Small Firms And Technological Change In Markets for Technology. The Pharmaceutical Industry After The Revolution In Molecular Biology

Fabio Pammolli, Massimo Riccaboni[1]

University of Siena and Sant'Anna School of Advanced Studies

April 10, 2000

[1]The authors whish to thank Luigi Orsenigo, Giovanni Dosi, participants to the International Workshop on Institutions, Entrepreneurship, and Firms Growth, Jonkoping, Jan. 13-15, 2000, and, moroever, John Sutton and participants to a seminar held at the London School of Economics (Feb 25, 2000) for useful comments and discussions. The usual disclaimers apply. The study is part of EPRIS, a research project supported by the Merck Foundation, Whitehouse Station, New Jersey, USA.

1 Introduction

This paper studies the nature and the evolution of a system of interfirm R&D contractual relationships in the pharmaceutical industry, a domain that has been characterized by structural breakthroughs in underlying knowledge bases.

The goal of this essay is twofold.

First, the case of the pharmaceutical industry after the revolution in molecular biology is used here as a natural experiment to analyze how patterns of technological change shape the structure of local market interactions (see Kirman, 1998). In contrast with the old-line pharmaceutical industry, in which R&D was dominated by a 'routinezed mode of development' (Nelson, Winter, 1982) and, correspondingly, by a small number of large firms that were relatively self-sufficient, the new paradigm (Dosi, 1982) of molecular biology and biotechnology has fostered the emergence of an *entrepreneurial regime* (Winter, 1984), since research breakthroughs have been so widely distributed that no single firm has all the internal capabilities necessary for success (see Powell et al., 1996). Starting from the beginning of the Eighties, hundreds of new science-based entrepreneurial companies, located mostly in the U.S., have entered the industry acting as specialized suppliers whithin specific R&D trajectories, and giving origin to a market for the exchange of intermediate technological inputs (*market for technologies:* see Arora, Fosfuri, Gambardella, 1999). In this paper, we do represent the market for technologies as a graph, and we show that such a representation can reveal how relevant technological conditions induce distinguishable patterns of structural change in a complex set of contractual

relationships. Our graph theoretical tools and measures enable us to illustrate, whitout any reference to standard classifications of industrial figures, how patterns of technological change act splitting the overall market in a number of more or less distinct submarkets (technological trajectories), characterized by various degrees of interdependence (Sutton, 1998). It is our claim that such an analytical apparatus can be used in any R&D intensive industry to assess the implications of entrepreneurship and markets for technologies for patterns of specialization and division of labor, industry structure and, ultimately, economic growth.

Second, while the economic and managerial literature have touched upon some aspects of markets for technology, a sytematic understanding of how they work and what are their economic implications is still in its infancy. Against this background, this essay reveals, even if in an indirect way, that markets for technology can realize a synthesis of market-based, technology-based, and firm-based coordination mechanisms, succeeding in the integration of a variety of learning processes by legally distinct entities that are heterogeneous in skills, competencies, access to information, and assets (see Powell et al., 1996).

The paper is organized in three Sections. Section 2 highlights the nature of the most relevant research heuristics and techniques developed by firms and institutions in the last twenty years in their efforts to discover and develop new effective drugs. In Section 3 the evolution of the overall system of R&D contractual relationships is analyzed. We investigate an extensive data set that covers around 3,000 research licensing agreements of known technological con-

tent between around 1,500 firms for 1978-1997. First, we do analyze some of the most relevant properties of the relationships of local interdependence, within the market, building a non-parametric statistical test that use information on firms and their neighborhood in order to assess the nature of the connection between technological bases and relational behaviors within the market. Then, we refer to the notion of Canonical Decomposition of a Graph in order to use an information on structural interdependencies wich is global in nature, to disentangle two major drivers/components of the structural evolution of the market over time. That is, *co-specialized* and *transversal actors* that rely on *co-specialized* and *transversal research technologies*. In Section 4 we sum up the main findings and implications of our analysis

2 Pharmaceutical innovation after the revolution in molecular biology

The last twenty-five years have witnessed a revolution in biological sciences, with significant basic advances in molecular biology, cell biology, biochemistry, protein and peptide chemistry, physiology, pharmacology and other relevant scientific disciplines. The application of these new bodies of knowledge to pharmaceutical industry has had an enormous impact on the nature of R&D activities, on the organizational capabilities required to introduce new drugs, and on patterns of industry evolution (see Galambos, Sturchio, 1996; Henerson, Orsenigo, Pisano, 1999).

In particular, it has been emphasized that the emergence of a dense set of collaborative relationships among firms of different types and other research institutions has been a major feature of the recent evolution of the pharmaceutical industry.

Let us briefly summarize the basic properties of the dynamics of knowledge within the industry during the last twenty years (a far more detailed account can be found in Orsenigo, Pammolli, Riccaboni, 2000).

First, a process of fast *expansion* of biological knowledge in the fields of biochemistry, physiology and pathology has been upsurging within the industry.

Secondly, the growth of biological knowledge has been taking the form of a *specification process with novelty,* in which general hypotheses give origin to a variety of new sub-hypotheses, that in turn develop other sub-hypotheses at

lower levels of generality, and so on.

Third, as a consequence, the structure of knowledge comes to have a distinct *hierarchica*l nature.

Fourth, the overall process of growth of biological knowledge is highly *cumulative*, since it is based on a dynamics which introduces progressive specifications of biological hypotheses at each level of the hierarchy.

Fifth, the very nature of the dynamics of knowledge imposes a specific structure on the *degree of stability* of the hypotheses: at higher levels of the hierarchy, hypotheses tend to stay relatively stable, since their falsification occurs over a relatively long time scale, being based on the falsification/selection of hypotheses at lower levels of generality.

Sixth, during the Nineties, in response to the dramatic increase of the number of novel biological targets for therapeutic intervention, new research technologies, which achieve a higher breadth of applications in terms of both disease areas and biological targets, have been developed (see Harvey, 1998): from *Polymerase Chain Reaction* to protein structure modelling, to rapid computer based drug assay and testing, to recombinant chemistry techniques, to chemical separation and purification techniques that allow researchers to screen thousands of potentially promising compounds.

All in all, the role of individual entrepreneurs notwithstanding, the recent evolution of research strategies and heuristics in pharmaceutical R&D can be characterized by distinguishing, two main *search regimes*, that coexist and complement each other within the industry.

