The Evolution of Technology-based Alliance Networks in Pharmaceutical biotechnology

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Abstract The dominant focus in the literature until now has been on how networks enable and constrain action, whereas the question what factors enable and constrain networks has been largely ignored. To fill this void, this paper aims to develop an understanding of the role of ex ante factors and processes that influence network evolution. Empirically, we study network evolution in the biotechnology industry along two levels of analysis: network and dyad level. One of the key findings is that these two levels seem to change relatedly in response to exogenous environmental change and that network evolution, within a changing context of technological innovation, seems to be supportive of the idea of a path from weak ties and non-density in the early phase towards strong(er) ties and increasing density in later phases. More generally, our framework contributes by elucidating not only *how* networks evolve but also *why* they evolve in ways they do.
Key words network evolution, technological change, pharmaceutical biotechnology industry

1 Introduction

Despite the burgeoning literature on interfirm networks and strategic alliances (e.g. Ahuja, 2000; Hagedoorn, 2002; Powell et al., 1996), surprisingly little attention has been paid to their evolution. Although an increasing number of scholars clearly acknowledge the importance of studying network evolution, such studies have remained scarce to date (Nohria, 1992; Madhavan et al. 1998; Powell et al., 2005; Koka et al., 2006). In most of the network literature, the predominant focus has been on two issues, namely on why ties form between firms and on the structural determinants of performance (Gulati, 1998; Moldoveanu et al., 2003). Although there have been studies on the development or adaptation of alliances, their focus has remained at the firm level or dyad level, with an emphasis on interpartner dynamics (e.g. Gulati et al., 1994; Doz, 1996; Dyer, 1996; Reuer, Zollo and Singh, 2002; Reuer and Zollo, 2005; Rothaermel and Deeds, 2004). More recently, a number of descriptive empirical studies has analyzed network formation and evolution (Walker et al., 1997; Orsenigo et al., 2001; Gay and Dousset, 2005). Although these studies have yielded valuable new insights, they are based on the (implicit) premise that the network itself forms the causal factor for its change and evolution. Such an endogenous view on network evolution elucidates especially *how* networks evolve but leaves unexplained what form causal antecedents of network evolution (Salancik, 1995; Madhavan et al., 1998; Koka et al, 2006). To fill this void, we develop a theoretical framework that aims to provide us with an understanding of the role of ex ante factors and processes that influence network evolution. In this way, we contribute by elucidating not only *how* networks evolve but also *why* they evolve in ways they do.

We study network evolution within the context of technological innovation. More specifically, we analyze how a collaborative network of interfirm relationships evolves from a setting with a predominant focus on creating technological inventions towards a setting with a predominant focus on turning these inventions into marketable innovations. As argued by Schumpeter (1939), the creation of an invention versus developing its corresponding innovation, are economically and sociologically, two entirely different processes. If Schumpeter is right, we may expect a substantial change in network properties when it evolves from the former setting towards the latter. In this respect, the network literature seems to distinguish between two seemingly contradictory views on network evolution. According to one idea, networks follow a natural evolution from strong ties and closure towards weak ties and structural holes (Baum and Ingram, 2001). According to others, a common evolutionary path is formed by more weak ties and non-density in the early phase and strong(er) ties and increasing density in later phases (Kenis and Knoke, 2002; Rosenkopf and Padula, 2008). Although the two ideas seem to reflect rather opposite views, they share an implicit universalistic tone as if there is only one type of

'common' or 'natural' pattern. In stead, we feel it is more likely that both ideas may contain some truth, depending on the environmental conditions under which networks are formed and further unfold. In this respect, our assessment of the validity of the two different views holds under changing conditions of technological innovation.

Theoretically, to develop a comprehensive understanding of the forces underlying network evolution, we combine two strands of literature. One body of literature is formed by the economics of technology and innovation (Nelson and Winter, 1982; Dosi et al. 1988) with its intellectual origins in the work of Schumpeter. Here, it has been argued, among others, that there is first a pre-paradigmatic stage with a focus on inventions, which then moves into a paradigmatic stage once this variety of novel findings is reduced through consolidation into a dominant design (Abernathy and Utterback, 1978; Anderson and Tushman, 1990; Dosi, 1982). So, whereas progress has meanwhile been made in elucidating in what ways these two processes differ economically, how interfirm networks evolve under such different conditions has remained unaddressed in the literature until now. Within the sociological literature, various concepts and theories have been developed to analyse the structural properties of social networks (Granovetter, 1973; Coleman, 1988; Burt, 1992). Due to this strong focus on structural elements of networks though, the identification of relevant environmental conditions and how they influence the structure and evolution of networks has generally been ignored. As a consequence, there is a rather universalistic tone in this literature that abstracts from the role of the environmental context in how it influences the structure and evolution of networks (Gulati, 1998; Koka et al., 2006). It is the central claim of this paper that changing (economic) environmental conditions have a profound effect on network evolution. To study this in more detail, we analyze how two economically different environmental conditions affect the formation of network structures as well as how a change from one environmental context to the other affects network evolution.

Empirically, in order to be able to disentangle network evolution along its various levels, we need to take a historical perspective regarding the development of a network, from its nativity through infancy to adolescence and beyond (Kenis and Knoke, 2002; Powell et al., 2005). In this respect, there are various reasons to study network evolution in the biotechnology industry for the purpose of our study. Firstly, the biotechnology industry clearly forms an industry in which the structural drivers of network evolution are formed predominantly by technology (Orsenigo et al., 2001; McKelvey et al., 2004; Gay and Dousset, 2005). Secondly, the developments in this industry have taken place at breathtaking pace since its inception in 1973, and have been well documented. This allows us to make use of recent and well documented phenomena that enable us to reliably reconstruct the evolution of interfirm networks in this industry. Thirdly, the biotechnology industry has evolved and matured, over a period of about 25 years, from an initial focus on the generation of technological inventions towards a focus on commercialization of these inventions. In this way, we can analyze network evolution within the same industrial context, which enhances the internal validity and reliability of our analysis.

This paper proceeds as follows. In section 2, we analyze theoretically how network structural properties change in response to a transition from a context with a focus on the development of inventions towards a context of developing innovations. Here, we consider two different levels, namely the network level and dyad level. In section 3, we present a qualitative, empirical analysis of the process of network evolution - along these two levels - in the pharmaceutical biotechnology industry over the period from 1973 towards the end of the 1990s. This empirical study indicates that the creation of an invention versus that of an innovation not only differs economically but also differs from a sociological perspective, along the two levels. Finally, in section 4, we summarize and draw a number of conclusions.

2 Theory

Our theoretical analysis rests on the idea that networks change primarily in response to changes in the environment (Barley, 1986; Madhavan et al., 1998; Koka et al., 2006). As we will study network evolution within the context of technological innovation, we will focus on how technological change affects network evolution. Here, we start from the insights as developed in the evolutionary economics literature on innovation and technological change and then specify the sociological implications in terms of network formation and evolution. More specifically, we will study how a transition from a sectoral context with an initial focus on technological discovery and development towards a sectoral context with a focus on commercialization, shapes the formation and evolution of a technology-based alliance network. Here, our analysis will focus on the evolution of a network that is built up of relations that are

formed in view of developing *new* technology. As a consequence, relations between firms that refrain from these new activities, by retaining a focus on *established* technologies, are left out from the analysis. Regarding the relations of the firms that do engage in the process of *new* technology development, we will analyze network formation and evolution along two different levels of aggregation.

First, we consider the type of relation. This could be considered as the lowest level of aggregation as ultimately it are relations between actors that form the building blocks of a network. In our study, these are formed by technology-based linkages that make up an alliance network. In particular, we consider the 'strength' of the relation. As strong ties and weak ties serve different purposes (Granovetter, 1973), we anticipate relational strength to differ between a context of invention creation and innovation development. In this way, considering relational strength may serve as a good indicator to monitor network evolution at the dyad level. Second, we consider network centralization. This construct may be considered as a property of the total network as it indexes the tendency of a single firm to be more central than all others in the network (Freeman, 1979). Central firms are in demand for collaboration by others and changes in their centrality may possibly reflect underlying changes in an industry, in what makes firms attractive or 'in demand' as a partner over time (Madhavan et al., 1998). Although this suggests centrality to form a good indicator for analyzing structural change (Burt, 1992), it forms a property of a single firm and cannot inform us on changes of the whole network. As our interest entails the evolution of the network as a whole, we will consider network centralization as it indicates changes in the differences between the centrality of those firms that form network members. Since centrality forms such an important source of social capital for firms, changes in the relative centrality of firms can be considered as key indicators of structural change(s) at the network level (Madhavan et al., 1998).

In sum, we consider tie strength and network centralization to monitor network evolution both on the level of 'building blocks' as on the level of the total network made up of these 'building blocks'. In addition, by also considering these two different levels in joint consideration, we may get an understanding for the degree in which the two different network structural properties change relatedly in response to environmental change.

