardt, D. (2000). Redundant governance structures: An analysis of structural and relational embeddedness in the steel and semiconductor industries. Strategic management journal, 369-386.

Russell, M. G., Huhtamäki, J., Still, K., Rubens, N., & Basole, R. C. (2015). Relational capital for shared vision in innovation ecosystems. Triple Helix, 2(1), 1-36.

Russell, M. G., Still, K., Huhtamäki, J., Yu, C., & Rubens, N. (2011, July). Transforming innovation ecosystems through shared vision and network orchestration. In Triple

Helix IX International Conference. Stanford, CA, USA.

Salavisa, I., Sousa, C., & Fontes, M. (2012). Topologies of innovation networks in knowledge-intensive sectors: Sectoral differences in the access to knowledge and complementary assets through formal and informal ties. Technovation, 32(6), 380-399.Sampson, 2004

Saxenian, A. (1994). Regional networks: industrial adaptation in Silicon Valley and route 128.

Saxenian, A. (1996). Regional advantage. Harvard University Press.

Shane, S., & Cable, D. (2002). Network ties, reputation, and the financing of new ventures. Management science, 48(3), 364-381.

Simard, C., & West, J. (2006). Knowledge networks and the geographic locus of innovation. Open innovation: researching a new paradigm, 220-240.
Simoni, M., & Schiavone, F. (2009). Il ruolo della grande impresa nello sviluppo dei poli innovativi. McGraw-Hill.

Singh, J. (2005). Collaborative networks as determinants of knowledge diffusion patterns. Management science, 51(5), 756-770.

Soete, L. (2012). Maastricht reflections on innovation: Tans lecture 2011.

Sorenson, O., & Stuart, T. E. (2008). Bringing the context back in: Settings and the search for syndicate partners in venture capital investment networks. Administrative Science Quarterly, 53(2), 266-294.

Sorenson, O., Rivkin, J. W., & Fleming, L. (2006). Complexity, networks and knowledge flow. Research policy, 35(7), 994-1017.

Soy, S. K. (1997). The case study as a research method. Unpublished paper, University of Texas at Austin, 1-6.

Still, K., Huhtamäki, J., Russell, M. G., & Rubens, N. (2014). Insights for orchestrating innovation ecosystems: the case of EIT ICT Labs and data-driven network visualisations. International Journal of Technology Management 23, 66(2-3), 243-265.

Storper, M. (2005). Society, community, and economic development. Studies in Comparative International Development (SCID), 39(4), 30-57.

Stuart, T., & Sorenson, O. (2003). The geography of opportunity: spatial heterogeneity in founding rates and the performance of biotechnology firms. Research policy, 32(2), 229-253.

Sunley, P. (2008). Relational economic geography: a partial understanding or a new paradigm?. Economic Geography, 84(1), 1-26.

Sytch, M., Tatarynowicz, A., & Gulati, R. (2012). Toward a theory of extended contact: The incentives and opportunities for bridging across network communities. Organization Science, 23(6), 1658-1681.

Tallman, S., Jenkins, M., Henry, N., & Pinch, S. (2004). Knowledge, clusters, and competitive advantage. Academy of management review, 29(2), 258-271.

Teece, D. J. (1986). Profiting from technological innovation: Implications for integration, collaboration, licensing and public policy. Research policy, 15(6), 285-305.

Ter Wal A.L.J (2014) The dynamics of the inventor network in German biotechnology: geographic proximity versus triadic closure. Journal of Economic Geography 14(3): 589-620

Ter Wal, A. L., & Boschma, R. A. (2009). Applying social network analysis in economic geography: framing some key analytic issues. The Annals of Regional Science, 43(3), 739-756.

Todtling, F., & Kaufmann, A. (1999). Innovation systems in regions of Europe--a comparative perspective. European planning studies, 7(6), 699.

Tödtling, F., Lehner, P., & Kaufmann, A. (2009). Do different types of innovation rely on specific kinds of knowledge interactions?. Technovation, 29(1), 59-71.

Torre, A. (2008). On the role played by temporary geographical proximity in knowledge transmission. Regional Studies, 42(6), 869-889.

Torre, A., & Rallet, A. (2005). Proximity and localization. Regional studies, 39(1), 47-59.

Travers, J., & Milgram, S. (1967). The small world problem. Phychology Today, 1, 61-67.

Trippl, M., Tödtling, F., & Lengauer, L. (2009). Knowledge sourcing beyond buzz and pipelines: evidence from the Vienna software sector. Economic Geography, 85(4), 443-462.

Tsai, W. (2001). Knowledge transfer in intraorganizational networks: Effects of network position and absorptive capacity on business unit innovation and performance. Academy of management journal, 44(5), 996-1004.

Uzzi, B. (1996). The sources and consequences of embeddedness for the economic performance of organizations: The network effect. American sociological review, 674-

698.Uzzi, 1996

Uzzi, B. (1997). Social structure and competition in interfirm networks: The paradox of embeddedness. Administrative science quarterly, 35-67.

Uzzi, B. (1999). Embeddedness in the making of financial capital: How social relations and networks benefit firms seeking financing. American sociological review, 481-505.

Von Hippel, E. (2005). Democratizing innovation. MIT press.

Walker, G., Kogut, B., & Shan, W. (1997). Social capital, structural holes and the formation of an industry network. Organization science, 8(2), 109-125.

Wasserman, S., & Faust, K. (1994). Social network analysis: Methods and applications (Vol. 8). Cambridge university press.

Watts and Strogatz (1998

Welser, H. T., Gleave, E., Fisher, D., & Smith, M. (2007). Visualizing the signatures of social roles in online discussion groups. Journal of social structure, 8(2), 1-32.

Weterings, A., & Ponds, R. (2009). Do Regional and Non-regional Knowledge Flows Differ? An Empirical Study on Clustered Firms in the Dutch Life Sciences and Computing Services Industry. Industry and Innovation, 16(1), 11-31.

Yeung, H. W. C. (2005). Rethinking relational economic geography. Transactions of the Institute of British Geographers, 30(1), 37-51.Yeung, H. W. C. (2005). Rethinking relational economic geography. Transactions of the Insti

tute of British Geographers, 30(1), 37-51.

Yin, R. K. (2003). Design and methods. Case study research.

Yin, R. K. (2009). Case Study Research: Design and Methods, Essential guide to qualitative methods in organizational research. Applied Social Research Methods Series, 219.

Yin, R. K. (2015). Qualitative research from start to finish. Guilford Publications.

Yli-Renko, H., Autio, E., & Sapienza, H. J. (2001). Social capital, knowledge acquisition, and knowledge exploitation in young technology-based firms. Strategic management journal, 22(6-7), 587-613.

Zaheer, A., & Bell, G. G. (2005). Benefiting from network position: firm capabilities, structural holes, and performance. Strategic management journal, 26(9), 809-825.

Zhao, L., & Aram, J. D. (1995). Networking and growth of young technology-intensive ventures in China. Journal of business venturing, 10(5), 349-370.