A first regime is based on firms that are endowed with research techniques that stay coupled with specific biological hypotheses and are specific to given fields of application (*co-specialized technologies)*, while a second regime is characterized by the entry of firms that control new *generic research tools and techniques* (*transversal technologies)*. In the case of *co-specialized research technologies*, the design and experimentation of each new drug requires individual analysis, and lessons learned from the design and experimentation of one therapeutic cannot be immediately transferred to the development of other classes of drugs. Conversely, the appearance of *transversal technologies* for the production and screening of new molecular structures has introduced a new dimension in the organization of the relevant knowledge bases, since the new technologies tend to be applicable to (couple with) multiple biological targets and diseases.

Finally, and most important, given that pharmaceutical R&D is particularly costly, uncertain, and lengthy, since it deals with a system — the human body — far more complex than any mechanical or electronic system (see Gambardella, 1995), economic actors tend to integrate co-specialized and transversal techniques in their exploration and problem solving activities, originating new interdependencies among submarkets and technological trajectories, with the emergence of new interconnections within the system.

3 Markets for technology in pharmaceuticals

In this section we analyze the structure and evolution of what we call "Market for Technologies" in the pharmaceutical industry, worldwide, for 1978-1997.

First, we do highlight some qualitative, global, properties of the structure of the market. Second, we analyze its most relevant local properties.Third, we show that the recent evolution of technological knowledge within the industry has been inducing an upsurge in the degree of interdependency among R&D trajectories and submarkets, with important consequencies on patterns of industry evolution .

3.1 Data and notation

Data used for this study are drawn form the Pharmaceutical Industry Database (PHID) developed at the University of Siena. It integrates information from several sector-specific fonts including a *proprietary database* on more than 14,000 R&D projects and — as for collaborative agreements — *Bioscan*, *Recombinant Capital*, *IBI and Pharmaventures Databases*, annual reports (*SEC files*) and specialized press news (*Scrip*, *Spectrum*). PHID provides information on the typology, technological content and date of signing for 2,785 R&D licensing agreements signed by 1,709 Firms and Institutions[1] during the pre-clinical de-

[1] Every agreement may include different contract typologies. Information on the technological content is available for every agreement, as it refers to the underlying discovery technology. Merger and Acquisitions have been taken into account by collapsing the information relative to the firms engaged in consolidation deals starting from the date of subscription.

velopment phase. Specifically, our sample includes 349 leading pharmaceutical firms, 1,112 new biotechnology firms and 248 among universities, hospitals and other public and private institutions.

Throughout this work, the market is defined as it follows:

1 - V : Firms & Institutions with at least one R&D project in their pipelines;

2 - E : Pharmaceutical R&D projects included in the data set;

3 - $o = f(e)$: A function f, whose domain is E, and whose range is contained in V, which single out the *Originatotor* of each project, i.e. the company or institution that started the R&D project e;

4- $d = s(e)$: A function s, whose domain is E, and whose range is contained in V, where d is identified as the *Developer* of the R&D project e;

As we are dealing with the structural evolution of the market, we only focus on projects for which $o \neq d$. That is, projects in which an Originator can been identified and distinguished from a Developer.

According to the above definitions, market structure can be represented at any given time τ between 1978 and 1997 by means of a directed graph $M_\tau(E, V)$, where V is the set of vertices and every edge e within the graph is an oriented link defined by a couple (o, d)[2]. Alternatively, the directed graph M_τ can be represented by an *adjacency matrix* $M_\tau \Longleftrightarrow A(M_\tau) = [a_{do}]$. Matrix entry a_{do} equals 1 if an edge $e(d, o)$ does exist and 0 otherwise. In fact, matrix rows report

[2] see Harary et al., 1975; Slepian, 1968; Diersel, 1997.

all the vertices D (*Developers),* while matrix columns consist of all the vertices O (*Originators*).

In order to enable an analysis of the evolution of the structure of the market, a time ordering has been associated to the directed graph. In particular:

5 - $t(d)$ = time in which firms/institutions o and d started their R&D cooperation on project e;

6 - $t(o)$ = time in which firm/institution o started the R&D project e;

7 - $t(v)$ = date of $v \in V$ entry.

It follows that $t(d)$ is always greater than $t(o)$. Hence, every edge in the graph is time-oriented. That is to say, we are able to distinguish the Firm/Institution that originated every R&D project from the one that took the lead for its development.

On the other hand — with reference to the structural evolution of the market — a time ordering has been established according to both year of foundation and year of entry of any given firm/institution[3]. Back to the matrix notation, we can permute the adjacency matrix in order to obtain the ordered matrix: $A(M_{\square\tau}) = [a_{do}]_{\square\tau}$, where $\{t(1) \square ... \square t(d) \square ... \square t(n) \square \tau\}$, and $\{t(1) \square ... \square t(o) \square ... \square t(m) \square \tau\}$, with m and n representing the total

[3] IThe time ordering induced by $t(v)$ is complete, while the time-oriented graph generated by the distinction between Originators and Developers corresponds to a partial order set.

On the relationships between order set theory and graph theory see Asratian et al., 1998, Ch. 10.

number of Originators and Developers active within the market at time τ. Sometimes — for the sake of synthesis — we shall refer to the block matrix $B(G)_{\square\tau(\theta)}$ obtained after collapsing rows and columns of matrix $A(M_{\square\tau})$ that correspond to firms/institutions belonging to a common cohort of entrants $\theta = [\tau, \tau + \theta)$ (*Generation)*. In that case, entries b_{do} of $B(G)_{\square\tau(\theta)}$ indicate the total number of contractual relationships between *Generations* d and o.

In sum, the overall market for technology in pharmaceuticals is referred to as a directed graph (digraph). The digraph is then identified according to a time orientation, as for every R&D project it is possible to distinguish the Originator from the Developer. In addition, the digraph has been *ordered* according to dates of foundation and dates of entry within the market. As a result, two distinct time dimensions have been identified: the first one is defined at the project level (the distinction project *Originator/Developer*); the second is singled out at the *macro* level (the emergence of the overall market as a result of firms entry and new contractual relationships).

3.2 Entry, complementarities and centralization

The influence of different technological waves on the structural evolution of the market can be appreciated, at a first glance, by looking at Figure 1. Figure 1 is based on a 3D graphical representation of the graph by means of level curves. Columns correspond to the x axis (*Originators*), while rows correspond to the y axis (*Developers*). Levels $z(x, y) = b_{do}$ indicate the cumulated number of agreements between Developers d and Originators o, classified according to the

year of entry into the network, with darker regions representing areas of higher relational intensity.

