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INTER-FIRM R&D NETWORKS IN THE GLOBAL PHARMACEUTICAL BIOTECHNOLOGY INDUSTRY DURING 1985–1998: A CONCEPTUAL AND EMPIRICAL ANALYSIS

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Inter-firm R&D Networks in the Global Pharmaceutical Biotechnology Industry during 1985–1998: A Conceptual and Empirical Analysis*

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Abstract

This paper analyses a large database on inter-firm R&D cooperation formed in the pharmaceutical biotechnology industry during the period 1985–1998. The results indicate that network size largely grows, whereas the density of the network declines during the periods. In the network analysis that emphasizes individual structural positions, the empirical results show that small biotechnological companies had a crucial bridging role for the large pharmaceutical firms in the second half of the 1980s. In the 1990s, the bridge role of biotechnology companies became less important and established pharmaceutical companies developed into dominant start players with many collaborators while holding central roles in the research network. The current analysis also shows that degree-based and betweenness-based network centralization are both low implying that the overall positional advantages are relatively equally distributed in the inter-firm R&D network of the pharmaceutical biotechnology industry.

JEL Classification: C88, D85, L24, L65, O32

Key Words: R&D networks; Pharmaceutical biotechnology; Network analysis; Conceptual centrality; Network visualization software

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1 Introduction

The main purpose of this paper is to provide a conceptual and empirical analysis of inter-firm research and development (R&D) networks in the pharmaceutical biotechnology industry. In this context, the research is conducted in pharmaceutical biotechnology R&D cooperation, formed by large established pharmaceutical firms and a range of biotechnology companies, during three different time periods (1985–1989, 1990–1994, and 1995–1998[1]). The analysis will be based on methods used in Social Network Analysis (Wasserman and Faust, 1994) and supported by the network analysis and visualization programs of Ucinet (Borgatti *et al.*, 2002) and Pajek (de Nooy *et al.*, 2005). The data source that has been implemented in this paper is the Recombinant Capital database[2].

To understand the cooperation between pharmaceutical companies and biotechnology firms, it is essential to study the developments of these industries in the past. The modern pharmaceutical industry which emerged as an R&D-intensive industry has a long history. Early efforts to implement R&D in the pharmaceutical industry can be traced back to the late 19th century and were the results of cooperation between individual scientists and industry (Galambos and Sturchio, 1998). For instance, the German chemical company Bayer, which is regarded as one of the first modern pharmaceutical companies, successfully developed aspirin in cooperation with scientists in 1899 and was later selling it all over the world (Verg, 1988). In the 1940s, many more industries became actively involved in pharmaceutical research and some of them are actually current industry leaders: e.g., Bayer and Hoechst from Germany, Beecham and Pfizer from the UK and Eli Lily, Merck and Abbott Laboratories from the US (Roijakkers, 2003). These companies are to a great extent dependent on new research of medicines, cooperation with scientists, and effective patent protection. The business

[1] For the data analysis, 3 periods of 5 years were considered but could not be fully exercised due to missing data from the second half of 1999. A test analysis conducted for the first half of 1999 revealed that the missing data influenced the results. Thus, the year 1999 was completely excluded from the analysis in this paper.

[2] Recombinant Capital is a San Francisco Bay Area-based consulting firm specializing in biotechnology alliances and reputed to have built some of the largest and most detailed biotech business intelligence databases in the world. Its clients include biotechnology and pharmaceutical companies, plus several universities active in the biotechnology area.

of biotechnology started much later than that of pharmaceutics. It emerged around the 1980s and was triggered by the discovery of two scientists at the University of California and the University of Stanford in 1973. These scientists developed a recombinant DNA technology, which became widely known as genetic engineering. The advent of biotechnology had an immense impact on the pharmaceutical industry since it provided various opportunities for innovation with new research methods. Large pharmaceutical companies soon perceived the importance of innovation and established access to the new technology by creating different forms of inter-firm partnerships with the biotechnology firms. These inter-firm partnerships added a completely new element to the networks of academia-industry cooperation which traditionally characterized the pharmaceutical industry (Roijakkers, 2003).

Established pharmaceutical companies and newly founded biotechnology firms cooperate on R&D through a specific set of organizational modes of cooperation, which is primarily related to two basic categories: contractual modes, such as R&D contracts and joint R&D agreements, and equity-based agreements, such as research joint ventures and minority holding (Hagedoorn and Roijakkers, 2006). During 1985–1998, as more and more firms became aware of the value of cooperation, the pharmaceutical biotechnology R&D network gradually changed from isolated pairs of cooperating companies with only small multi-collaborator networks to a large complex network with numerous interrelated firms (Figures 1 and 2). This intriguing change in the pharma-biotech partnership was also observed by Hagedoorn and Roijakkers (2006). Their research indicated an overall annual growth in the number of newly established R&D partnerships. However, cooperating firms within the same R&D network do not obtain equal opportunities and advantages. The firms that are situated in a favoured structural position access information much more easily and rapidly and can control the circulation of information of others, and thus attain a central role. In contrast, the firms that are located on the network periphery face plenty of structural disadvantages. There are three basic approaches to the centrality of individual positions as summarized by Wasserman and Faust (1994): degree, closeness, and betweenness. Degree centrality takes only direct neighbours of an actor into account and if the indirect contacts need to be considered, we look upon closeness centrality, which measures the distance from one actor to all other actors in the network. The closeness

centrality of an actor is higher if the total distance to all other actors is shorter. The importance of an actor to the circulation of information is captured by the concept of betweenness centrality. An actor with higher score of betweenness is more likely a link in more information chains between other actors and therefore has an important role as an intermediary in the communication network. Measures of network centralization correspond to the approaches in actor centrality and can be computed from the centrality scores of the actor within the network. If a network contains very central actors as well as very peripheral ones, the network would have a high centralization score (de Nooy *et al.*, 2005). Note that in the present paper, centrality will be used to refer to positions of individual actors within the network, whereas centralization will be used to characterize an entire network. Another widely used network-level index is density, which is simply the proportion of all possible ties that are actually present and inversely related to the network size.

Network characterization, as conducted in the social network literature, usually embodies several aspects. In this paper, four aspects are considered: network size, network density, actor centrality and network centralization. We will focus on these four characteristics of the network to construct a conceptual and empirical analysis for the inter-firm R&D cooperation in pharmaceutical biotechnology. This paper sees inter-firm cooperation in the pharmaceutical biotechnology industry from a different angle than Hagedoorn and Roijakkers (2006). In terms of changes of major players, we partly confirm the results of these authors. However, we use an entirely different approach by employing measures and indices for a thorough and detailed analysis of structural position change at both the actor level and the network level. The remaining part of the paper is structured as follows. The second section describes the network evolution of pharmaceutical biotechnology industry in three time periods and the insights of the network density. Section 3 discusses relevant features and empirical findings with regard to actor centrality, and then identifies the putative central players in the inter-firm R&D network in different time periods. Section 4 provides the conceptions of the network centralization and then applies the conceptual ideas into the empirical analysis of R&D network in the global pharmaceutical biotechnology industry. In the final section different perspectives on the nature of firm relation are discussed and the main conclusions of this paper are drawn.