This section is structured as follows. First, in section 2.1, we analyze the properties of these two levels within a context with a predominant focus on the creation of technological inventions. Next we discuss, in section 2.2, how the properties of these levels change in response to the transition towards a context with a predominant focus on the development of innovations. Based on the theory as developed in each section, we derive a number of propositions that specify these dyad and network level properties and how they change.

2.1 The creation of technological inventions: exploration of novel combinations

A novel, radical invention often results from a technological discontinuity that marks the beginning of a newly emerging knowledge base (Schumpeter, 1939). Such an embryonic knowledge base is initially highly tacit and located within a few firms, bound up in specific assets and people (Nelson and Winter, 1982). The search process can often be characterized by a strong focus on learning-by-doing, in which serendipity plays a key-role. It tends to be highly empirical and driven by technological opportunities rather than demand or economic opportunities (Stankiewicz, 2002)[1]. In this discovery process firms will develop linkages to others with complementary knowledge and skills, generating a potential for the creation of novel combinations (Schumpeter, 1939). Moreover, another reason for collaboration is to spread and share risks. Due to the specific and tacit nature of knowledge in this early phase, monitoring the input and contribution of the involved firms is only possible by means of close interaction among a limited number of people. Therefore, the size of these newly forming 'exploration clusters' is generally small. Although firms within these clusters may grow technologically closer due to the mutual exchange of knowledge, the technological distance between these isolated clusters will be large. This results into a compartmentalized structure among these different exploration clusters.[2] Such a structure inhibits the generation of 'collective action' like for example the establishment of common

[1] This context of exploration closely resembles the idea of a 'discovery-driven' technological regime, (Stankiewicz 2002).

[2] This is in line with Kuhn's analysis of the evolution of science. In the early phase of a new scientific paradigm new variables are poorly connected, not only to each other but also to those existing in the old paradigm. In this respect, the emergence of a new paradigm can be associated with a (very) limited number of links whereas in the subsequent phase of normal science, the number of links will grow (Kuhn, 1962; Saviotti, 2004)

standards, which reinforces the compartmentalized nature of the network structure and leads to a low degree of network centralization. This suggests our first proposition:

Proposition 1:
In the phase of invention creation, network centralization will initially be low.

Within these developing exploration clusters, coordination of the intensive search processes is generally 'light' as it is based on a combination of formal contracts and informal mechanisms such as direct personal communication and social norms, which also function as selection mechanisms of who gets access to these newly forming clusters (Smith Ring and van de Ven, 1994). Once these social mechanisms have emerged, also some tentative, shared technological concepts and norms may develop. These help to reduce technological distance and in this way improve the build-up of mutual understanding, which enables further exploration (Nooteboom, 2004). In addition to these social and technological norms, other outcomes are formed by all kinds of demo's, experimental products as well as new (technological) standards, procedures and interorganisational routines (Smith Ring and van de Ven, 1994). Such an emerging infrastructure enables firms to increasingly start moving beyond their clusters and create relations with firms in other clusters. This furthers the creation of novel combinations and will reduce the compartmentalized structure of the network. Increasingly, it becomes clear who is participating, what are the new aims and purposes and which novel combinations may be useful to pursue further. In this process, firms that develop important inventions will gain in status and will attract others that seek collaboration opportunities with them (Stuart, 1998). As a result, over time the initially highly fragmented nature of the network will increasingly vanish and make room for a somewhat more centralized network. This suggests our second proposition:

Proposition 2:
In the phase of invention creation, network centralization will increase over time.

At the dyad level, flexibility of relations is important for facilitating rapid reconfigurations of cooperative ties in view of creating novel combinations. In other words, relations should have a limited duration since long duration would conflict with this need for flexibility (Gilsing and Duysters, 2008). Contractual, non-equity based partnerships offer such flexibility, opposed to equity-based alliances, which makes them more suitable to be used in the highly risky process of new business development (Hagedoorn and Hesen, 2007; Hagedoorn, 2002). In addition, a set of contractual partnerships offers firms the possibility to oversee different kinds of technologies at the same time and, in this way, to spread risks. Furthermore, the relatively hands-off nature of these partnerships also makes that they consume rather limited managerial resources so that a key focus on promising in-house R&D projects can be maintained as well (Ahuja, 2000). This suggests the following proposition:

Proposition 3:
In the phase of invention creation, the strength of the collaborative relations will be low.

2.2 The transition towards the development of innovations: optimization of novel combinations

As argued, the creation of inventions entails an ongoing process of exploration of creating novel combinations. This process may yield a large volume of (highly) diverse information throughout the network. Monitoring this constant supply of novel findings consumes time and resources of firms that cannot be allocated for absorption or integration. Such absorption and integration are required for commercializing the novel findings (Cohen and Levinthal, 1990). Furthermore, a sole focus on searching and recombination may result in a random drift so that novel findings change continuously in different and unrelated directions, which further reinforces the difficulty to absorb and integrate them (Fleming and Sorenson, 2001; Ahuja and Katila, 2004). In other words, abundant exploration tends to drive out exploitation and carries a risk of chaos (Levinthal and March, 1993). In evolutionary economics parlance, a process of selection is now required so that a differentiation can be made which of the novel findings justify further investments and upscaling, and which others need to be terminated (Nelson and Winter, 1982). The role of demand and stringent requirements regarding economic returns can serve as such selection mechanisms (Dosi, 1982). It is here where the role of incumbents may come into play. They can 'initiate' a transition towards exploitation, if they possess specialized, complementary assets that are needed in view of commercializing the new technology. An assumption made here is that these assets cannot, due to their specialized nature, be contracted for in the open

market by the new players.[3] In this case of specialized complementary assets, investing in collaboration with the holders of the novel technology can be highly attractive for the established players, and they may even come to dominate the market (Teece, 1986; Tripsas, 1997; Rothaermel, 2001).

So, promising new technology and ownership of critical, complementary assets make that incumbents may play a crucial role in commercializing the novel findings. By collaborating with the new players who possess the new technology, separation with exploration will vanish, facilitating a transition from a context of invention creation to one of innovation development. The effect of such an emerging 'exploitation logic' is substantial. It entails the establishment of a new paradigm and leads to a common understanding of selected problems and the general search direction for appropriate solutions (Nelson and Winter, 1982; Dosi et al., 1988). It is through this increasing clarity that stability is created and that new technology may gain in 'sociopolitical legitimacy', i.e. the phenomenon that key stakeholders such as the general public, key opinion leaders and governmental agencies will start to view it as appropriate and right (Aldrich and Fiol, 1984). Furthermore, the earlier recombinant nature that characterized interfirm collaboration and search makes room for an increasingly well structured search process, yielding more predictable outcomes. R&D collaboration no longer focuses on the creation of *new* novel combinations but in stead on optimising a selected set of already created novel combinations by means of incremental improvements and attempts for upscaling (Stankiewicz, 2002). In defining these new search directions both lead users (Von Hippel, 1988) for identifying technological bottlenecks and/or improvement areas as incumbents who dispose over resources and infrastructure to facilitate upscaling activities, may play an important role (Abernathy and Utterback, 1978).

This transition towards a context of innovation development reflects a key structural change in the industry with dire consequences for established network positions in the initially secluded 'exploration' network. Firms that were in the apex of control during the period of invention creation will lose their central positions to incumbents with control over specialized, complementary assets. Whereas within a context of invention creation such central positions facilitated the creation of novel combinations, now they yield the power to enforce certain ways of operating. Such 'coercive isomorphism' (DiMaggio and Powell, 1983) is needed for steering partners to search in those specific directions that have been identified as most promising in view of (future) commercialization (Breschi and Malerba, 1997). The implication for network centralization is twofold. It declines first, as the players that can be most associated with creation of the new technology are losing terrain, reflecting the demise of an 'exploration logic'. Along with incumbents moving into more central positions and the emergence of a new 'exploitation logic', it will start to increase again. This leads to the following propositions:

Proposition 4a:
The transition from invention creation towards innovation development leads to a sharp decrease of network centralization.
Proposition 4b:
After this transition towards a context of innovation development, network centralization will increase again.
Proposition 4c:
Central positions switch from the holders of key new technologies to the holders of complementary assets that are needed in view of commercialization.