Figure 1 shows that *Originators* have entered the market by introducing successive waves of new research technologies, reshaping the overall market structure. Firms already active within the market have not played a major role as *Originators* in new technological trajectories emerged after their entry. Rather, earlier entrants have gained access to the new technological trajectories mainly as *Developers*. As times goes by, the rate of entry in any given technological trajectory tends to slow down. That is to say, entrants are closely related to the emergence of new technological trajectories.

All in all, the evidence on patterns of entry, on relational roles of earlier and later entrants (Originators/Developers) and, finally, on new technological waves, suggests the existence of a dynamic process in which new technological breakthroughs initially induce the entry of new firms/institutions as specialized technology *Originators*. As times goes by, *Developers* succeed in developing internal capabilities in the new fields. Correspondingly, relational intensity, as well as flows of entry, shift forward to new technologies and firms. In addition, especially after 1992, the emergence of *transversal technologies* like combinatorial chemistry has been perturbating the structure of the market. In particular, while during the Eighties the extent of inter-generational collaboration was much more significant than intra-generational collaboration, new entrants based on *transversal technologies* have been establishing contractual relations with a large variety of *Developers*, irrespective of their age.

Fig 1 — *Technological waves within the network*

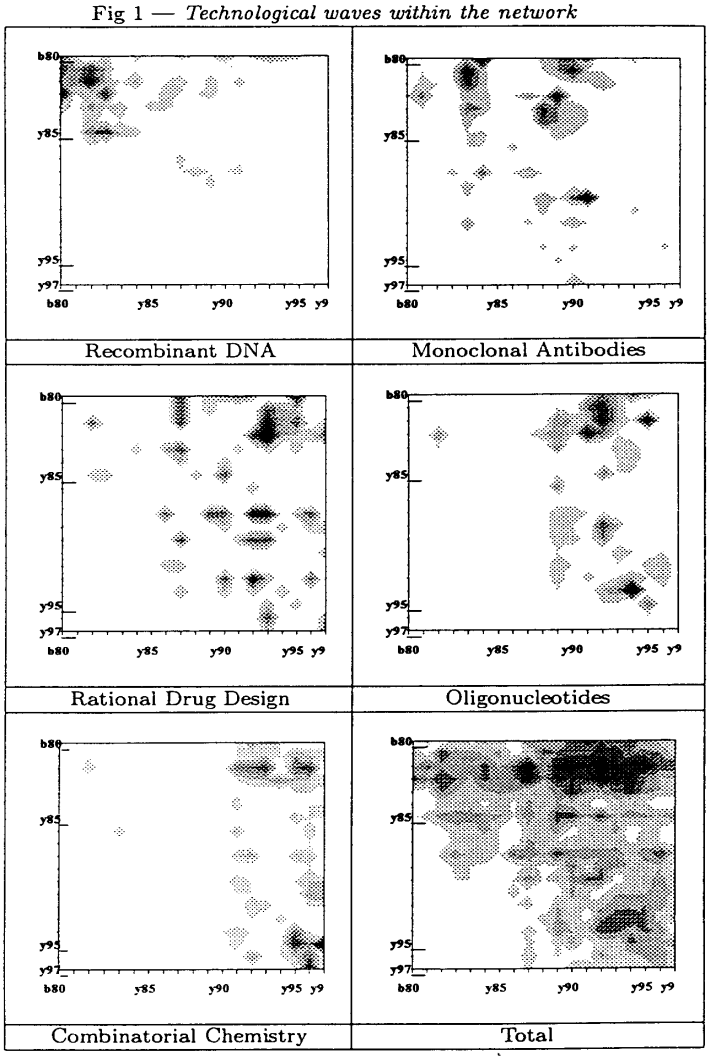

Figure 1: *Technological waves within the market*

In order to move a step forward in the analysis of the most important drivers of the structural evolution of the market, let's suppose that the total number of R&D collaborations of a firm/institution i at time τ as Developer $D(i,\tau)$ and as an Originator $O(i,\tau)$ depends only upon the overall pattern of entry (ε) — that is the total number of potential partners within the market — and on the length of presence within the market (a_i). In particular, since we noticed that new entrants tend to act as Originators of new search hypothesis while incumbents consolidate their presence within the market as Developers, we suppose that the potential Originators are younger than potential Developers. So, for each firm/institution that entered the market at time ε, we weight the *actual* number of collaborations for the *potential* number of agreements they could subscribe as Developer $\overline{D}(i,\tau)$ and as Originator $\overline{O}(i,\tau)$ until time τ calculated as follows:

$$\overline{D}(i,\tau) = m(\varepsilon,\tau)$$

$$\overline{O}(i,\tau) = n(0,\varepsilon)$$

where $m(\varepsilon,\tau)$ is the total number of Originators entered between time ε and τ while $n(0,\varepsilon)$ is the total number of Developers entered before firm i.

Figure 2 depicts the weighted number of collaborations signed as a Developer (crosses) and Originator (triangles) plotted against time of entry, ε. It is straightforward to notice that — even after controlling both for differences in time horizons and number of potential partners — early entrants (firms and institutions that entered the market before 1981) establish a larger number of agreements than later ones, with a remarkable *first mover advantage* (see also Powell et al, 1996). Besides, firms which entered the market after 1992 have

established more agreements as Developers than expected.

Taken together, these findings suggest that some of the most relevant features of the structural evolution of the market for technology in pharmaceuticals cannot be analyzed and interpreted only by referring to parameters like size of the market and flows of firms entry.