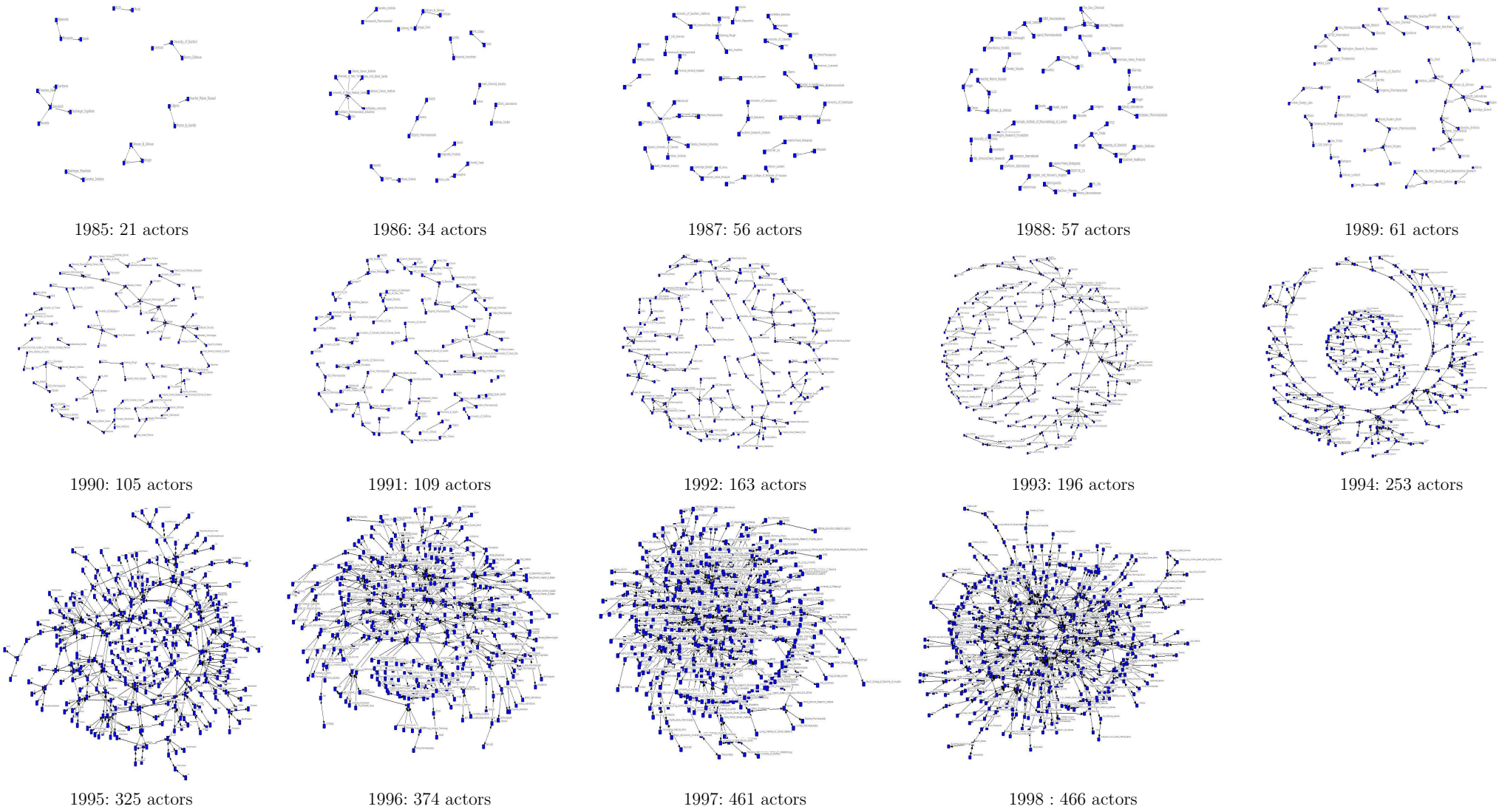


Figure 1: Inter-firm R&D networks amongst cooperating companies in pharmaceutical biotechnology, 1985–1998; *source:* Recombinant Capital.

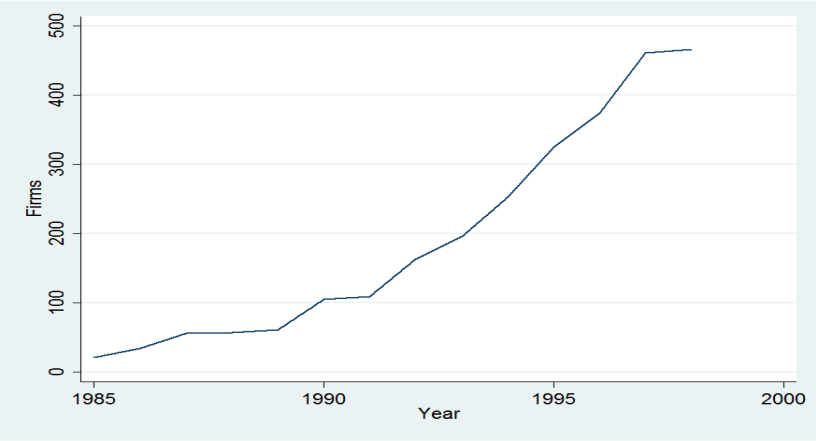


Figure 2: The growth of firms in pharmaceutical biotechnology R&D network, 1985–1998; *source*: Recombinant Capital.

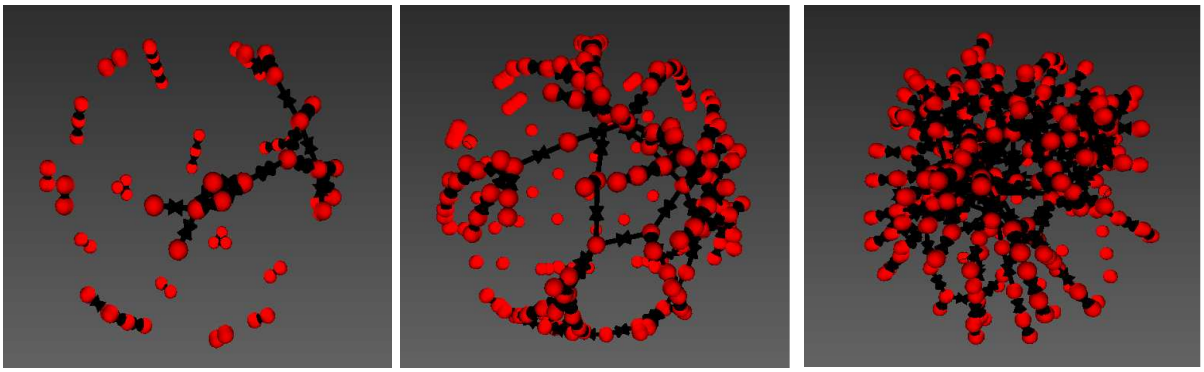
2 Network Size and Density

2.1 Network Evolution

The network size is an important element in the analysis of a network, which can be indexed simply by counting the number of actors. In undirected networks there are $g(g-1)/2$ unordered pairs of actors, where g is the number of actors. The number of possible relationships then grows as the number of actor increases. Thus, the range of possible social structures changes as the network size increases (Hanneman and Riddle, 2005). For instance, in a larger network, an actor can receive a more diverse and complete set of resources from his own network (Burt, 2000).

The pharmaceutical biotechnology industry experienced a significant change in its network size and structure over three different time periods as presented in Figure 3. During the period 1985–1989, large pharmaceutical firms built up absorptive capacity for assimilating new biotechnology knowledge and established joint R&D agreements with newly founded biotechnology companies. As a result, by 1989, 61 firms were involved in this research network of which 16 were relatively well connected, whereas there were numerous one-on-one ties and some isolated research clusters (Figure 1 and 4). For the period 1990–1994, Figure 3 shows a denser, more connected research

network in which more than 250 firms were engaged in a multitude of joint R&D agreements. This is because of common research efforts and many newly established joint R&D agreements between established large pharmaceutical firms and new biotechnological companies during these years. Although the majority of firms were connected to most other firms through many partnerships, there were still a few isolated firms cooperating amongst themselves, not linking to any of the other network participants. However, in the second half of the 1990s, a very large, extremely dense R&D network had developed involving 466 companies (by 1998) that were nearly all connected to each other by numerous direct and indirect ties (Figure 1 and 3). The R&D network in pharmaceutical biotechnology industry which had undergone these transitions gradually developed into one of the most successful communication networks in high-tech industries.



1985–1989 **1990–1994** **1995–1998**

Figure 3: Inter-firm R&D 3D networks amongst cooperating companies in pharmaceutical biotechnology, 1985–1989, 1990–1994 and 1995–1998; s*ource:* Recombinant Capital.