This transition to innovation development and commercialization also carries implications for the strength of the interfirm R&D relations. Given the need for more specific and fine-grained search in this phase and the pressure for rapid commercialization, it is important that optimization of already created novel combinations occurs in a predictable, speedy and cost-effective manner. To achieve this, collaborating firms need to act more in tune. This induces a need for firms to make specific investments, both for the build-up of mutual understanding and for the development of refined, common search routines that can yield the required incremental improvements. As a consequence, durability of relations needs to increase in order to be able to recoup these investments. Here, equity-based partnerships seem

[3] Here we limit the analysis to a context of *specialized* complementary assets in order to understand how a transition from exploration and exploitation can possibly occur. The alternative mode is formed by the possibility of *generic* complementary assets that may lead to the wipe-out of incumbents (Teece, 1986; Tripsas, 1997; Rothaermel, 2001). However, that constitutes a different setting that we do not consider here.

to be the most likely mode for cooperation as this form enables firms to achieve these objectives of predictability, speed and cost-effectiveness in a combined manner. Equity-based collaboration brings separate partners together under common ownership, in a distinct organization, which makes it unattractive for partners to behave opportunistically as such behavior would lead to a decrease of the venture's total equity value (Buckley and Casson, 1988). In this way, equity-based collaboration enables to align incentives for engaging in common, long-term R&D and creates room for the build-up of trust (Nooteboom, 2004). Trust is very important in R&D collaboration as it reduces the costs of coordination and enhances the velocity with which decisions can be made and implemented (Sampson, 2007). Such potential for cost reduction and speed is attractive in view of (future) commercialization of the created inventions as for that purpose considerations of efficiency and being first-to-market typically form key success factors (Breschi and Malerba, 1997). The presence of trust also makes that partners will behave in line with expectations, which enhances the predictability of the collaboration (Gulati and Garguilo, 1999). Furthermore, trust facilitates the mutual exchange of tacit knowledge (Nooteboom, 2004) and the development of common search routines (Sampson, 2007), forming both key inputs in the process of finetuning and optimizing the set of selected technologies (Miller et al., 2007).

Overall, quick, efficient and predictable R&D collaboration 'upstream' in the value chain, enables the reliable and cost-effective production and delivery of new products to users and/or consumers 'downstream' in the value chain. This is critical for gaining and reinforcing the sociopolitical legitimacy of the new technology (Aldrich and Fiol, 1984) and hence for increasing its attractiveness to a larger market. This suggests our final proposition.

Proposition 5 :
In the phase of innovation development, the strength of the collaborative relations increases.

3 Empirical Analysis

In this section we present a qualitative, empirical analysis of the process of network evolution in the pharmaceutical biotechnology industry over the period from 1973 towards the end of the 1990s. To do so, we first discuss in section 3.1 methods of data collection and the calculation of the key network constructs. Next, in section 3.2, we provide the empirical analysis of the process of network evolution for the period of invention creation. In section 3.3 we do so for the subsequent period of innovation development. In section 3.4 we discuss some key findings as they come out of the empirical analysis.

3.1 Data collection and calculation of network constructs

For this analysis we rely on data from the MERIT-CATI database (see Appendix 1), a comprehensive database that contains information on R&D partnerships, as well as on secondary sources such as former studies on this particular industry (e.g. Galambos and Sturchio, 1998; Gordon et al., 1994; Henderson et al., 1999; McKelvey et al., 2004; Pisano, 1991, 2002; Powell et al., 1996; 1999; 2005).

Boundary specification of the network that we study is based on the idea of core technology as its key defining characteristic, constituting an important determinant for its evolution (Silverman and Baum, 2002; Gay and Dousset, 2005). More specifically, we study the evolution of pharmaceutical biotechnology R&D alliances formed by those companies that are active in the high-tech pharmaceutical biotechnology industry and define the network as built up of those relations that are formed in view of developing *new* biotechnology. As a consequence, relations between firms that refrain from these activities, by retaining a focus on *established* technologies (i.e. organic chemistry) are left out from the analysis. Following this network boundary specification, the network players are formed by dedicated biotech companies (DBFs), large pharmaceutical companies as well as diversified chemical companies. We focus specifically on R&D alliances, defined as technology-based inter-firm collaborations where two or more independent firms share part of their R&D activities (Hagedoorn, 2002; Hagedoorn et al., 2000). Other types of alliances such as production and marketing agreements are not included.

Figures 1 and 2 give us a graphical representation of the structure of research partnering networks in pharmaceutical biotechnology during the period 1978-1980 and 1983-1985, using a non-metric multidimensional scaling (MDS) technique. MDS is a data reduction procedure somewhat comparable to principal component analysis and other factor-analytical methods. One of the main advantages of MDS is that it can usually fit an appropriate model in a two-dimensional picture. Particularly, MDS offers a scaling of similarity data into points lying in an X-dimensional space. The purpose of this method is to provide coordinates for these points in such a way that distances between pairs of points fit

as closely as possible to the observed similarities. In order to facilitate interpretation, the solution is given in two dimensions, provided that the fit of the model is acceptable. A stress value indicates the goodness-of-fit of the configuration as this measures the proportion of the variance of the disparities that is accounted for by the MDS model, implying that lower values indicate a better goodness of fit (Hair, Anderson, Tatham, and Black, 1998). For the two MDS solutions presented in this paper Kruskal's stress values (Kruskal and Wish, 1978) range from very good, e.g. 0.001 for the period 1978-1980 to good e.g. 0.022 for the period 1983-1985.

Using the network visualization software tool Najojo (see Appendix II), we enhance the interpretability of these MDS pictures, first, by adding company labels to the dots, and, second, by drawing lines of different styles and thickness between pairs of firms with varying degrees of partnering intensity. Dotted lines represent one R&D partnership between companies, whereas solid lines indicate 2 or 3 partnerships (See also Cloodt et al., 2006; Hagedoorn and Roijakkers, 2002 and Roijakkers and Hagedoorn, 2006). See Appendix III for company labels.

Besides a graphical representation of the structure of research partnering networks, we also computed the Network Centralization Index by the use of UCINET VI to measure the centralization of the entire network (Borgatti, Everett and Freeman, 2002). This measure is based on the mathematical definition of network centralization according to Freeman (1977). Figure 3 shows the changes in network centralization during the period 1975-1999.

Concerning the dyad level we can state that companies cooperate in R&D through a specific number of organizational modes: equity-based agreements, such as research joint ventures, and minority holdings, and a number of contractual modes, such as research contracts and joint R&D agreements (Hagedoorn, 2002). These different types of organizational modes can be weighted according to the 'strength' of the relationships as some authors did previously (see Contractor and Lorange, 1988; Gulati, 1995; Nohria and Garcia-Pont, 1991). In analogy with preceding research we tracked all of the organizational modes that the sample firms established during the period of our analysis. We then categorized the tie strength of these modes as strong in the case of equity alliances or weak in the case of non-equity alliances (Duysters and Hagedoorn, 2000; Hagedoorn, 2002). We proxied equity alliances by the *sum* of the total number of research joint ventures and minority holdings. We proxied non-equity alliances by the *sum* of the total number of contractual R&D alliances. Besides this more aggregate measure of non-equity alliances, we also created more disaggregate indicators such as the total number of R&D contracts and the total number of joint R&D agreements, each measured *separately*.

3.2 Network evolution in pharmaceutical biotechnology: invention creation

The birth of the pharmaceutical biotechnology industry is marked by the discovery of the double helix structure of DNA by Cohen and Boyer in 1973 (Pisano, 2002). At this very early stage of industry development, from 1975 towards 1980, a few of the pharmaceutical incumbents made some first attempts to collaborate with DBFs, through research contracts, in order to engage in the exploration of biotechnology. In figure 1 we see various isolated research clusters and a few one-on-one R&D partnerships, revealing the highly compartmentalized structure of the network. As a consequence, centralization of the emerging network in this early period was very low. See also figure 3. This is in line with our first proposition.

From the end of the 1970s towards the mid 1980s, however, the number of DBFs increased substantially, at the expense of positions held by pharmaceutical and chemical incumbents. See also table 1.

During the very early days in the 1970s, they entered R&D partnerships in the expectation that they could develop new products rapidly and then commercialize these accordingly. They soon found out that this required large investments in both basic and developmental research across a wide range of opportunities, with highly uncertain returns (Galambos and Sturchio, 1998). So, once it became clear that this became a lengthy and costly process, their interest started to wane (Powell et al., 2005). Apart from the very high investments, risks were also formed by the uncertainty whether stiff governmental controls regarding biotechnological research would be imposed as well as by ambiguity about the possibility to patent genetic inventions (Galambos and Sturchio, 1998). Furthermore, an important reason was also formed by the fact that biotechnology appeared to be very difficult to understand for incumbent companies. The skill loss for a scientist making the transition from the traditional chemical screening paradigm to that of genetic engineering was estimated to exceed 80% (Rothaermel, 2001). In other words, the transition to biotechnology appeared to be very painful for existing personnel in R&D as in some other functional disciplines (Galambos and Sturchio, 1998). Moreover, at this point in time, insights in the limitations of organic chemistry were not present yet, and became only readily apparent

towards the late 1980s and throughout the 1990s (Gilsing and Nooteboom, 2006). But during the 1970s and early 1980s, immediate economic payoffs of investments in organic chemistry seemed to remain sound so that most incumbents invested the lion's share of their resources in established programs of research that still carried the promise of delivering important new drugs in the future (Galambos and Sturchio, 1998). In other words, there were no clear indications yet that the major chunk of their existing investments in organic chemistry became useless once biotechnology further developed. As a consequence, most incumbents adopted a wait-and-see attitude, which resulted in these large pharma firms being pushed to the periphery or dropping out from the network altogether (Powell et al, 2005). Meanwhile, interfirm partnering between Dedicated Biotechnology Firms (DBFs), with a clear focus on R&D collaboration, began to take off and led to a growing number of relations in a network that slowly on started to lose its compartmentalized structure. See also figure 2.