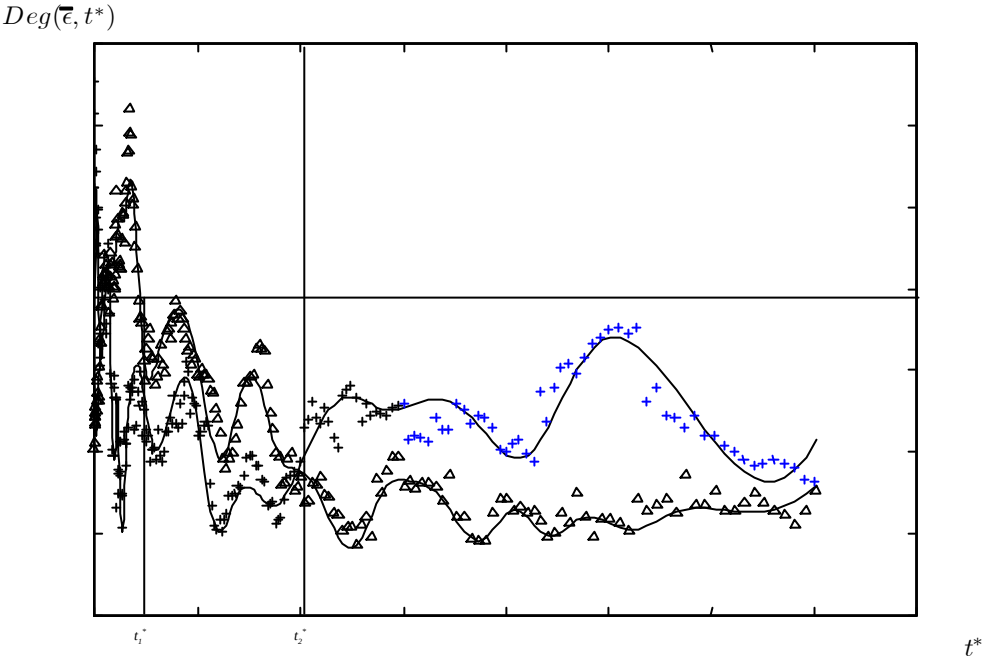

Figure 2: *Contractual relationships, relational roles, and dates of entry*

In a companion paper we perform a comprehensive analysis of the structural properties of the market by means of graph theoretical measures, unequivocally showing that the digraph is asymmetric, intransitive and hierarchically structured (Orsenigo, Pammolli, Riccaboni, 2000)

In the context of this work, we test a stochastic model of market interdependence to estimate the impact of technology and timing of entry on the relational behavior of firms and institutions within the market.

A logit p-star model (Strauss, Ikeda, 1990) is applied, in order to detect how structural variables affect the probability of a tie being present or absent within the graph. The presence or the absence of a tie going from o to d is characterized as the dichotomous stochastic variable a_{do}, conditionally dependent on the presence or absence of other ties in a given 'neighborhood'.

Since every tie is dependent on the ties of its neighborhood and, at the same time, it is part of the neighborhood of other ties, the graph instantiates a *local self-organizing process,* given by the joint probability of particular local substructures to occur. In p* models, the specification of the relevant neighborhood is based on *Markov graphs*. As a matter of fact, the Markovian assumption greatly simplifies the dependence structure within the graph, naturally leading to a maximum pseudo-likelihood estimation technique (Wasserman, Pattison, 1996; Pattison, Wasserman, 1997; Anderson, Wasserman, Crouch, 1999). As for our analysis, it is important to notice that the application of a p* model is consistent in principle with the characterization of the market as an interacting system (see Kirman, 1998). However, one has to remember that p-star models rest upon two crucial assumptions:

Ass. 1 - *Markov property*. Edges within the graph are conditionally dependent if and only if they have a node in common; i.e., a lattice structure is introduced in order to represent the relevant technological neighborhood of each firm/institution. In the contest of our analysis, the Markov property implies that the probability of a given firm to take part to different collaboration agreements, given the overall market structure, is not simply equal to the prod-

uct of their marginal conditional probabilities. The Bernoulli model, in which all edges are conditionally independent, can be considered as an extreme case, and more complex local interdependence configurations can be taken into account.

Ass. 2 - *Homogeneity property*. In order to make the model identifiable, different firms/institutions must react in the same way to isomorphic local market configurations. This assumption rules out any source of heterogeneity in the dependence structure, since it implies that the probability to observe a tie depends on the same local graph configuration irrespectively of differences among agents.

As for the plausibility of Assumptions 1 and 2 in the context of our work, it is reasonable to assume that, for every firm, the number of external linkages depends on both its strategy and technological background. Hence, external linkages in R&D of a given firm are interdependent, since they draw on a common technological basis and are realized in the context of a common general strategy. As a consequence, a Markov assumption is more plausible than an assumption of independence, while it does not imply a strong restriction as compared to an hypothesis of general interdependence. On the contrary, the homogeneity assumption appears to be particularly restrictive, and it suggests a careful interpretation of regression outcomes. In fact, in order to obtain informative results and appropriate conditioning information, one should take into account the existence of technological capabilities that are heterogeneous across firms. To mitigate this problem, we test a second relational model, which incorporates a classification of firms according to dates of foundation and entry

within the market.

Given the Markov and the Homogeneity assumptions, the general logit p-star model that we test can be written as:

$$\varpi_{ij} = \log \left\{ \frac{\Pr\left(A_{do} = 1 \mid \mathbf{A}_{do}^{c}\right)}{\Pr\left(A_{do} = 0 \mid \mathbf{A}_{do}^{c}\right)} \right\} = \boldsymbol{\beta}' \left[d\left(\mathbf{a}_{do}\right) \right]$$

We calculate the Maximum Pseudo-Likelihood Estimations of parameters $\boldsymbol{\beta}$ for different change statistics $d\left(\mathbf{a}_{do}\right) = z\left(\mathbf{a}_{do}^{+}\right) - z\left(\mathbf{a}_{do}^{-}\right)$, where $z\left(\mathbf{a}_{do}^{+}\right)$ is the value of a given vector of network statistics with $\mathbf{a}_{do}$ set equal to 1 and $z\left(\mathbf{a}_{do}^{-}\right)$ with $\mathbf{a}_{do}$ set to 0.

We report the output of two relational models. The two models are based on the same three variables, which correspond to the most fundamental relational roles detectable within the market: *Cos (cospecialization)*, *Gen (generality),* and *Syn (synthesis)* which correspond to three network change statistics: *edges* [$\longrightarrow$], *2-out stars* [$\nwarrow\nearrow$] and 2-*in stars* [$\searrow\swarrow$]. These measures have been selected among the stars of size three or less defining the neighborhood of every node as they came out to be the most significant in terms of both Wald and Likelihood Ratio tests[4]. The *Cos* parameter measures the effect of one-to-one relationships within the market, and substantiates the tendency towards *co-specialized* research activity, while the other two parameters denote the *transversality* effect, measured through two out and in stars, for Originators (*Gen*), and Developers (*Syn*).