2.2 Network Density

The network size has an impact on structural network characteristics such as density. In general, the larger the network group is, the lower is its density. Density is calculated as the number of present connections between actors divided by the number

of potential connections between actors in a network, expressed as the proportion of the maximum possible numbers of ties (de Nooy *et al.*, 2005). Let T denote the ties that are present, g denote the number of actors, then the density in an undirected network is

$$Density = \frac{T}{g(g-1)/2}. \tag{1}$$

Based on this formula, the network density for the pharmaceutical biotechnology industry in three time periods was calculated with Ucinet as presented in Table 1. In the period 1985–1989, the density of the inter-firm network is very low at 0.0268, which indicates that only 2.68% of all the possible ties are present. In the first half of the 1990s, this number drops sharply to 0.75% and finally falls below 0.6% in 1998. Following this declining density, global pharmaceutical biotechnology firms actually experienced a significant rise in the size of R&D network at an average rate of 29.08%. This is due to the fact that there is a limit to the number of putative collaborators for each firm and hence the network density is to a large degree reduced, although the network size is enlarged.

Table 1: Density in the pharmaceutical biotechnology inter-firm R&D network in 1985–1989, 1990–1994 and 1995–1998

Period	Density
1985–1989	0.0268
1990–1994	0.0075
1995–1998	0.0054

Source: Recombinant Capital.

Density also provides insights into the speed at which information and knowledge diffuses among the actors within a network (Hanneman and Riddle, 2005). Low densities as in Table 1 indicate the potentiality of the social constraint, which could be a low level of trust, a low need for regular interaction, or other factors that create "distance" between the firms (Allee and Schwab, 2011). As the R&D network in

pharmaceutical biotechnology is widely expanded all over the world during the period 1985–1998, the geographic diversification of the cooperation might also be a likely factor for the low density underlying the social constraint.

3 Actor Centrality

This section will turn to another aspect of the network analysis, centrality, which can be used to characterize the actors' positions by measures of degree, closeness and betweenness. Based on the conceptions and empirical findings with regard to these three measures, putative central players in pharmaceutical biotechnology R&D networks are identified for different time periods.

3.1 Degree Centrality

One effective measure to centrality is the degree, which is based on the idea that actors are central in a communication network if information can easily reach them. The actors with high degree centrality would have more social ties to access information and constitute social capitals, and thus they are at more central positions than others. In contrast, actors with low degrees are peripheral in the network. Even if such an actor decides to leave the network, it would hardly affect present ties. According to Wasserman and Faust (1994), a degree-centrality measure for an individual actor should be the degree of the node $d(n_i)$, which is simply the number of an actor's direct neighbours. Let $C_D(n_i)$ denote an actor-level degree centrality index, then

$$C_D(n_i) = d(n_i). \tag{2}$$

Assume the network size is g, this index equals $g-1$ at a maximum and attains the value of zero at a minimum. In a directed network, we must distinguish the number of arcs received by an actor (indegree) and the number of arcs sent (outdegree). However,

in terms of inter-firm R&D cooperation, data structure is symmetric and hence each firm is simply characterized by its degree. The higher the degree of a firm, the larger and quicker information will reach this firm, and the more central is this firm. Table 2 shows the firms with the highest degrees in pharmaceutical biotechnology in the three time periods.

Table 2: A comparison of firms with the highest degrees in pharmaceutical biotechnology in 1985–1989, 1990–1994 and 1995–1998 (number of degree in brackets)

	1985–1989		1990–1994		1995–1998	
1.	Abbott Laboratories	(5)	University of Stanford	(10)	Schering Plough	(16)
2.	Genentech	(5)	Eli Lilly	(9)	Affymetrix	(16)
3.	Bayer	(4)	Chiron	(8)	Pfizer	(16)
4.	Johnson & Johnson	(4)	Affymetrix	(7)	SmithKline Beecham	(16)
5.	Baxter International	(3)	Rhone-Poulenc	(7)	Bristol-Myers Squibb	(14)
6.	Chiron	(3)	Targeted Genetics	(7)	Bayer	(13)
7.	Genetics Institute	(3)	University of California	(7)	Eli Lilly	(13)
8.	Merck	(3)	Boehringer Mannheim	(6)	Incyte Pharmaceuticals	(12)
9.	Rhone-Poulenc	(3)	Genentech	(6)	NIH	(12)
10.			Molecular Dynamics	(6)	Novartis	(11)
11.			Novartis	(6)	Roche	(11)
12.			University of Harvard	(6)		

Source: Recombinant Capital.

For the period 1985–1989, Abbott Laboratories and Genentech are each characterized by the highest degree of 5 (Table 2). Hence, they might be regarded as the most central and most important players in this time period. Other firms which share the information with these two seem to distribute the information to others (Figure 4), possibly because they recognize the central positions of Abbott Laboratories and Genentech, and consider it worthwhile influencing other firms in the network. As shown in Figure 4, the top eight firms (Table 2) in the period 1985–1999 are all well connected, whereas Rhone-Poulence belongs to another research cluster and is unable to share information with any of them. In contrast, the firms with the highest degrees (Table 2) in the periods 1990–1994 and 1995–1998 are all connected to each other (Figure 5 and Figure 6), and have much higher scores of degree centrality compared to

that in the period 1985–1989, i.e. the University of Stanford has a degree of 10 in the period 1990–1994, and Affymetrix, Pfizer, Schering Plough and SmithKline Beecham each have 16 direct research partners in the second half of 1990s (Table 2).

3.2 Closeness Centrality

The closeness centrality of an actor focuses on how close an actor is to all other actors in the network. It depends not only on direct ties, but also on indirect ties, especially when any two actors are not adjacent. The actor with high centrality scores can reach all the other actors in a minimum number of steps and thus communicates more efficiently with others. Closeness centrality is measured as a function of geodesic distances but inversely related to distance: when geodesic distance increases, the closeness centrality scores decrease. Let $d(n_i, n_j)$ denote the number of lines in the geodesic linking actors i and j, $\sum_{j=1}^{g} d(n_i, n_j)$ denote the total distance that i is from all other actors. The actor-level of closeness centrality index is then

$$C_C(n_i) = \left[\sum_{j=1}^{g} d(n_i, n_j) \right]^{-1} \quad \text{where } j \neq i. \tag{3}$$

Assume the network size is g, its maximum value is $(g-1)^{-1}$ and the minimum value is zero. However, if the network is not strongly connected, closeness centrality could fail to be calculated since the distance between disconnected actors is infinite. That is the case in the pharmaceutical biotechnology R&D network, so instead of using closeness index, actor's closeness centrality can be calculated with reach closeness, which is an index of reach distance from each actor to all others. A smaller reach distance yields a higher closeness centrality score. Table 3 presents a list of pharmaceutical biotechnology firms with the highest reach closeness over three time periods.

Table 3: A comparison of firms with the highest reach closeness in pharmaceutical biotechnology in 1985–1989, 1990–1994 and 1995–1998 (number of reach closeness in brackets)

	1985–1989		1990–1994		1995–1998	
1.	Abbott Laboratories	(9.7)	University of Stanford	(43.7)	Schering Plough	(127.7)
2.	Johnson & Johnson	(9.5)	University of Harvard	(42.4)	Incyte Pharmaceuticals	(124.0)
3.	Chiron	(9.3)	Procept	(41.6)	Bayer	(119.4)
4.	Bayer	(9.2)	Chiron	(41.0)	SmithKline Beecham	(117.0)
5.	Genentech	(8.8)	Novartis	(40.8)	Affymetrix	(116.7)
6.	Merck	(8.0)	Ariad Pharmaceuticals	(39.9)	Pfizer	(115.5)
7.	Baxter International	(7.8)	Genentech	(39.8)	Novartis	(113.7)
8.	Genetics Institute	(7.8)	Affymetrix	(37.3)	OncorMed	(113.5)
9.	Anesta	(6.7)	University of California	(37.0)	Zeneca	(113.2)
10.	Biogen	(6.7)	NIH	(36.8)	Eli Lilly	(112.0)
11.	Cambridge Biotech	(6.7)	Bristol–Myers Squibb	(36.8)	Abgenix	(111.8)
12.	ALZA	(6.7)	Alexion Pharmaceuticals	(36.7)		
13.			Ligand Pharmaceuticals	(36.6)		
14.			Eli Lilly	(36.5)		

Source: Recombinant Capital.