Furthermore, following table 1, we see that during this first half of the 1980s (especially from 1981 – 1983) the top of the partnership list covered mainly biotechnology companies such as Genentech, Biogen, Genex and Amgen. Compared with the previous period, the second half of the 1970s, cooperation between DBFs grew much faster than cooperation between DBFs and large pharma firms. This is indicative of some degree of 'separation' between DBFs and pharmaceutical incumbents. In this way, DBFs could maintain some of their academic orientation and culture, characterized by informal and non-hierarchical structures, which set them apart from the hierarchically structured pharma companies that remained focused on exploitation of the existing technology of organic chemistry (Pisano, 1991; McKelvey et al., 2004). So, in the first half of the 1980s, we see an increasingly coherent R&D network developing that operated somewhat secluded from incumbents with their vested interests in existing technologies and established ways of operating. This finding seems to be in line with our second proposition

The emergence of this secluded niche coincided with an increase in network centralization, from 1980 onwards. See also figure 3. This increase in centralization indicates that some firms moved towards increasingly central positions. Here table 1 shows that these central positions were mostly occupied by biotech companies such as Genentech, Biogen, Genetic systems, Genex and others. It are such central positions in an R&D network that allow for linking different pieces of knowledge from unconnected parts of the network in order to create a novel combination. This increase in centralization in the later phase of invention creation is in line with our third proposition.

Regarding the type of relations, previous research shows that well over 80% of R&D collaborations between the late 1970s and mid 1980s were contract-based and not equity-based (see Roijakkers and Hagedoorn, 2003; Roijakkers and Hagedoorn, 2006). A closer inspection of the data reveals that throughout this period the use of research contracts exceeded that of joint R&D agreements (MERIT-CATI database). This kind of arrangement enabled firms to engage in a portfolio of highly flexible partnerships that facilitated a rapid reconfiguration of ties, which furthered the efficient creation of novel combinations. Once the job was completed, the collaboration ended and firms could depart gracefully (Powell et al., 2005). This in particular formed an attractive feature of using contracts, given the highly volatile conditions in these early days of pharmaceutical biotechnology. This conforms proposition 4.

In this period, the major focus of DBFs was on the creation of new technologies, whereas commercializing these technologies seemed to constitute a long(er) term issue. As a consequence, the generation of regular streams of cash-flow proved to be (very) difficult, making most DBFs become dependent on venture capitalists and other investors. Throughout the second half of the 1980s, however, it became clear that biotech companies proved to be unable to commercialize their novel findings independently. In stead, it became evident that for successful commercialization, key complementary assets were required such as capabilities to deal with (pre)clinical drug testing and regulatory approval procedures as well as access to marketing and distribution channels (McKelvey et al., 2004). DBFs lacked these skills and these could not be contracted for in the open market due to their highly specialized nature. As a consequence, the interest in biotechnology of venture capitalists and investors started to wane as they increasingly lost confidence in its commercialization potential, a trend that was further reinforced by 'black monday' on Wall Street in October 1987 (Galambos and Sturchio, 1998; Pisano, 2002). As a consequence, venture capitalists and other investor started to pull out from biotechnology and forced many DBFs into bankruptcy. This initiated a transitional process from a context of invention creation towards one of innovation development.

3.3 Network evolution in pharmaceutical biotechnology: innovation development

With the exit of venture capitalists, large pharma firms now entered the scene and started to cooperate with DBFs on an increasing basis. They disposed over the specialized capabilities and skills that were required for getting drugs successfully tested and legally approved, and had access to marketing and distribution outlets. Another important driving force for their entry was formed by growing insights into the limitations of organic chemistry, which had been the dominant technology for almost a century (Gilsing and Nooteboom, 2006). Its limitations became increasingly visible in the late 1980s and grew more and more apparent throughout the 1990s, when it became manifest that existing patents hold by pharma companies were expiring whereas the number of potential 'blockbusters' in the pipe-line was decreasing steadily (Nightingale, 2000; McKelvey et al., 2004; Gilsing and Nooteboom, 2006).

These two developments – the exit of venture capitalists and the entry of pharmaceutical incumbents – made that a risk of 'exploration' driving out 'exploitation' has eventually not taken place in the evolution of the pharmaceutical biotechnology industry. Crucial here was that large pharmaceutical incumbents increasingly started to understand the new technology and combined it with their existing knowledge base on organic chemistry. They started to develop these internal capabilities through a combination of acquiring biotech firms and investing in in-house scientific personnel (Galambos and Sturchio, 1998). Incorporation of biotechnology enabled these firms to take a more rational approach to the design of new drugs: the search space could be more accurately defined and the screening process could be far better structured (Nightingale, 2000; Gilsing and Nooteboom, 2006). So, towards the end of the 1980s, seclusion with the exploration efforts by DBFs started to vanish as a focus on commercialization of a combined trajectory of molecular biology and organic chemistry developed. In this way initially abundant variety, associated with the process of creating novel combinations, was now increasingly being subjected to selection forces such as regulatory procedures regarding clinical testing and drug approval. This reflected the transition to a focus on subsequent innovation development and commercialization as is also illustrated by the gradual decrease of the R&D-to-Sales ratio from 4 to about 1. See also figure 4

Table 1 provides further empirical evidence for this transition. In the period 1984 – 1986 the top ranking is still formed by DBFs, such as Genentech, Biogen and Chiron. Nevertheless, large pharma companies are slowly increasing their positions. This trend continues in the next period from 1987 - 1989 and becomes even more pronounced in 1990 – 1992, in which the top five positions are held by incumbent firms. So, compared with the period from the late 1970s until the mid 1980s where DBFs still held central network positions, the centrality of this group diminished from the late 1980onwards. In line with this are the findings on network centralization. Throughout a substantial part of the 1980s, centralization was at a fairy high and relatively constant level, reflecting the central positions held by biotech firms. Towards the end of the 1980s, however, centralization dropped significantly. It started to rise again slowly in the early 1990s but now reflected the increasing centrality of large pharmaceutical companies. This volatility in centralization and its 'U-turn' in who occupied the most central positions reflected the profound changes that the industry was going through when moving from invention creation towards innovation development and subsequent commercialization. Overall this seems to support our propositions 5a, 5b and 5c, predicting network centralization to decrease first, followed again by an increase and a switch in which firms hold the most central positions.

For the final years of our analysis, from 1996 to 1999, table 1 clearly portrays which incumbent companies formed the most central players, such as Roche, SmithKline Beecham, Pfizer, Bristol-Myers Squibb, Glaxo Wellcome, Eli Lilly and so on. These companies created many new partnerships, most of which were established in 1996. An important driving force here was formed by a second wave in the molecular biological revolution: genetic engineering. This new technology developed in the early 1990s and opened up completely new areas for innovation, as it altered the drug discovery process in profound ways. In contrast to the period of random screening through which drug compounds were basically 'discovered', genetic engineering constituted a far more rational approach. It enabled firms to 'design' new drugs, based on a scientific understanding of the biological underpinnings of diseases (Nightingale, 2000; McKelvey et al., 2004). Moreover, genetic engineering also offered important possibilities for process innovations, which induced the newly developing field of 'combinatorial chemistry'. Combinatorial chemistry opened up the possibility to produce proteins synthetically, which brought the advantage that in comparison with organically derived proteins they became available in large amounts. This improved their cost-effectiveness and their reliability of supply. Especially the latter formed an important issue as securement of supply made them suitable to conduct clinical trials first and then to foresee in the demand for the new therapies (Gordon et al., 1994; Galambos and Sturchio, 1998;

Henderson et al. 1999). In this way, combinatorial chemistry opened up new opportunities for process innovations, which may explain the growing importance in the network of a group of more chemically oriented firm such as Rhone-Poulenc, Hoechst and Bayer, which disposed over key process capabilities (Pisano, 2002).

Regarding the governance mode and strength of the relations, there are a number of observations to be made. With the very first indications of emerging exploitation, from about 1985 onwards, we see that firms increasingly preferred joint R&D agreements over R&D contracts. This was because also large pharma firms started to establish their own research centres, indicating that they were internalizing new biotechnological knowledge and tried to build up absorptive capacity. This enabled them to move towards such joint R&D agreements, which were well suited to conduct such routinized R&D. Overall, this implied a move away from R&D contracts that had been heavily in use by DBFs until then. This latter mode provided strong flexibility that enabled them to monitor the development of several technologies at once, and facilitated a rapid reconfiguration of cooperative ties in view of creating novel combinations. When moving towards exploitation, however, this very high degree of flexibility was not desirable any longer as the shift in focus towards finetuning a selected set of technologies required (much) more predictability and cost-effectiveness of R&D collaboration in stead. Another finding is that firms still preferred contractual R&D agreements over equity-based forms of cooperation, which is *not* in line with proposition 6. Although this is in line with our theoretical argument that relational strength increases here, it does not so to the extent as expected, namely by a growth in the use of equity-based relations relative to non-equity-based relations.