[4] Frank, Strauss, 1986 demostrate that stars of size three or less are sufficient statistics for the network dependence structure.

Tables 1 and 2 summarize the results of our econometric estimates. Notably, the high, negative, and significant values of *Cos* in both models constitute reliable measures of the importance of coupled firms/institutions within the market. In fact, most of the firms and institutions entered the market by means of a co-specialized relationship, while the probability of a second collaboration drops considerably. Even more interestingly, the other two parameters are positive, indicating that *transversality*, in particular by Developers (*Syn*), lead to a higher propensity to establish new external linkages.

All in all, these results are coherent with those obtained by previous analyses in this field, but they are far more accurate in terms of the structural insights they convey. As an example, we are able to detect both the *complementary effect* captured in Arora, Gambardella, 1994, and the *centralization effect* characterized in Powell et al., 1996, as well as the absorptive and integrative capabilities effect illustrated in Henderson, 1994.

Table 1: *Model A*

Variables	β	S.E.	Wald	exp(β)
Cos.	-7.1519	0.0400	31919.99	0.0008
Gen.	0.0781	0.0013	3712.16	1.0812
Syn.	0.1840	0.0051	1288.07	1.2021

-2 Log Likelihood: 17618.80 Overall fit: 99.80

Goodness of Fit: 531635.25 Residual (Absolute): 2758.80

Model Chisquare: 964046.73 df: 3 Residual (Squared): 1403.91

The model *A* presented in Table 1 does not take into account any kind of heterogeneity among actors. Needless to say, this assumption represent a severe

limitation both from a theoretical and an empirical point of view. In fact, we already know that differences in technological content of R&D collaborations can induce differences in market structure.

Thus, as we have already shown that new technologies have been introduced by new entrants, we test a second model with a generational structure (model *B*). On the basis of an analysis of peaks of entry within the industry (dates of foundation), four generation of firms and the set of institutions have been distinguished (see also Orsenigo, Pammolli, Riccaboni, 2000). As for firms generations, Established Pharmaceutical Firms, Institutions, and NBFs founded before 1981, from 1982 to 1989, and after 1990 have been distinguished and — coherently with our previous discussion — a hierarchical structure is assumed (Table 2).

Despite the additional constraints, the general fit of the model remain almost the same. Notably, the values of *Syn* become higher for Pharmaceutical Firms and older NBFs than for younger NBFs and Institutions, qualifying, in a different way, the existence of a temporal hierarchy within the network. On the other hand, parameter *Gen* is almost the same for all NBFs, but now the standard error is lower for younger generations. The lower value of *Gen* standard error after 1990 suggest that a high fraction of younger NBFs have a generalist attitude, as compared to the very few of previous generations (like Genentech, Chiron, Amgen).

All in all, we have shown that the market for technology in pharmaceuticals has a distinct hierarchical structure. Clearly, lead pharmaceutical firms play a

pivotal role as project Developers, as they are able to sustain a large number of R&D trajectories. On the contrary, only a restricted group of NBFs stand out as general purpose Originators, while the overwhelming majority of them have been confined to R&D trajectories that have tended to become more and more specific over time.

Table 4(a): *Model B, Block matrix structure*

		Originators				
		Pharma	NBF □ 81	NBF 82-89	NBF 90-97	Inst.
Developers	Pharma	b_{11}	b_{12}	b_{13}	b_{14}	b_{15}
	NBF □ 81	0	b_{22}	b_{23}	b_{24}	b_{25}
	NBF 82-89	0	0	b_{33}	b_{34}	b_{35}
	NBF 90-97	0	0	0	b_{44}	b_{45}
	Inst.	0	0	0	0	b_{55}

Table 4(b): *Model B (with generation blocks)*

Variables	Block	β	S.E.	Wald	exp(β)
Cos.	-	-6.8537	0.0364	35506.39	0.0011
Gen.	*Pharma*	0.0615	0.0034	319.57	1.0635
Gen.	*NBF <81*	0.0808	0.0041	396.91	1.0841
Gen.	*NBF 82-89*	0.0804	0.0023	1180.02	1.0837
Gen.	*NBF 90-97*	0.0807	0.0019	1758.94	1.0840
Syn.	*Pharma*	*0.3024*	*0.0120*	*451.37*	*1.2670*
Syn.	*NBF <81*	0.2250	0.0113	398.32	1.2524
Syn.	*NBF* 82-89	0.2074	0.0106	386.21	1.2304
Syn.	*NBF* 90-97	0.1378	0.0101	187.97	1.1478

-2 Log Likelihood: 17897.27 Overall fit: 99.80

Goodness of Fit: 622573.47 Residuals (Absolute): 2747.59

Model Chisquare: 963768.26 df: 8 Residuals (Squared): 1397.97

3.3 Technologies and market interdependencies. A bridge to local interaction

So far, we have imposed an a priori definition of local relationships within the market. That is, we have assumed that R&D collaborations are interdependent as long as they pertain to a given firm/institution. Here, we abandon this *local interdependence assumption,* trying to meaningfully decompose the overall market for technology into specific submarkets.

In order to identify almost independent technological submarkets, we look for strongly interconnected subgraphsby means of the methodology of Canonical Decomposition of a Graph introduced by Dulmage and Mendelsohn (1958, 1959).

A graph $\overline{M}_\theta$ is extracted from the overall market for technology M by considering the contractual relationships between two independent set of firms/institutions (*Originators* and *Developers)* at any given period θ.

In Figure 3 we synthetize the logic of the Dulmage-Mendelsohn decomposition. Boxes $\overline{M}_1, \overline{M}_2$ represent two non trivial submarkets. In our analysis, a non-trivial submarket is a strongly connected component; that is, a subgraph in which it is possible to couple each Originator with a different Developer (for further details, see Diersel, 1997; Orsenigo, Pammolli, Riccaboni, 2000). Each submarket includes a subset of Developers and Originators. Some Developers in submarket $\overline{M}_1$ link with Originators in box $\overline{M}_2$: they correspond to what we call *Transversal Developers* (*TransDev*) and *Transversal Originators* (*TransOr*). The remaining Originators and Developers are wholly specialized in submarkets