The results in Table 3 are to some degree similar to those of the earlier analysis of degree centrality: in the periods 1985–1989, 1990–1994 and 1995–1998, Abbott Laboratories, University of Stanford and Schering Plough seem to be most central players respectively in both Table 2 and Table 3. However, Schering Plough has a much higher centrality score (127.7) in the period 1995–1998 compared to Abbott Laboratories (9.7) in the period 1985–1989 and University of Stanford (43.7) in the first half of 1990s. Those firms with the highest closeness scores in Table 3 are much easier and quicker to reach the information in the network since they are closer to all other firms. But if one of them leaves the network, this would have a strong impact on the overall network structure. If Abbott Laboratories, for instance, had quit from the pharmaceutical biotechnology network in the period 1985–1989, Anesta, Biogen and Cambridge Biotech would have been completely isolated from the knowledge flow (Figure 4). If the University of Stanford had ceased all cooperations with its research partners in the period 1990–1994, the University of Washington, University of

California, Affymetrix, Lawrence Livermore National Laboratory and Molecular Dynamics would only have cooperated amongst themselves but would have been isolated from the large research network (Figure 5). Furthermore, if the University of Harvard had left the network, the entire R&D network in the period 1990–1994 would have been split into two separate parts (Figure 5).

3.3 Betweenness Centrality

Degree and closeness centrality that have been applied earlier are mainly based on the reachability of an actor within a network. Another factor that could be considered for centrality is betweenness, which regards an actor as more central when he is more important as an intermediary in the communication network. More specifically, the more actors depend on this actor to make connections with others, the more important is the role of this actor in the information flow. Thus, an actor with a high betweenness centrality score is strongly needed in a network as a link in the chains of contacts that help distribute information. In line with Wasserman and Faust (1994), let g_{jk} denote the number of geodesics linking actor j and k, $g_{jk}(n_i)$ denote the number of geodesics linking the actors j and k that contain actor i. The actor betweenness index for n_i is then given by

$$C_B(n_i) = \sum_{j<k} \frac{g_{jk}(n_i)}{g_{jk}} \qquad \text{for } i \neq j \neq k\,. \tag{4}$$[3]

This index takes a minimum value of zero and a maximum[4] of $(g^2 - 3g + 2)/2$. Based on this approach, the firm's betweenness in pharmaceutical biotechnology in different time periods was calculated with Ucinet as presented in Table 4.

[3] According to Wasserman and Faust (1994), $1/g_{jk}$ is the probability that a message passes along any one of the actor j and k, and thus $g_{jk}(n_i)/g_{jk}$ is the probability that actor i falls on a random selected geodesic linking actor j and k, under the assumption that geodesics are equally likely to be chosen for the path.

Table 4: A comparison of firms with the highest betweenness in pharmaceutical biotechnology in 1985–1989, 1990–1994 and 1995–1998 (number of betweennesses in brackets)

	1985–1989		1990–1994		1995–1998	
1.	Chiron	(54.0)	University of Harvard	(6649.5)	Schering Plough	(12711.8)
2.	Bayer	(50.0)	Procept	(5810.5)	Incyte Pharmaceuticals	(9540.1)
3.	Johnson & Johnson	(47.0)	Genentech	(5160.7)	SmithKline Beecham	(9453.0)
4.	Abbott Laboratories	(39.0)	Chiron	(5041.0)	Affymetrix	(8421.4)
5.	Genentech	(27.0)	Ariad Pharmaceuticals	(4414.3)	Bayer	(7956.8)
6.	Merck	(27.0)	University of Stanford	(4326.8)	Pfizer	(7106.9)
7.			Bristol–Myers Squibb	(4209.0)	Novartis	(6463.9)
8.			Ligand Pharmaceuticals	(3876.0)	NIH	(6088.6)
9.			Axys Pharmaceuticals	(3520.7)	Bristol-Myers Squibb	(5836.3)
10.			Eli Lilly	(3367.0)	Eli Lilly	(5625.7)

Source: Recombinant Capital.

By the measure of betweenness centrality, Chiron is clearly the most important mediator in 1985–1989 (Table 4). It can be seen from Figure 4 that Chiron plays an important role in the communication between Merck and Xenova. In contrast, Baxter International and Genetics Institute are less important because even if they both failed to pass on information, Bayer could directly connect to Genentech and the communication chain between Merck and Xenova would still be intact. In the period 1990–1994, a number of universities joined the pharmaceutical biotechnology R&D network and began to play a crucial role as intermediaries. For instance, the Universities of Harvard and Stanford are the two most important universities in terms of betweenness centrality (Table 4). They are both pivotal to the communication between the University of California and StressGen Biotechnologies (Figure 5). The University of Washington is less important because even if it failed to pass on information, the University of California could still contact the University of Stanford

[4] Since maximum betweenness centrality can be obtained only when there is an actor n_i that falls on all geodesics of length greater than one, the upper limit of $C_B(n_i)$ is simply to compute the number of paths connecting pairs of actors where n_i falls on the path between them. We know if all actors are reachable, there are $g(g-1)/2$ paths connecting the unordered pairs in the network and of these, $g-1$ are connected to n_i, so the maximum betweenness centrality is then $\max C_B(n_i) = g(g-1)/2-(g-1) = (g-1)(g-2)/2 = (g^2-3g+2)/2$.

directly or via other cooperating firms (e.g. Lawrence Livermore National Laboratory, Molecular Dynamics and Affymetrix) and the communication chain between the University of California and StressGen Biotechnologies would remain intact. In contrast, the Universities of Florida and South Florida hardly fall on any geodesic pathways between other pairs of firms. They only form a small research cluster with CV Therapeutics at an isolated network position that seems to be completely disconnected from knowledge generated outside this small cluster (Figure 5). For the second half of the 1990s, Schering Plough, which is the most central firm concerning degree centrality (Table 2) and closeness centrality (Table 3), appears to be the most important firm as well when geodesic flows are taken into account (Table 4). Besides, the betweenness centrality score of Schering Plough (12711.8) is twice as high as that of the University of Harvard in the period 1990–1994 and tremendously higher than the betweenness centrality score of Chiron (54.0) in the second half of the 1980s. The relationship among firms has developed into a more complex and multifaceted form over the years.

3.4 Putative Central Actors

Based on the measures that have been discussed above, there are three advantages for a firm to be the central actor in network relations. First of all, they have more ties (degrees) than others, that is, they have greater opportunities to obtain information than other firms since they have more alternative choices. This autonomy makes them less dependent on any specific other firms, and hence more central. Secondly, when they are at a more central position in the network, they are more reachable by other firms at shorter path lengths. This structural advantage makes them more independent and faster in reaching others. The third advantage is that they are situated on more pathways between other pairs of firms. This gives them the capacity to broker contracts among other firms or prevent contracts by isolating other firms. It is not necessary for a central actor to have all the advantages, since they may be located in a position that is advantageous in some ways, and disadvantageous in others (Hanneman and Riddle, 2005). In Table 5—Table 7 the putative central firms in the

pharmaceutical biotechnology R&D network of three time periods are presented based on the information in Table 2 (degree centrality), Table 3 (closeness centrality) and Table 4 (betweenness centrality).

As shown in Table 5, during the period 1985–1989, the majority of firms in the top list are large pharmaceutical companies, such as Bayer and Johnson & Johnson, whereas it also includes some smaller biotechnology companies, such as US-based Genentech and Chiron, which serve as very important connections between distant parts of the network (Figure 4). Baxter International and Genetics Institute do not fall on any geodesic distance between others (Table 5) as discussed in the betweenness centrality above, but they connect to the most central firms, i.e. Genentech and Bayer and are thus able to access new knowledge and technology (Figure 4). Therefore, they are still among the top firms in terms of their direct and indirect relations with others (Table 5).

Table 5: Putative central firms in the pharmaceutical biotechnology R&D network in 1985–1989

		Degree	Closeness	Betweenness
1.	Abbott Laboratories	5	9.7	39
2.	Genentech	5	8.8	27
3.	Bayer	4	9.2	50
4.	Johnson & Johnson	4	9.5	47
5.	Chiron	3	9.3	54
6.	Merck	3	8.0	27
7.	Baxter International	3	7.8	**0**
8.	Genetics Institute	3	7.8	**0**

Note: Baxter International and Genetics Institute are not showing up in the list of players with the highest betweenness (Table 4).