3.4 Key findings

In this section we discuss in how far our empirical findings are in line with the theoretical propositions at the network respectively dyad level. Next, we consider these two levels jointly in order to see if these two levels change relatedly or autonomously, which may further inform us on the process of network evolution. Finally, we discuss some new insights on the role of centralization, as they appear from the empirical analysis.

Empirical findings and theoretical propositions

Our empirical analysis seems to confirm most of our theoretical propositions as formulated in section 2. Our empirical findings are in line with propositions 1, 2 and 4 with regard to network centralization. With regard to relational strength we found evidence for proposition 3, predicting low strength in the phase of invention creation, but not for proposition 5, an issue that we will further address below.

As these propositions are formulated per level, i.e. dyad and network, it may now also be worthwhile to consider both levels jointly in order to learn in how far they change relatedly. This may help us in further decomposing the complexity of the process of network evolution. We do so for both periods.

Exploration of novel combinations: network and dyad level

In this period, we have seen that - at the network level - the initially highly compartmentalised structure created an enormous *potential* for new combinations among the isolated exploration clusters. At the dyad level, it was the low strength of the relations (largely contract-based) that enabled a rapid reconfiguration of cooperative ties so that this sheer potential could indeed be untapped through the *actual creation* of specific novel combinations. Through this dyadic collaboration, firms could develop a growing understanding of which novel combinations might be useful and might carry future economic value versus which combinations will prove to be dead-ends. In this process, firms that developed important inventions gained in status and attracted others that seeked collaboration opportunities with them. This made that the initially highly fragmented nature of the network increasingly vanished and that network centralization increased. In other words, we see how the dyad and network level operated in a related fashion and how in this way, the newly emerging network facilitated the creation of novel combinations.

Exploitation of novel combinations: network and dyad level

In this period, we see at the network level that there was a switch from DBFs to incumbents in who occupied the most central positions, which was followed then by a steady increase in network centralisation. This provided stability and allowed for a systemic coordination by incumbents, who could now enforce specific ways of operating in view of obtaining drug approval and subsequent commercialisation. At the dyad level, the governance mode changed from contracts to joint research

agreements. This indicated that relational strength increased to some extent, in view of facilitating mutual knowledge exchange and securing reliability of production and supply of products and services. Still somewhat unexpected was the finding that towards exploitation contractual arrangements were still clearly preferred over equity-based relations. This was not in line with proposition 5. Here, the explanation may be that the large stability provided by equity-based cooperation might still have been too much during and immediately after the volatile, transitional process from invention creation to innovation development, in which it was still important to maintain a sufficient degree of flexibility. Nevertheless, also here the empirical analysis indicates how the dyad level and network level changed in a coherent fashion and in this way facilitated the transition towards optimisation of created novel combinations in view of commercialisation.

Centralization: invention creation versus innovation development

Although network centralization was definitely higher for the period of innovation development than it was for the period of invention creation, it certainly also played a role within this first context. This seemingly similarity between both contexts of the role of network centralisation obscures the fact that there is a profound difference in the force underlying this tendency of one or a few firms to be more central than others. In the context of invention creation, there was initially a total lack of centralisation as reflected by the highly compartmentalised network structure. It was precisely this fragmented structure that carried a seemingly unlimited potential for novel combinations. But this potential reservoir would have remained of limited value if no linkages among the various isolated parts could develop. Because knowledge and skills were so *widely scattered* across the network, some degree of network centralisation was needed to untap this potential and to be able to actually create the novel combinations and then assess their technological novelty value. In the context of innovation development, the focus was on commercialization and here the aim was primarily to create and assess economic value. In the pharmaceutical biotechnology industry that required specialised skills in view of obtaining regulatory approval, which were in the hands of a few large incumbent companies. Here, a central position provided the possibility to enforce specific search directions in view of optimizing a selected set of technologies, boosting economic value. So, in contrast, here it was the *scarcity* of specialised knowledge and skills and a need for power and stability that drove network centralisation. This profound difference in the underlying force driving network centralisation explains its substantial decrease in the transition from invention creation to innovation development, after which it rose again but now indicative of an emerging 'exploitation logic'.

4 Discussion and Conclusions

The dominant focus in the literature until now has been on how networks enable and constrain action, whereas the question what factors enable and constrain networks has been largely ignored (Nohria, 1992; Madhavan et al., 1998; Koka et al., 2006). As a consequence, we still have a rather limited understanding how networks change in response to exogenous environmental change(s). To address this, we have developed a theoretical framework that aims to provide us with an understanding of the type of exogenous factors and processes and their role in shaping network evolution. In this respect, our study forms an important complement to Madhavan et al.'s study (1998), who studied the effect of discrete, exogenous events. In contrast, our study shows how processes of network change emerged in response to a cascade of relatively small(er), continuous exogenous 'events' that accumulated over time and then led to a reinforcement respectively break of the prevailing structure. With regard to these two types of network change, we have 'structure strengthening' change seen occurring during the period of exploration respectively exploitation – both before as after the transition from exploration to exploitation – whereas this transition itself formed a clear case of 'structure loosening' change.

In sum, our study leads to a number of conclusions. First, as seen from a solely evolutionary perspective, the process of network evolution itself remains invariant between the two contexts, forming structure strengthening change. However, a process of structure loosening change is required in order to accommodate the transition from structure strengthening change in the former context towards structure strengthening change in the latter. Second, network structural properties - at dyad and network level – do differ between the two contexts and form a set of properties that, through network strengthening change, changes relatedly. This combination of properties clearly offers value in one context, but then loses its meaning in another, requiring a process of structure loosening change in order to make it fit

again with the new context. Third, these differences in network properties between the two contexts are basically a matter of degree. In this respect, our study provides a more nuanced view on Schumpeter's original claim (1939) on the two contexts as being 'entirely different': as far as R&D-based collaboration is concerned, the creation of an invention versus that of an innovation seems to be rather 'gradually different' from a sociological perspective. A final conclusion is that network evolution within a changing context of technological innovation seems to be supportive of the idea that networks change from weak ties and non-density in the early phase towards strong(er) ties and increasing density in later phases (Kenis and Knoke, 2002; Rosenkopf and Padula, 2008). The alternative view of a path from strong ties and closure early on towards weak ties and structural holes in later phases (Baum and Ingram, 2001) does not apply here.

Implications for firms

Many studies have focused on how alliances and networks matter for a firm's economic and innovative performance, but have ignored network change and how firms may anticipate that. Following the aim of this paper to understand the role of antecedent factors shaping network evolution, we have not considered the (performance) implications for individual firms. Nevertheless, we can derive some insights that may inform firms on how to deal with network evolution. As it follows from our study, we have shown that the structure of interfirm relationships, in response to exogenous sectoral innovation dynamics, changes in rather predictable ways. In this respect, our framework for understanding the dynamics of alliance networks offers the possibility to predict its future structure to some extent and to derive suggestions for path creation strategies that enable firms to secure or improve key positions. Within a context of invention creation, it seems to be most beneficial to initiate relations across different exploration clusters in order to create novel combinations. Such dyadic collaboration may enable firms to create (breakthrough) inventions and assess their technological value. Within a context of upscaling and commercialization, it seems to be most beneficial to improve centrality in order to be able to provide stability and enforce specific search directions in view of optimizing a selected set of technologies. In this way, a central position may enable firms to boost the economic value of the created inventions. Structure loosening change, such as the transition from exploration to exploitation, seems open to open up opportunities for more peripheral firms to improve their position, if they dispose over the 'right' complementary assets. Here, central players may want to develop a defensive strategy to protect their position if they are able to anticipate this change timely. Overall, these ideas contribute to a more rigorous understanding of a basic pattern of network formation and evolution. Such an understanding forms an important prerequisite before we can specify in a more detailed way what firms should do, or refrain from, when dealing with network changes (Madhavan, 2003).

Limitations and future research

When interpreting the results of our study, we should remain conscious of some of its limitations. A first limitation is that we have considered a context of technological innovation. Although focusing on a specific context like this enhances the internal validity of our findings, it puts some restriction on the extent in which these can be generalized. Our theoretical framework has specified the role of sectoral innovation dynamics and their effect on network change in such a way that it holds for industries which inception lies in the development of a technological breakthrough and the evolutionary process that subsequently unfolds. As a consequence, our theory and empirical findings may not be replicated for industries of which the origins cannot be traced back to such a breakthrough nor for industries in which technological innovation plays no role of great importance. Furthermore, we have considered an industrial context of *specialized* complementary assets and studied how their possessors, by investing in collaboration with the holders of novel technology, can initiate the transition from exploration to exploitation. This clearly differs from a context of *generic* complementary assets that may lead to the wipe-out of incumbents, which would constitute a different setting than the one considered here (Teece, 1986; Tripsas, 1997; Rothaermel, 2001). In this respect, an issue worth investigating further is to study network evolution in contexts that are dominated by a different type of technology or with no role of technology whatsoever. It could well be that also in such cases networks evolve along similar lines as predicted and found here or, alternatively, that they may evolve from strong ties and closure early on towards weak ties and structural holes in later phases (Baum and Ingram (2001). On the firm level, it will be interesting to see in how far firms may benefit differentially from such exogenous change events and to what degree that depends on, for example, their innovation strategy, their ability to attract (new)

partners, their motivation to improve position (Burt, 1992) and the speed with which they adopt new technology (Burkhardt and Brass, 1990).