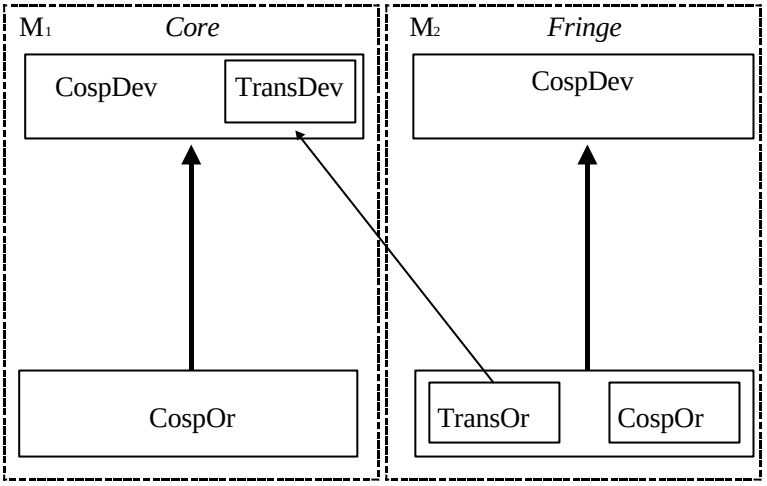

Figure 2: Figure 3: *Transversal and cospecialized nodes within the graph*

$\overline{M}_1$ or $\overline{M}_2$ so we call them respectively *Co-specialized Originators* (*CospOr*) and *Co-specialized Developers* (*CospDev*).

The two sets of firms/institutions denoted as *TransDev* and *TransOr* can be thought of as the structural attractors of the overall market, as they attract most of the agreements in each period of time. On this, it is important to notice that while Co-specialized firms are localized within specific and well identified technological trajectories/submarkets, *TransDev* and *TransOr* firms *cannot be assigned unambiguously* to any given submarket/R&D trajectory, and prevent the market from being fully decomposable. In other words, firms that are classified as *Transversal Developers* and *Originators* are delocalized within the market, since they establish several relationships with a wide variety of firms in different technological submarkets.

As for our empirical analysis, it is possible to demonstrate that the relational

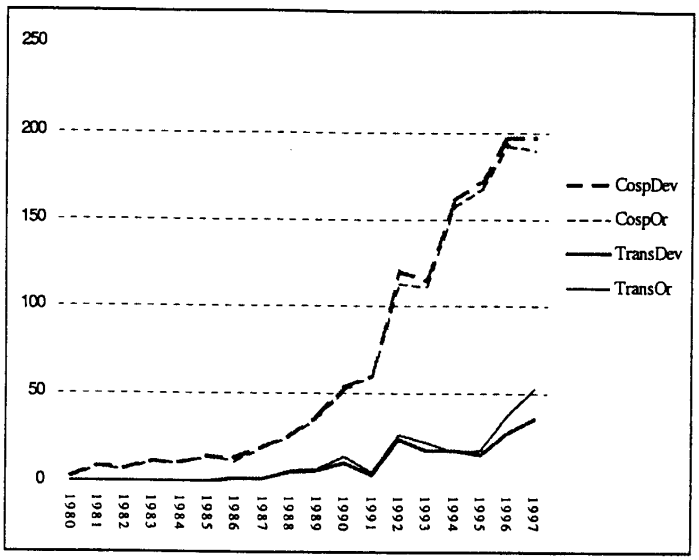

Figure 3: Figure 4: *Number of firms by relational category*

roles that have been identified correspond to firms embodying different types of technologies and that the changes over time in such roles correspond to the emergence of a new set of technologies, i.e. transversal technologies.

Figure 4 plots the moving average of the number of firms classified according to relational categories in terms of co-specialization/transversality. As it is clear, the set of firms playing a transversal role within the market has taken off only after 1992, the year in which the first new general purpose research technology, entered the market. At the same time, throughout the whole time period under observation, the number of firms that have been acting as *CospOr* steadily increase. Correspondingly, from 1992 to 1997 the market has been characterized by the coexistence of both *CospOr* and *TransOr* firms.

As an example of the implications of the emergence of the new transversal component within the market, Figure 4 refers to R&D agreements subscribed in 1997, after the emergence of the transversal component of the market. Submatrices A_1, A_2 correspond to submarkets $\overline{M}_1, \overline{M}_2$, while T marks the matrix area in which transversal R&D collaborations are confined[5]. The area T is the area that corresponds to transversal firms. Starting from the beginning of the Nineties, the new technological paradigm driven by the entry of new general purpose research technologies has started to couple with the previous one, mainly based on the growth through specification of biological knowledge. The coupling between the two regimes seems to have induced a dramatic increase of the overall degree of interdependence within the market. That is to say, the market has started to be more and more indecomposable, because of the coexistence of a variety of decomposition criteria, integrative mechanisms and, moreover, because of a higher degree of interdependence among research trajectories.

Further information on *the technological bases of relational transversality* has been gained through a detailed analysis of the technological background of *Transversal Originators* based on personal interviews, information provided by 10K and 10Q SEC files reports, specialized press, and our proprietary data set on R&D projects within the industry. As a result,.we are able to state that relational roles that have been identified within the market correspond to firms embodying different types of technologies. In particular, our controls show that

[5] Since the number of connected components of $\overline{M}_\theta$ is always greater than one, by permuting rows and columns the adjacency matrix $A(\overline{M})_\theta$ corresponding to $\overline{M}_\theta$ can be put into the form of Figure 4.

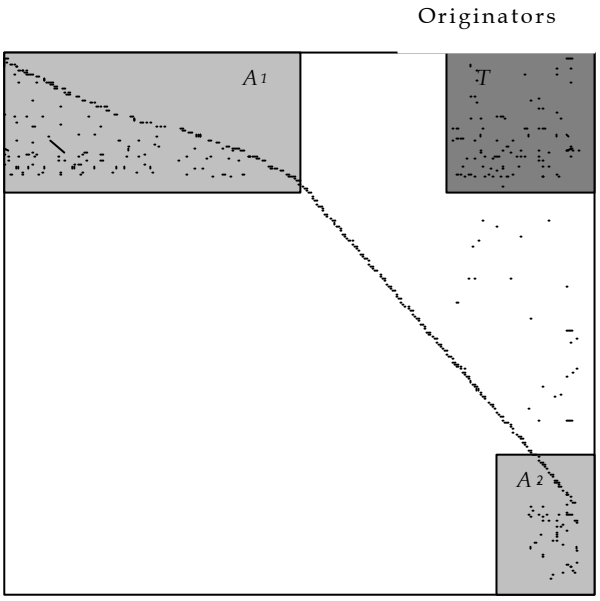

Figure 4: Figure 5: *Canonical Decomposition of the market, 1997*

technological transversality is a major determinant of relational transversality within the market. In fact, *all the firms that have been identified as Transversal Originators* have been active in fields characterized by transversal research technologies, such as new drug delivery systems, combinatorial chemistry, genomics, genomic libraries, proteomics, highthroughput screening, and bioinformatics (for more details on this see Orsenigo, Pammolli, Riccaboni, 2000). Almost all the firms which are included in PHID as active in general purpose research technologies have been classified by the algorithm as *Transversal Originators*. Conversely, and most important, all the *firms that have been identified as Transversal Originators into the graph by means of our analytical procedures embody Transversal Technologies*.