Source: Recombinant Capital.

In the period 1990–1994, Chiron has grown to a medium-sized biotechnological firm (Hagedoorn and Roijakkers, 2006) and is embedded in a denser cluster structure involving eight research partners (Table 6). Being the first biotechnological firm in the

list of putative central actors, Chiron holds an important position in the research network. In this time period the pharmaceutical company Bristol-Myers Squibb has fewer collaborators compared to other putative central firms, but keeps in close contact with all other firms and also plays an important role as mediator within the network (Table 6). So a relatively low degree does not prevent a company from being a central player. The biotechnological firm Affymetrix and the University of California do not fall on the geodesic flows as often as other top players, but they have more research partners and build up strong connections with other firms and can still efficiently access large amounts of information even though they play a less important role as intermediaries.

Table 6: Putative central firms in the pharmaceutical biotechnology R&D network in 1990–1994

		Degree	Closeness	Betweenness
1.	University of Stanford	10	43.7	4326.8
2.	Eli Lilly	9	36.5	3367.0
3.	Chiron	8	41.0	5041.0
4.	Affymetrix	7	37.3	**947.0**
5.	University of California	7	37.0	**639.0**
6.	Genentech	6	39.8	5160.7
7.	University of Harvard	6	42.4	6649.5
8.	Bristol–Myers Squibb	**4**	36.8	4209.0

Note: Affymetrix and University of California are not showing up in the list of players with the highest betweenness (Table 4), and Bristol–Myers Squibb is not in the list of players with the highest degree (Table 2).

Source: Recombinant Capital.

In the final period, from 1995 to 1998, large established pharmaceutical companies, such as Pfizer, SmithKline Beckman, and Bristol-Myers Squibb, form the most central group of firms (Table 7). These firms have become star network players that are embedded in dense local research clusters with many participating partners (Figure 6). An important driving force here was formed by a second wave in the molecular

biological revolution: genetic engineering, which opened up completely new areas for innovation (Gilsing *et al.*, 2008). Also in this time period, most of the important network players are directly connected to the research networks of other large companies and do not depend on small firms to bridge the relations (Figure 6). Besides, as Table 7 shows, Bristol-Myers Squibb and NIH do not have closeness centrality scores that are as high as those of other top firms, but since there is a total of 466 firms by 1998, their scores still belong to the top 10 percent. Thus, this slight disadvantage does not seem to have a strong impact on their favoured structural position.

Table 7: Putative central firms in the pharmaceutical biotechnology R&D network in 1995–1998

		Degree	Closeness	Betweenness
1.	Affymetrix	16	116.7	8421.4
2.	Pfizer	16	115.5	7106.9
3.	Schering Plough	16	127.7	12711.8
4.	SmithKline Beecham	16	117.0	9453.0
5.	Bristol–Myers Squibb	14	**108.5**	5836.3
6.	Bayer	13	119.4	7956.8
7.	Eli Lilly	13	112.0	5625.7
8.	Incyte Pharmaceuticals	12	124.0	9540.1
9.	NIH	12	**100.9**	6088.6
10.	Novartis	11	113.7	6463.9

Note: Bristol–Myers Squibb and NIH are not showing up in the list of players with the highest closeness (Table 3).

Source: Recombinant Capital.

Comparing Table 5, Table 6 and Table 7, the putative central firms in different time periods change a great deal, however, there are some overlapping actors between the different periods. The large and established pharmaceutical company Bayer, for instance, is a central player in two periods (1985–1989 and 1995–1998), and Eli Lily, Affymetrix and Bristol-Myers Squibb are the central firms in the 1990s. Chiron and

Genentech, two of the few companies that succeeded in marketing new biotechnological drugs, were among the most central firms in the first two periods (1985–1989 and 1990–1994). Universities only appear in the first half of the 1990s as central players. As shown in Table 6, there are three universities among the top eight central players on the list, i.e. University of Stanford, University of California and University of Harvard, which highlights the importance of research institutes for the network in this time period. In addition, some similar lists of important players in pharmaceutical biotechnology R&D network have been compiled in other references (Table 1 in Baker et al., 2008; Table 1 in Gilsing et al., 2008; Table 1 in Hagedoorn and Roijakkers, 2006; Table 4.2 in Roijakkers, 2003). Due to different databases, analytical methods, chosen time periods and definitions, the lists of important players greatly differ between these papers but also differ from those identified in the present study (Table 5—Table 7). It is not that one approach is right and the other wrong. Depending on the aims of the analyses, each author may wish to target specific advantages that firms could have within a network. In any case, finding central actors is of crucial importance in understanding the main relations and functions in a social network.

The above section provides insights into the structural development of pharmaceutical biotechnology R&D networks over time by evaluating the importance of particular network participants for the overall structure of the networks. Apart from this individual level, it is useful to study research cooperation at the level of general networks. Thus, the next section will focus on the conceptions of the network centralization and then apply the conceptual ideas into the empirical analysis of R&D network in the pharmaceutical biotechnology industry.

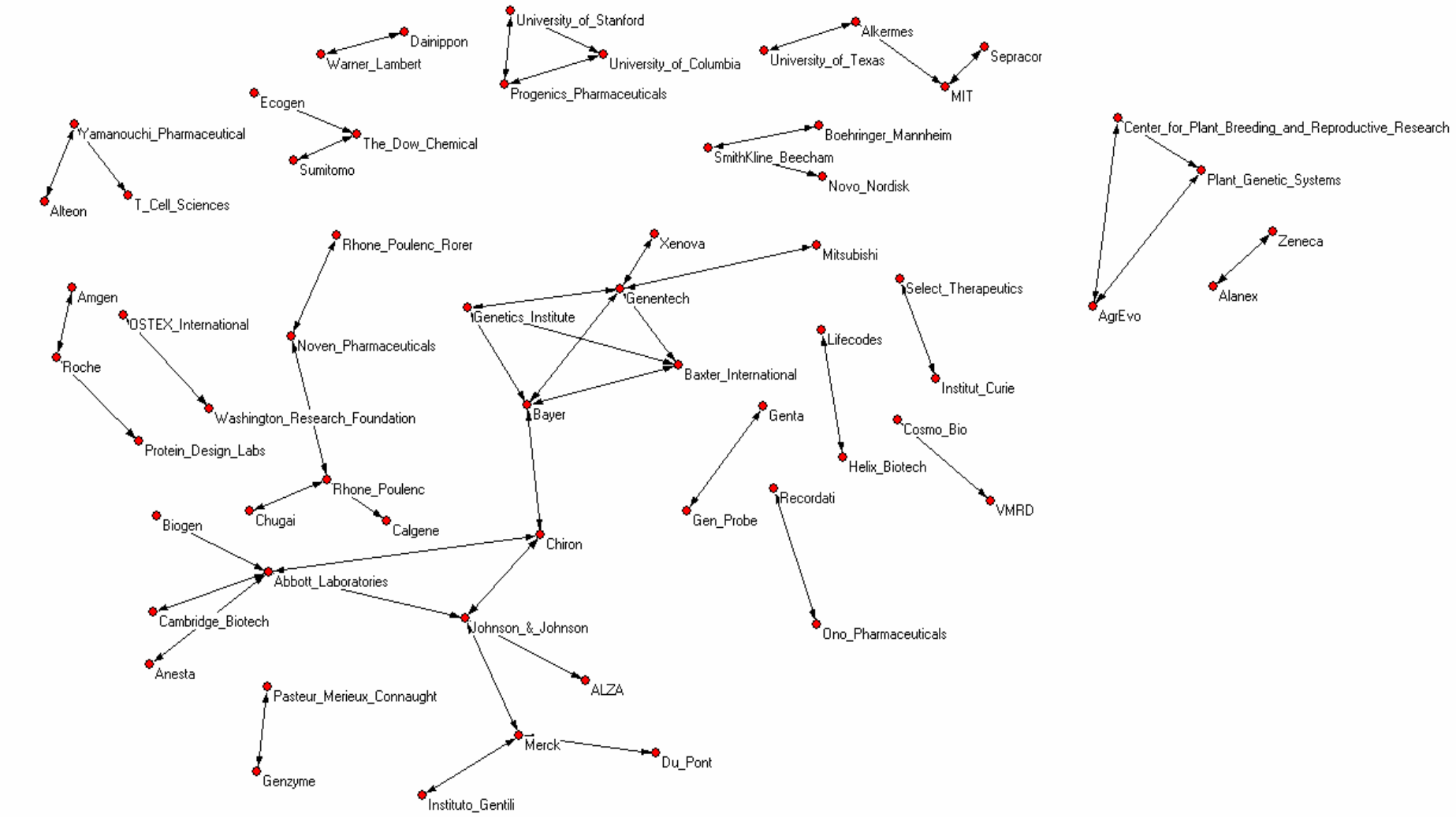


Figure 4: Inter-firm R&D network amongst cooperating companies (61) in pharmaceutical biotechnology, 1985–1989; *source*: Recombinant Capital.