Overall, the main contribution of this study is formed by providing a more in-depth understanding of network evolution and, in particular, of why networks may evolve in ways they do. Although our empirical analysis did not entail a formal test, it nevertheless clearly indicated that our framework seems to carry validity and that network evolution can be predicted by explicating its antecedents and their role. In this way, our study contributes to the literature in several ways. First, we contribute to the learning and innovation literature. Although in this literature the importance of interfirm collaboration and processes of 'interactive leaning' is clearly acknowledged, insights into the associated social structural implications still remain in their infancy (Malerba, 2004). Here, our study has shown how a context of invention creation versus subsequent innovation development has a differential impact on a network of technology-based alliances: how it acts as a channel for the diffusion of existing information and knowledge in view of efficient commercialization versus how it carries a recombination potential in view of new knowledge creation. Especially this latter insight is also highly informative to the alliance literature that has largely ignored the role of alliances and interfirm collaboration in view of novelty creation, and is therefore unable to explain the development of new knowledge and competencies (Hagedoorn et al., 2000; Nooteboom, 2004; Gilsing et al. 2008).

Our study also contributes to the social network literature. By studying the process of network formation and evolution as a response to exogenous environmental change, we consider network structural properties as a *dependent variable*. This serves as an important complement to the current literature in which network structural properties have mostly been treated as independent variables. In this way, our study addresses an important void in the literature that has focused until now only on how each structure can be used to advantage (Coleman, 1998; Burt, 1992), but has ignored their antecedents (Salancik, 1995). Here, our study shows under which conditions a network rich in structural holes respectively reaching closure may be expected. Under conditions with a focus on invention creation, the emerging network is highly compartmentalized and contains many structural holes between its varies compartments. Under conditions with a focus on innovation development, the network starts to grow more connected. This is caused by the establishment of a new paradigm that provides the basis for developing a common understanding and a well-defined search space. As a consequence, technological distance between firms becomes increasingly smaller which greatly facilitates the creation of linkages and exchange of knowledge. Furthermore, the more connected structure facilitates the development of trust which enables the exchange of tacit knowledge, stimulating further collaboration (Nooteboom, 2004). So, following Schumpeter's original distinction, the process of recombination leading to new inventions can be associated with networks that are rich in structural holes, whereas the subsequent process of commercializing these inventions can be associated with relatively well connected networks. In this way, our theoretical framework also provides a basis for comparing different network structures at different points in time, a topic that has remained unaddressed in the network literature until now (Moldoveanu et al. 2003).

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APPENDIX I: DATA AND SAMPLE

For our analysis, we make use of data on inter-firm R&D partnerships. These data are taken from the MERIT-Cooperative Agreements and Technology Indicators (CATI) information system (see Hagedoorn, 1993). This databank contains information on nearly 10,000 cooperative agreements in various sectors, ranging from high technology sectors, such as information technology and biotechnology, to less technology intensive sectors, such as chemicals and heavy electrical equipment. Cooperative agreements are defined as mutual interests between independent industrial partners that are not linked through majority ownership. In the CATI database, only those agreements are being recorded that involve either a technology transfer or some form of jointly undertaken R&D. Information is also collected on joint ventures in which new technology is received from at least one of the partners, or on joint ventures having some R&D program. Other types of agreements such as production and marketing alliances are not included. Agreements formed between companies and governmental or academic institutions are generally not included in the database unless they involve at least two commercial companies.

The current paper focuses on those partnerships that were established in the period 1975-1999. In the CATI databank a total of 1469 global R&D agreements in the pharmaceutical biotech industry involving 890 firms were recorded during this time frame. Our data include equity agreements, joint ventures, as well as non-equity alliances that consist of joint R&D pacts and joint development agreements. The data excludes agreements that are established within the context of national and international, government sponsored, R&D cost-sharing programs. For our purpose, the most relevant information for each partnership is the number of companies involved, their names as well as the year in which the agreement was established.

APPENDIX II: NAJOJO

To facilitate our analysis and visualize the different R&D networks that have come into existence during each of the three-year sub-periods examined in this paper, we make use of the network visualization software tool Najojo (owned by UNU-MERIT). As existing visualization software has serious difficulties in handling this kind of large-sized research networks, new software has been developed. This tool, capable of visualizing large, dense networks involving more than 500 companies, was ultimately created by Johan Willekens.

There are two separate input (text) files underlying the generation of networks in Najojo: one file holding the MDS coordinates for each of the individual companies participating in the network and one file holding all unique company pairs and their numbers of research partnerships. On the basis of the first input file, Najojo determines whether the particular network will be visualized in landscape (see for example figures 1 and 2) or portrait orientation (not applicable in this study). As a second step in the visualization process, the tool divides up the landscape in an X number of points. The firm coordinates held by the first input file are then mapped onto these points and visualized as dots. While creating this scatter plot, the program makes sure that the relations between dots are held constant and that dots belonging to different companies do not overlap. Thirdly, company labels are placed with the dots in such a way that they do not overlap with other labels or dots. Najojo variably determines the font size of company labels depending on network density and the number of companies participating in the network. Fourthly, on the basis of the second input file, Najojo visualizes the total number of partnerships entered into by all unique company pairs making up the network. The tool first identifies both research partners, i.e. the beginning and ending dots, and subsequently draws polybezier lines between these dots, making sure that these lines do not cross dots belonging to companies that are not part of the partnership. The type of line (dotted, solid, thick solid) can be determined by the user.

APPENDIX III: LISTING OF NETWORK PARTICIPANTS

Label	Company Name	Label	Company Name
ABBOTT	Abbott Laboratories Inc.	GARVAN	Garvan
AJINOMOT	Ajinomoto	GENENTEC	Genentech Inc.
AMBIONUC	American BioNuclear	GENET-IN	Genetics Institute Inc.
AMCYAN	American Cyanamid Co.	GENET-SC	Genetics Systems Corp.(GSC)
AMGEN	AMGen Inc.	GENEX	Genex Corp.
ANHEUSER	Anheuser-Busch Companies Inc.	GLAXO	Glaxo Holdings Plc.
APPIMUM	Applied Immunesciences	GREEN-CR	Green Cross Corp.
APV	APV Holdings Plc.	GRUNENTH	Grünenthal GmbH
ARES-SER	Ares-Serono S.A.	HANA-BIO	Hana Biologics
ASAHI-CH	Asahi Chemical Industry Co.Ltd.	HAYASH-B	Hayashibira Biochemical
BASF	Basf A.G.	HOF-ROCH	Hoffmann-La Roche & Co. A.G.
BAXTER-T	Baxter-Travenol Labs.Inc.	HYBRITEC	Hybritech Inc.(Hybrid Technology)
BAYER	Bayer A.G.	ICN-PHAR	ICN Pharmaceuticals
BEECHAM	Beecham Group Plc.	IMMUNEX	Immunex Corp.
BIOGEN	Biogen Inc.	IMMUNOM	ImmunoMedics Inc.
BIOINVST	Bioinvest	INTE-GEN	Integrated Genetics Inc.
BIOTECHN	BioTechnica Int.Inc.	INTERF-S	Interferon Sciences
BIOTECRL	Biotech Research Labs.	I-PASTEU	Institut Pasteur
BOHR-ING	Böhringer-Ingelheim	J&J	Johnson & Johnson Inc
BRBOOTS	Boots Co.	KODAK	Eastman Kodak Co.
BRIST-MY	Bristol-Myers Co.	KYOWA-HK	Kyowa Hakko Kogyo
CALBIO	California Biotechnology Inc.	LIPOTECH	Liposome Technology Inc.(CTI)
CAMR	Camr	LRC	London Rubber Co.(LRC) Int.Plc.
CARDO	Cardo A.B.	MARION	Marion Laboratories
CELLTECH	Celltech Group PLC	MEIJI-SK	Meiji Seika Kaisha Ltd.
CETUS	Cetus	MERCK	Merck & Co. Inc
CHIRON	Chiron Corp.	MITSUBIS	Mitsubishi Corp
CIBA-G	Ciba-Geigy A.G.	MITSUI	Mitsui Group
CNTS	CNTS	MONSANTO	Monsanto Co.
COLLAGEN	Collaborative Genetics Corp.	MORISHIT	Morishita Pharmaceutical
COLLARES	Collaborative Research Inc.	NISSAN	Nissan Motor Co.Ltd.
CONNAUGH	Connaught Biosciences Inc.	NORDISKG	Nordisk Gentofte A.S.
CORNING	Corning Glass Works	NOVO-IND	Novo Industri A.S.
CYTOGEN	Cytogen Corp.	NPM	Nederlandse Participatie Mij.
DADE	Dade	ONO	Ono Pharmaceutical Co.
DAINIPPH	Dainippon Pharmaceutical Co.Ltd.	ORGANOGN	Organogen
DAMON-B	Damon Biotech	OTSUKA	Otsuka Pharmaceutical Co.Ltd.
DKB	Dai-Ichi Kangyo Bank (DKB) Group	PANDEX-L	Pandex Labs
DOW	Dow Chemical Co.	PARNIB	Participatiefonds NIB (Parnib)
DUPONT	Du Pont de Nemours	PFIZER	Pfizer Inc.
ELF-AQUI	Elf Aquitaine	PHARMACI	Pharmacia A.B.
ELILILLY	Eli Lilly & Co.	PIERREL	Pierrel SpA.
ENI	Ente Nazionale Idrocarburi (ENI)	PROCOR-N	Procordia Nova A.B.
ENZO-BIO	Enzo Biochem	PROMEGAB	Promega Biotec
FUJI-HI	Fuji Heavy Industries Ltd.	RABO-BVF	Rabobank Biotech Venture Fund
FUJISAWA	Fujisawa Pharmaceutical Co LTD	RECORDAT	Recordati Industria Chimica E Farmaceutica
FUJIZOKI	Fujizoki Pharmaceuticals	REVLON	Revlon Group