Given this first correspondence between firms market position and their technological background, we analyze the *Developers* (*Table 5a*) and *Originators* (*Table 5b*) turnover in terms of market position (co-specialized/transversal). This analysis is useful as it shows the effect of the entry of the new transversal technologies after 1992. The number of transversal firms acting as Originators is almost four times greater after 1992. Moreover, only a small subset of the initial set of transversal Originators (active in the drug delivery area) persist after 1992, while a relevant proportion of new entrants act as general purpose search technology providers. Despite the steady increase of the degree of market transversality, most of the firms still co-operate in specialized submarkets. In particular, new transversal entrants have started to act as *Originators* not only in their relationships with early entrants, but also with young entrants, en-

dowed with powerful research hypotheses associated with the biology of a given pathology, but lacking capabilities and skills in fields such as *chemical diversity generation and screening.* Co-specialized firms experience a high mortality and turnover within the market. New waves of firms/institutions enter specific therapeutic markets with co-specialized technologies, and only a very small minority of them survive, becomes more diversified, and transversal.

As for transversal firms on the Developers side, it is possible to notice that the group of transversal Developers is composed by a highly stable oligopolistic core, which benefits from a relevant first mover advantage and consolidates after 1992, as a consequence of the coupling between the two basic search regimes. As shown in Table 6, the set of firms active within the industry playing a *TransDev* role is composed by the very same group of large R&D intensive pharmaceutical firms that entered the market for technology very early on, and that have been playing a role of structural attractors during the whole history of bio-pharmaceutical industry. Moreover, Table 5 and Table 6 reveal that those firms that started to act as *TransDev* since the beginning of the Nineties were already part of the core of the market in the previous years.

Tab. 5 — Transition Probability Matrix of relational roles, ante/post 1992.

(a)	*exit*	*CospDev*	*TransDev*
entry	-	95.75	4.25
CospDev	65.15	31.74	3.11
TransDev	16.67	43.33	40

(b)	*exit*	*CospOr*	*TransOr*
entry	-	93.88	6.12
CospOr	65.23	32.17	2.60
TransOr	50.51	42.93	6.56

Table 6: *First 15 firms active as TranDev,1981-1997*

TransDev Firms	Number of years
Hoffmann-La Roche*	7
Glaxo Wellcome*	6
SmithKline*	6
Abbott*	5
Bayer*	4
Bristol-Myers Squibb*	4
Merck & Co*	4
Pfizer*	4
Schering-Plough*	4
Ciba-Geigy/Novartis*	4
DuPont*	3
Hoechst Marion Roussel	3
Lilly*	3
Sandoz/Novartis*	3
Wyeth-Ayerst*	3

(*) Firms that were *CospDev* before 1992

4 Concluding discussion

In this paper we have analyzed the structural evolution of the market for technologies in pharmaceuticals in the last twenty years.

On the positive side, this essay confirms that some fundamental structural properties observed at the level of relevant knowledge bases are preserved in the structural evolution of the overall system of relationships (see also Orsenigo, Pammolli, Riccaboni, 2000). Specifically, both the growth of knowledge and the structural evolution of the market have been characterized by fast expansion, proliferation of research trajectories and techniques, and hierarchization. The cumulative nature of such processes has been imposing different degrees of structural stability within the market. Finally, major changes in the market structure have occurred in correspondence with the emergence of a new set of general purpose technologies.

Moreover, relevant knowledge bases and related learning processes have induced particular patterns of division of labour between different types of firms active within the market. Our results indicate that two different logics of exploration and technological advance have been coexisting and complementing each other in the process of market evolution. The first avenue has been following a trajectory of increasing specification of biological knowledge and research hypotheses. The second has been progressing towards the development of transversal techniques to generate and screen compounds and molecules. The first trajectory has been generating patterns of division of labour in which older generations of firms have been working at higher levels of generality linking

with successive generations of new entrants, who typically embodied increasingly specific hypotheses and techniques. The second trajectory has tended to alter this inter-generation structure. All in all, several mechanisms, rooted on markets, firms, and technologies, have influenced the patterns of division of labour, dynamically interacting to produce quite complex structures.

In both cases, established R&D-intensive pharmaceutical firms have been able to absorb the new knowledge by interacting with new entrants. In fact, the expansion of the network has been driven mainly by the entry of new agents embodying new techniques. The network has taken a distinct hierarchical structure, with different firms operating at different levels of generality, which was perturbed but not broken by transversal techniques. The above evidences support, in our view, two hypotheses already advanced in the literature, namely: a) the cumulativeness of learning and competence building processes (see Henderson, Orsenigo, and Pisano, 1999); b) the significant capabilities by a core of established multi—technology, R&D intensive, corporations to absorb new knowledge and techniques generated outside firms boundaries, despite major technological discontinuities and breakthroughs initially resulting in the growth of specialized technology producers. (see Henderson, 1994).

The evidence presented in this paper suggests also that firms tend to be persistent in their structural position within the market. Put it in another way, specialist firms have tended to remain specialists, while early entrants have enjoyed significant first mover advantages, precisely because they have been able to embody knowledge at a high level of generality. Thus, a major asymmetry

has characterised the evolution of the market: while in many cases "generalist" firms have been able to (gradually) absorb increasingly specific knowledge (at least along particular trajectories of research), specialist firms found it much harder to move into the opposite direction.