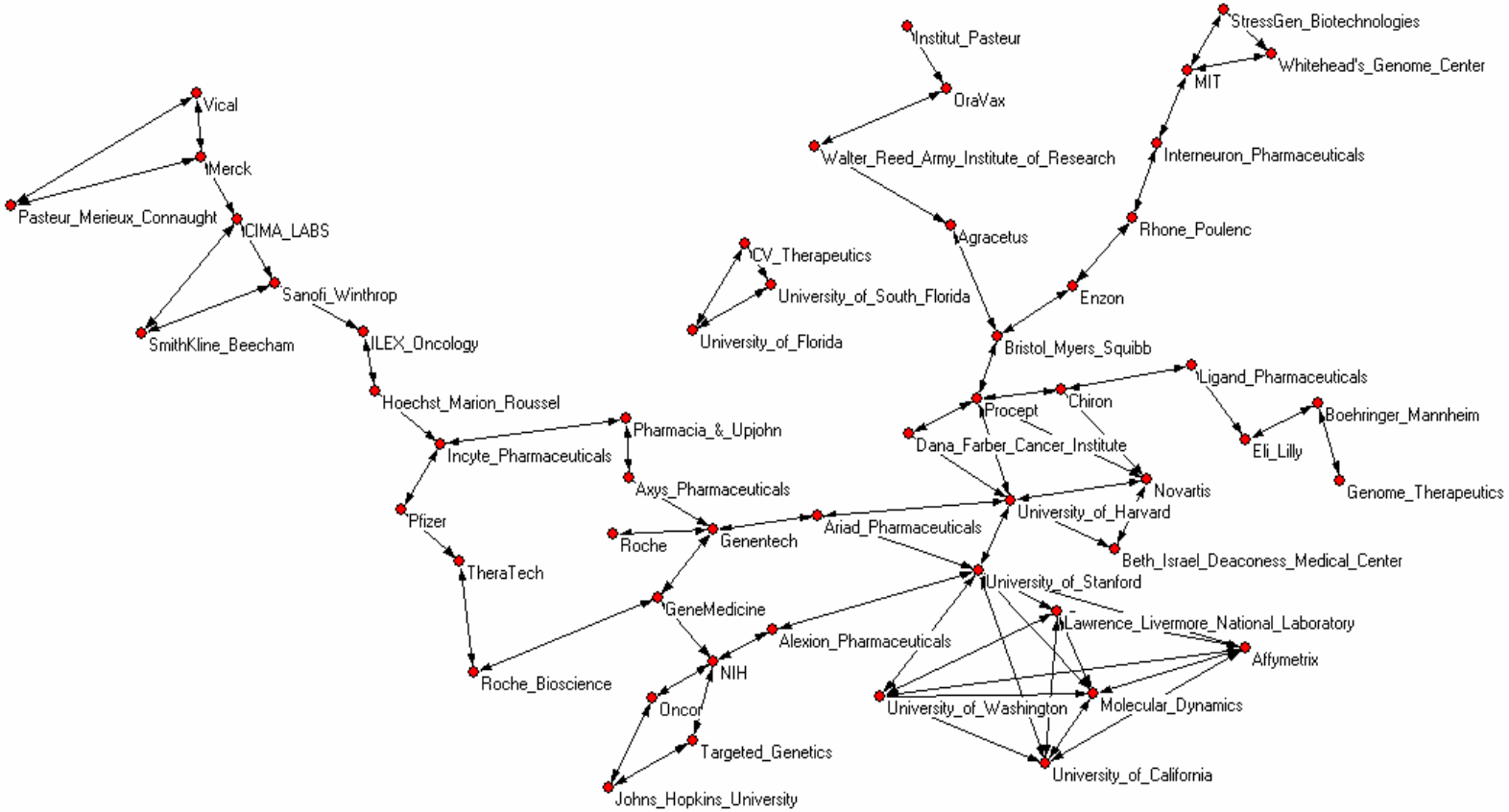


Figure 5: Inter-firm R&D network amongst cooperating companies (53 out of 253) in pharmaceutical biotechnology, 1990–1994; *source*: Recombinant Capital.

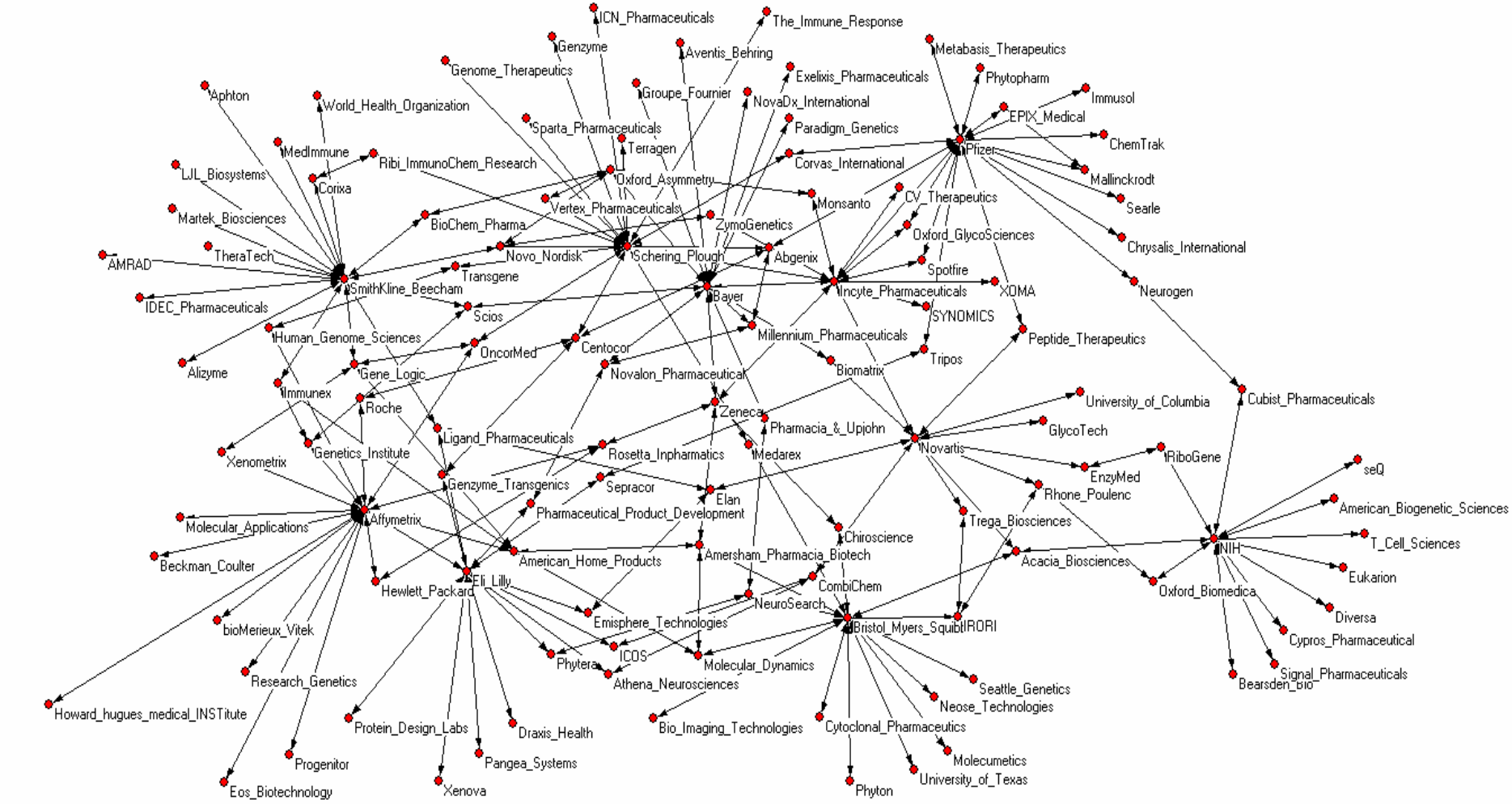


Figure 6: Inter-firm R&D network amongst cooperating companies (125 out of 466) in pharmaceutical biotechnology, 1995–1998; *source*: Recombinant Capital.