Label	Company Name	Label	Company Name
RHONE-P	Rhône-Poulenc	SYNTEX	Syntex Corp.
SAGAMI	Sagami Chemical Research	TAIHO	Taiho Pharmaceutical Co LTD
SANDOZ	Sandoz A.G.	TAKARA	Takara Shuzo
SANKYO	Sankyo Co.	TAKEDA	Takeda Chemical Industries LTD
SANWA	Sanwa Group	TANABE	Tanabe Seiyaku Co.
SCHERING	Schering A.G.	TOYOBO	Toyo Boseki (Toyobo) Co.Ltd.
SCH-PLOU	Schering-Plough Corp.	TOYOSODA	Toyo Soda (Tosoh) Corp.
SHELL	Shell Plc./N.V.	TRANSGEN	Transgène
SHIONOGI	Shionogi & Co.Ltd	UN-TECHN	United Technologies Corp.(UTV)
SIB/IA	Salk Institute Biotechnology / IA	UPJOHN	Upjohn Co.
SINO-GEN	Sino Genetic	VINELAND	Vineland Laboratories
SMKB	SmithKline Beckman Corp.	WARNER-L	Warner-Lambert Co.
SQUIBB	Squibb Corp.	WELLCOME	Wellcome Group
STERLING	Sterling Drug	WEYERH	Weyerhauser
SUMITOMO	Sumitomo Corp	WR.GRACE	W.R. Grace
SUNTORY	Suntory Ltd	YAMANOUC	Yamanouchi Pharmaceutical Co.Ltd.
SYNERGEN	Synergen Inc.	YOSHITOM	Yoshitomo Pharmaceutical

Table 1 A comparison of the top ten firms with the most R&D partnerships in pharmaceutical biotechnology in 1975-77, 78-80, 81-83, 84-86, 87-89, 90-92, 93-95, 96-99 (numbers in brackets).

1975-77		1978-80		1981-83		1984-86	
Ciba-Geigy	(3)	Institut Pasteur	(4)	Genentech*	(9)	Genentech*	(11)
Marion Laboratories	(3)	Ciba-Geigy	(4)	Biogen*	(8)	Biogen*	(11)
Procordia Nova	(2)	Genex*	(4)	Genetics Systems Corp*	(5)	Johnson & Johnson	(10)
Bayer	(1)	Genentech*	(3)	Collaborative Research*	(5)	Chiron*	(10)
Böhringer-Ingelheim	(1)	Baxter-Travenol Labs	(2)	Syntex*	(5)	Pharmacia	(9)
Chugai Pharmaceutical	(1)	Elf Aquitaine	(2)	AMGen*	(4)	Dai-Ichi Kangyo Bank (DKB) Group	(7)
Genentech*	(1)	Genetics Systems*	(2)	Cetus*	(4)	Procordia Nova	(7)
Laboratoires Servier	(1)	Johnson & Johnson	(2)	Green Cross	(4)	Eastman Kodak	(7)
Merck & Co	(1)	Procordia Nova	(2)	Mitsubishi	(4)	Sumitomo	(7)
Sandoz	(1)	Rhône-Poulenc	(2)	Genex*	(3)	Hoechst	(6)

Source: MERIT-CATI databank.

* Companies with an asterisk added - * - indicates that it is a Dedicated Biotechnology Firm (DBF). Otherwise, it is a pharmaceutical company.

Table 1 continued. A comparison of the top ten firms with the most R&D partnerships in pharmaceutical biotechnology in 1975-77, 78-80, 81-83, 84-86, 87-89, 90-92, 93-95, 96-99 (numbers in brackets).

1987-89		1990-92		1993-95		1996-99	
American Cyanamid	(9)	Merck & Co	(8)	Chiron*	(19)	Roche Holding	(32)
Chiron*	(7)	Ciba-Geigy	(7)	Ciba-Geigy	(18)	SmithKline Beecham	(18)
Johnson & Johnson	(7)	Eli Lilly & Co	(7)	SmithKline Beecham	(16)	Bristol-Myers Squibb	(16)
British Biotech*	(7)	SmithKline Beecham	(6)	Hoechst	(13)	Eli Lilly & Co	(15)
California Biotechnology*	(6)	Dow Chemical	(6)	Glaxo Holdings	(12)	Pfizer	(15)
Dow Chemical	(6)	Genentech*	(4)	Pfizer	(12)	Rhône-Poulenc	(13)
SmithKline Beckman	(6)	GeneLabs*	(4)	Rhône-Poulenc	(10)	Merck & Co	(11)
Merck & Co	(6)	Eastman Kodak	(4)	Eli Lilly & Co	(10)	Oxford Molecular Group	(11)
Hoffmann-La Roche & Co	(6)	Glaxo Holdings	(4)	Johnson & Johnson	(9)	Glaxo Wellcome	(11)
Sandoz	(6)	Enzon	(4)	Glaxo Wellcome	(9)	Arqule	(11)

Source: MERIT-CATI databank.

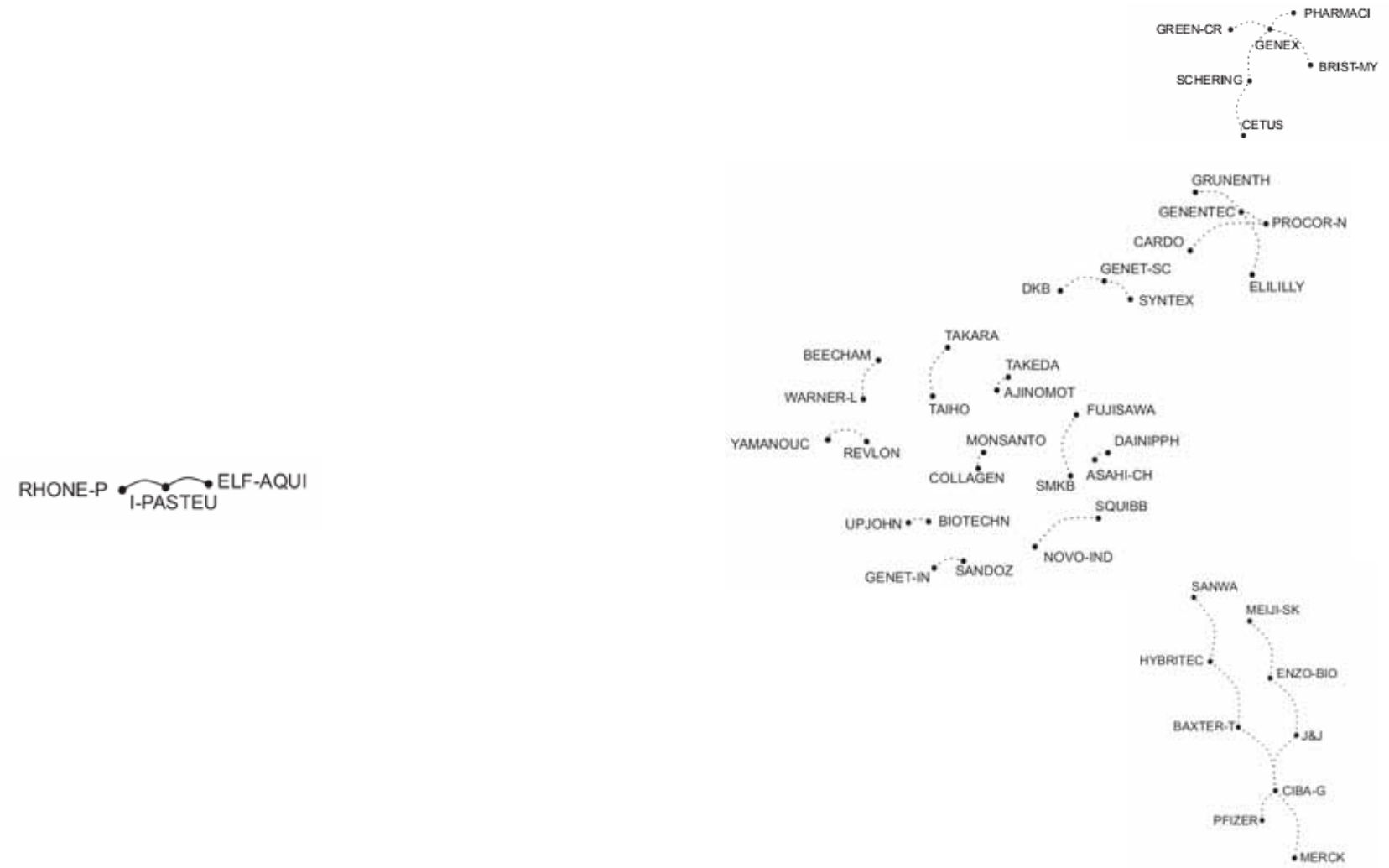

Figure 1 Inter-firm R&D partnerships amongst cooperating companies in pharmaceutical biotechnology, 1978-80; source: MERIT-CATI.