4 Network Centralization

Network centralization measures the variability or heterogeneity of the actor centralities. It can be viewed as a measure of how unequal the individual actor values are, to the extent that a single actor is quite central with the remaining actors residing on the periphery of the centralized system. Hence, the centralization measure roughly quantifies the variability, dispersion, or spread of the individual actor indices. Wasserman and Faust (1994) adopted a general mathematical definition for a network-level index of centralization. Let $C_X(n_i)$ denote one of the actor centralities defined earlier, and $C_X(n^*)$ denote the largest value of $C_X(n_i)$ for any actor in the network. The general network centralization index is then given by

$$C_X = \frac{\sum_{i=1}^{g}\left[C_X\left(n^*\right) - C_X\left(n_i\right)\right]}{\max\sum_{i=1}^{g}\left[C_X\left(n^*\right) - C_X\left(n_i\right)\right]}, \tag{5}$$

where the denominator shows the theoretical maximum possible sum of differences in actor centrality for a network of g actors. This maximum difference sum occurs only for the star network, since the star network is the most centralized network and has the maximum degree variation. The network is more centralized if the actors have more variation in terms of their centrality. The network centralization index varies from 0 to 1, with 1 representing the maximum level of centralization.

It was shown in the last section that three structural properties have been defined for the measures of actor centrality, i.e. degree, closeness and betweenness. In what follows, three different network centralization indices will be considered, each corresponding to one of the actor centrality measures defined above.

4.1 Degree Centralization

Degree-based measure of network centralization reflects the relative dominance of a single actor. Applying the general formula (5) for network centralization, we find

$$C_D = \frac{\sum_{i=1}^{g}\left[C_D(n^*) - C_D(n_i)\right]}{g^2 - 3g + 2}, \qquad (6)$$

where $C_D(n_i)$ in the numerator are the g actor degree indices, $C_D(n^*)$ is the largest observed value, and the denominator[5] of $g^2 - 3g + 2$ is actually the maximum sum of the differences in actor degree centrality. Therefore, degree centralization in the entire network is simply the degree of variability in the degrees of actors in the observed network divided by the degree variation of a star network of the same size (de Nooy *et al.*, 2005). This index is also a measure of the dispersion of the actor indices, since it compares each actor index to the maximum attained value (Wasserman and Faust 1994).

Now we analyse the degree-based network descriptive statistics and centralization in pharmaceutical biotechnology during three time periods. As shown in Table 8, firms have an average degree of 1.61, 1.90 and 2.51 in the respective periods, which is generally low. With the larger range of degree (minimum and maximum) over time, the value of variability varies greatly from 61.98 in the period 1985–1989 to 81.66 in the period 1990–1994, and reaches nearly 100 in the second half of the 1990s as a result of almost equalized mean and standard deviation. It implies that pharmaceutical biotechnology firms are more homogeneous in structural positions with regard to degrees in the period 1985–1989 than in the periods 1990–1994 and 1995–1998. Compared to the pure star network, the degree of concentration of the data is 5.75% of the maximum possible in the period 1985–1989, and it drops down to 3.23% in the period 1990–1994 and finally arrives at 2.91% by 1998 (Table 8). Due to this low

[5] If the network is a star, the maximum value of $C_D(n^*)$ is $g-1$ for an actor and $C_D(n_i) = 1$, and thus the maximum sum of differences for $g-1$ comparisons is $\left[(g-1)-1\right](g-1) = (g-2)(g-1) = g^2 - 3g + 2$.

amount of concentration in the whole network during the three time periods, the power of individual firms does not vary much. In other words, the overall positional advantages based on degrees tend to be relatively equally distributed in this network.

Table 8: A comparison of the degree-based inter-firm R&D network descriptive statistics and centralization in pharmaceutical biotechnology in 1985–1989, 1990–1994 and 1995–1998[6]

	1985–1989	1990–1994	1995–1998
Mean	1.61	1.90	2.51
Std Dev	0.10	1.55	2.50
Variability	61.98	81.66	99.64
Sum	98	480	1168
Variance	0.99	2.40	6.24
Minimum	1	1	1
Maximum	5	10	16
Network centralization	5.75%	3.23%	2.91%

Source: Recombinant Capital.

4.2 Closeness Centralization

The closeness centralization of the entire network is analogous to degree centralization in that we compare the amount of variation in the closeness centrality scores of the actors with the variation in closeness centrality in a star-network of the same size. Yet, the general network closeness index is based on the standardized[7] actor closeness centralities. Using the general network centralization index (equation (5)) given above, the closeness-based index of network centralization is

[6] Variability is computed as (standard deviation/mean)*100.

[7] The standardized actor closeness centrality simply adjusts the actor closeness centrality to its maximum value: $\left[\sum_{j=1}^{g} d(n_i, n_j) \Big/ (g-1)\right]^{-1} = (g-1) \Big/ \sum_{j=1}^{g} d(n_i, n_j) = (g-1) C_C(n_i).$

$$C_C = \frac{\sum_{i=1}^{g}\left\{(g-1)\left[C_C(n^*) - C_C(n_i)\right]\right\}}{(g^2 - 3g + 2)/(2g - 3)}, \tag{7}$$

where $(g-1)C_C(n^*)$ is the largest standardized actor closeness in the set of actors and the denominator[8] of $(g^2 - 3g + 2)/(2g - 3)$ is the maximum difference sum of the actor closeness centrality. Unfortunately, the closeness-based network centralization in pharmaceutical biotechnology industry cannot be computed since the star network does not necessarily have the highest variation in closeness centrality scores if the network is not strongly connected. But descriptive statistics as provided in Table 9 also disclose the information at the level of the whole network.

Table 9: A comparison of the closeness-based inter-firm R&D network descriptive statistics in pharmaceutical biotechnology in 1985–1989, 1990–1994 and 1995–1998[9]

	1985–1989	1990–1994	1995–1998
Mean	3.90	18.34	68.32
Std Dev	2.34	12.47	33.03
Variability	60.00	67.99	48.35
Sum	237.90	4640.65	31795.30
Variance	5.49	155.57	1091.00
Minimum	2	2	2
Maximum	9.67	43.72	127.71

Source: Recombinant Capital.

It can be seen from Table 9 that the value of variability (60.00) is not very large during the period 1985–1989. Although this value slightly increases to 67.99 in the first half of 1990s, it finally drops to 48.35 in the period 1995–1998. Overall, inequalities in

[8] The maximum possible closeness occurs when an actor is at a distance of 1 from all other actors, and all other actors are at a distance of 1 from the center and at a distance of 2 from each other. Therefore, the closeness sum for each is $(g-1)/\left[1 + 2(g-2)\right] = (g-1)/(2g-3)$ and yields a difference of $1 - (g-1)/(2g-3) = (g-2)/(2g-3)$. Thus, for $g-1$ comparisons, the maximum possible difference is $(g-1)g - 2/(2g-3) = (g^2 - 3g + 2)/(2g-3)$.

[9] with respect to variability, see fn. 6

actor centrality remain relatively moderate and firms are more homogeneous in the period 1995–1998 compared to the first two time periods.

4.3 Betweenness Centralization

The overall network centralization indices based on betweenness allow us to compare different networks with respect to the heterogeneity of the betweenness of the members of the networks. According to Wasserman and Faust (1994), betweenness centralization is simply the variation in the betweenness centrality scores of actors divided by the maximum variation in betweenness centrality scores possible in a network of the same size:

$$C_B = \frac{\sum_{i=1}^{g}\left[C_B(n^*) - C_B(n_i)\right]}{(g^3 - 4g^2 + 5g - 2)/2}, \tag{8}$$

where $C_B(n^*)$is the largest realized actor betweenness index for the set of actors and $(g^3 - 4g^2 + 5g - 2)/2$ is the maximum possible value for the difference sum[10]. The betweenness-based network centralization index for the pharmaceutical biotechnology industry was calculated with Ucinet based on this formula (Table 10).

As shown in Table 10, there is a lot of variation in actor betweenness during the three time periods, especially in the period 1985–1989, where the value of variability reaches nearly 300. This value goes down to 259.83 in the period 1990–1994 and then in the following period further decreases to 216.66 which shows a high variance. This suggests that firms are more heterogeneous in the first half of the 1980s than in the

[10] According to Freeman (1979), the betweenness-based network centralization index is defined as the average differences between the relative centrality of the most central actor and that of all other actors. This calculation of standardized indices can be made equivalently with the network centralization based on betweenness as follows:

$$C_B = \frac{\sum_{i=1}^{g}\left[\frac{C_B(n^*)}{(g-1)(g-2)/2} - \frac{C_B(n_i)}{(g-1)(g-2)/2}\right]}{g-1} = \frac{2\sum_{i=1}^{g}\left[\frac{C_B(n^*)}{g^2-3g+2} - \frac{C_B(n_i)}{g^2-3g+2}\right]}{g-1} = \frac{2\sum_{i=1}^{g}\left[C_B(n^*) - C_B(n_i)\right]}{(g-1)(g^2-3g+2)} = \frac{\sum_{i=1}^{g}\left[C_B(n^*) - C_B(n_i)\right]}{(g^3-4g^2+5g-2)/2}.$$

1990s. Despite this relatively high amount of variation, the degree of inequality in the betweenness centralities among the actors is fairly low compared to that of a pure star network. During the period 1985–1989, the network centralization index is only 2.86%, which is even much lower than the degree-based index value (5.75% in Table 10) of the same period. However, in contrast to the decreasing trend in degree-based centralization, the betweenness-based index in pharmaceutical biotechnology industry rises to 19.84% in the period 1990–1994 and then declines to 11.17% in the second half of the 1990s. However, even though the level of betweenness centralization in this network is not particularly high, it could still be an important factor for group formation and stratification (Hanneman and Riddle, 2005).

Table 10: A comparison of the betweenness-based inter-firm R&D network descriptive statistics and centralization in pharmaceutical biotechnology in 1985–1989, 1990–1994 and 1995–1998[11]

	1985–1989	1990–1994	1995–1998
Mean	4.26	399.78	688.10
Std Dev	12.51	1038.76	1490.80
Variability	293.45	259.83	216.66
Sum	260	101144	320654
Variance	156.42	1079022.13	2222483.25
Minimum	0	0	0
Maximum	54	6649.50	12711.78
Network Centralization	2.86%	19.84%	11.17%

Source: Recombinant Capital.

5 Discussion and Conclusions

Many theoretical and empirical studies of firm behaviour a based on the assumption that companies are primarily motivated by self-interest and therefore, inter-firm

[11] with respect to variability, see fn. 6

relationships are largely competitive in nature (Badaracco, 1991; Doz and Hamel, 1998). They argue that firms are atomistic actors, striving for their competitive advantage in a hostile market with the aim of earning superior profits (Roijakkers, 2003). For instance, new entrants would attempt to enhance their competitive position in order to ultimately replace incumbents. In such a competitive environment, each company tries to deal with competitive threats and gain a high level of market power. In this sense, the most powerful companies are those following a "going-it-alone"-strategy, so that they can avoid becoming overly dependent on other firms and in turn strengthen their market power in relation to their rivals (Hamel, 1991). Thus, from the firm-based view, it is best for companies to be primarily competitive in their relationships with others.

Apart from this firm-based view, there is another viewpoint focusing on the nature of inter-firm relations, i.e. the network-oriented perspective, which regards inter-firm relationships as a dynamic process in which companies act cooperatively with respect to other firms (Roijakkers, 2003). Specifically, it is argued that companies which are embedded in dense, tightly connected networks can largely benefit from participating in a cooperative network and thus are willing to accept a relatively high level of interdependence for mutual gain towards common goals (Contractor and Lorange, 2002). In this cooperative network, innovative products can be one of the most prominent outcomes of inter-firm partnerships since all cooperating companies can benefit (Hagedoorn, 2002). As in the case of pharmaceutical biotechnology industry, newly founded biotechnology firms potentially provide innovation opportunities for large and established pharmaceutical companies. Joining an integrated network of pharmaceutical biotechnology partnerships not only enables firms to reinforce their market power, but also allows them to effectively respond to the development of new technologies.

This paper adopts the latter perspective of the network-based view to analyse the inter-firm relations in the pharmaceutical biotechnology industry. The size of R&D inter-firm network largely grows over time driven by the need of large pharmaceutical companies to access new biotechnological knowledge. However, the density of the network declines as the network grows due to a limited number of cooperating partners for each company. The structural position of the firm in the network has an important effect on the extent of his proceeds. Central firms can obtain information much more

easily and rapidly and hence occupy advantageous structural positions, while peripheral firms hardly achieve any benefit from participating in a network. There are three structural properties to the actor centrality: degree, closeness and betweenness that have been defined in this paper. Based on these measures, lists of putative central firms in different periods are achieved. Hagedoorn and Roijakkers (2006) also presented lists of major players in pharmaceutical biotechnology for the periods 1985-1989, 1990-1994 and 1995-1999 based on the number of R&D partnerships using the MERIT-CATI database. Comparing their results with the putative central firms obtained in this paper, the list of major players partly differ due to different measures and databases, although the chosen time periods are quite similar. Baker *et al.* (2008) applied the same Recombinant Capital database to define most active pharmaceutical and biotechnology firms in strategic alliances, yet they applied a large 28-year time period from 1973 to 2001, which makes a direct comparison of the results difficult. Some authors use shorter time periods to observe changes in the top firm list in pharmaceutical biotechnology, for instance, Gilsing *et al.* (2008) divided the overall time period from 1975 to 1999 into eight periods of three years. This different time period division also does not allow for a direct comparison of results. However, with respect to the changing roles of biotechnology companies, our conclusions are similar to those of Hagedoorn and Roijakkers (2006): in the second half of the 1980s, small biotechnological companies did not only play a crucial role in the emergence of inter-firm networks, but also formed important links for large pharmaceutical companies. During the 1990s, however, the bridging role of these small biotechnology companies became less prominent. In contrast, large pharmaceutical firms have developed into more dominant, star players with many partnerships while holding a central position in the pharmaceutical biotechnology inter-firm R&D network. Besides evaluating the network on the individual level, this paper also provides the conceptions of network-level centralization and examines the research cooperation on the level of the entire network. Three distinct structural properties (degree, closeness and betweenness) that have been defined as bases for developing measures of actor-level centrality were also used to construct indices of network centralization. The empirical results show that degree-based and betweenness-based network centralization are both low in the three time periods, which implies that there is a low level of inequality in the whole network and

that the overall positional advantages are relatively equally distributed in the inter-firm R&D network of the pharmaceutical biotechnology industry. The current paper covers four aspects to characterize a network, i.e. size, density, actor centrality and network centralization. However, many other aspects such as structural holes, sub-network *etc.* that could also be taken into account when analyzing inter-firm relations should be considered in future research on the pharmaceutical biotechnology inter-firm R&D network.

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