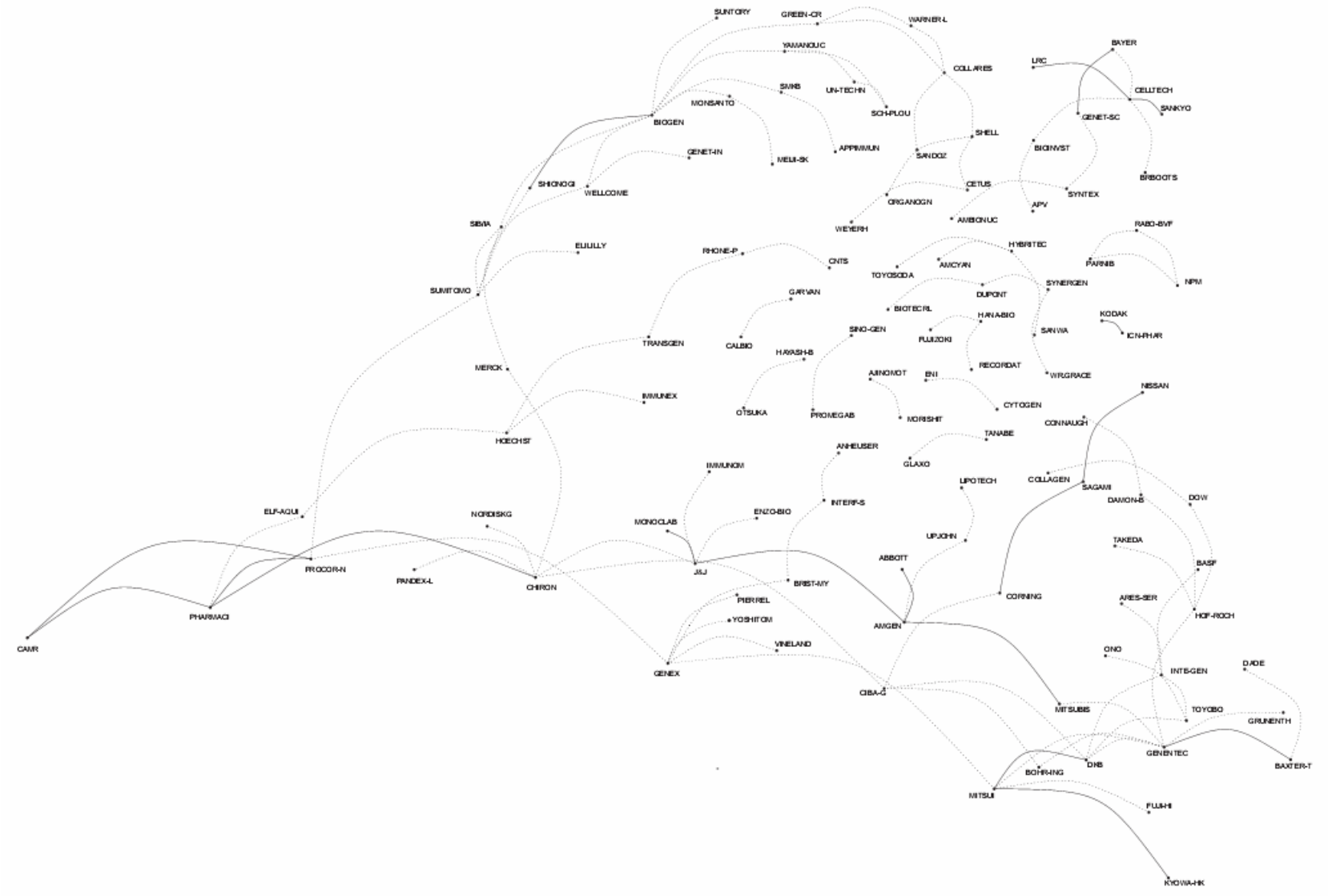

Figure 2 Inter-firm R&D partnerships amongst cooperating companies in pharmaceutical biotechnology, 1983-85; source: MERIT-CATI.

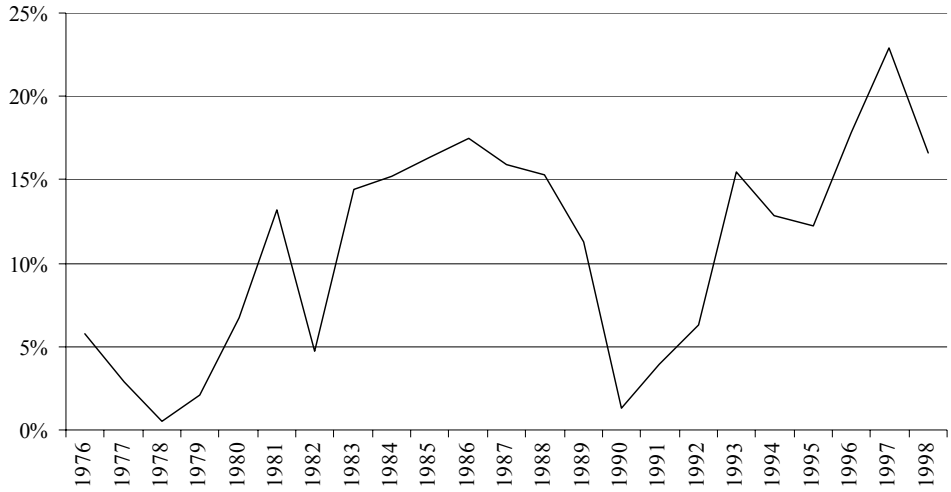

Figure 3 Changes in network centralization, three year moving averages, 1975-99; source: UCINET VI.

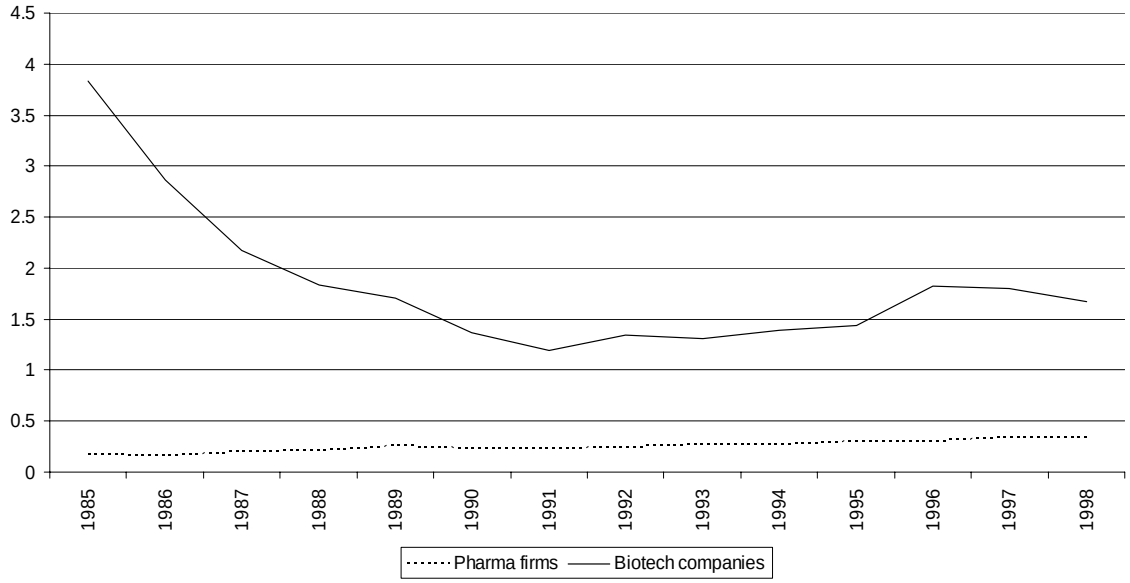

Figure 4 R&D expenses as a proportion of selling expenses for both pharmaceutical companies and biotechnological firms, 1985-1998.