Obviously, first mover advantages, the asymmetry between "generalists" and specialists and —more broadly— the observed process of hierarchization of the market, may well be related to other "more traditional" variables, such as firms size, degrees of diversification, available resources, etc. In more general terms, one can legitimately wonder if the observed dynamics of the market is after all an "unconditional object", which might have been generated by processes and influenced by different variables than those emphasised in this paper. Indeed, controlling for variables like firms size, diversification, propensity to make agreements, etc., constitutes an important part of our future research agenda. It is worth noting, however, that first, an explanation based on conventional firms features is not in contrast with our interpretation. Second, the results we get support the potential value of an approach.which emphasizes the relevance of the specific properties of relevants knowledge bases, learning, and technologies. In particular, one has to notice that the market for technology that we have been analyzing, even if it is the product of a collection of individual exchanges conducted through legal contracts (licensing agreements), cannot be analyzed as if it was a 'conventional' market. On the one hand, it changes its nature over time, sustaining a wide spectrum of structural configurations and fostering a continuous expansion of the set of productive opportunities. On the other

hand, firms and technologies that are embedded within it generate a degree of interconnectivity that one would expect within a given organization rather than in a decentralized system of autonomous agents linked through individual contractual relationships.

On a more methodological vein, the topological methods we have applied in the context of this paper seem to be a powerful device to deal with *the evolving nature of markets for technology*. Facing a system of contractual relationships that is perturbed by dramatic technological breakthroughs, they convey information that is global in nature and complements nicely the local information that is provided by local differential operators embedded in any econometric exercise. In particular, it is possible to compare alternative (qualitatevely diverse) structural configurations of the overall system at different points in time, distinguishing set of actors that play different relational roles within the market. Moreover, these graph theoretical tools and measures succeed in unraveling how technological change generates a number of more or less distinct submarkets characterized by different degrees of interdependence. On this, sectoral specificity notwithstanding, a more general issue which arises from this paper refers to admissible aggregations in the study of a market for technologies, analyzed as a dynamic interdependent system. That is, the conditions at which a large system of interacting economic agents can be clustered into a small number of groups, so that interactions among the nodes that pertain to every single group can be studied independently from interactions among groups and, conversely, interaction among groups may be analyzed without reference to the

interaction within groups. It is our claim that such an apparatus can be used in any R&D intensive industry, to assess the implications of entrepreneurship, technologies, and markets for patterns of specialization and division of labor, industry structure and, ultimately, economic growth

References

[1] Anderson C. J., Wasserman S., Crouch B., 1999, "A p* Primer: Logit Models for Social Networks", *Social Networks*, 21, 37 - 66.

[2] Arora, A., Fosfuri, A., Gambardella, A., "Markets for Technology. Why do we see them, why don't we see more of them, and why we should care" *University Carlos III*, wp, Madrid, Spain.

[3] Arora A., Gambardella A., 1994, "Evaluating technological information and utilizing it, Scientific knowledge, technological capability, external linkages in biotechnology", *Journal of Economic Behavior and Organization*, 24, 1, 91 - 114.

[4] Asratian A. S, Denley T. M. J., Haggkvist R., 1998, *Bipartite Graphs and their Applications*, Cambridge University Press, Cambridge.

[5] Besag J. E., 1974, "Spatial Interaction and the Statistical Analysis of Lattice Systems (with Discussion)", *Journal of the Royal Statistical Society*, Series B, 34, 75 - 83.

[6] Bollobas B., 1985, *Random Graphs*, Academic Press, New York.

[7] Diersel R., 1997, *Graph Theory*, Springer-Verlag, Berlin.

[8] Dosi G., 1982, "Technological Paradigms and Technological Trajectories. A Suggested Interpretation of the Determinants and Directions of Technical Change", *Research Policy*, 11, 147 - 162.

[9] Dosi G., Nelson R. R., Winter S., eds., *The Nature and Dynamics of Organizational Capabilities*, Oxford University Press, Oxford.

[10] Dulmage A. L., Mendelsohn N. S., 1958, "Some Generalization of the Problem of Distinct Representatives", *Canadian Journal of Mathematics*, 10, 230 - 241.

[11] Dulmage A. L., Mendelsohn N. S., 1959, "A Structure Theory of Bipartite Graphs of Finite Exterior Dimensions", *Transactions of the Royal Society Canada Ser.*, 53, 1 - 13.

[12] Föllmer H., 1974, "Random Economies with many Interacting Agents", *Journal of Mathematical Economics, 1, 51-62.*

[13] Frank O., Strauss D., 1986, "Markov Graphs", *Journal of the American Statistical Association*, 81, 832 - 842.

[14] Galambos L., Sturchio J., 1996, "The Pharmaceutical Industry in the Twentieth Century: A Reappraisal of the Sources of Innovation", *History and Technology*, 13, 2, 83 - 100.

[15] Gambardella A., 1995, *Science and Innovation. The US Pharmaceutical Industry during the 1980s*, Cambridge University Press, Cambridge.

[16] Goodwin R. M., 1947, "Dynamical Coupling with Especial Reference to Markets having Production Lags", *Econometrica*, 15, 181 - 204.

[17] Harary F., Norman R. Z., Cartwright D., 1975, *Structural Models: An Introduction to the Theory of Directed Graphs*, John Wiley & Sons, New York.

[18] Harvey A. L., ed., *Advances in Drug Discovery Technologies*, Wiley, New York, 1998.

[19] Henderson, R., 1994, "The Evolution of the Integrative Competence: Innovation in Cardiovascular Drug Discovery", *Industrial and Corporate Change*, 3, 3, 607 - 630.

[20] Henderson, R., Orsenigo, L., Pisano, G., 1999, "The Pharmaceutical Industry and the Revolution in Molecular Biology: Interactions Among Scientific, Institutional, and Organizational Change", in Mowery D., Nelson R., eds., *Sources of Industrial Leadership*, Cambridge University Press, Cambridge, Ma., 267-311

[21] Kirman A. P., 1998, "The Economy as an Interactive System", in Arthur W. B., Durlauf S., Lane D. (eds.), *The Economy as an Evolving Complex System II,* 419 - 531, Addison Wesley.

[22] Lovasz L., Plummer M. D., 1986, "Matching Theory", *Annals of Discrete Mathematics*, 29, North Holland, Amsterdam.

[23] Malerba F., Orsenigo L., 1993, "Technological Regimes and Firm Behavior", *Industrial and Corporate Change*, 2, 1, 45 - 72.

[24] Mirsky, L., 1971, *Transversal Theory. An Account of same Aspects of Combinatorial Mathematics*, Academic Press, New York.

[25] Nelson, R., Winter, S., 1982, *An Evolutionary Theory of Economic Change*, Harvard University Press, Cambrdige, Ma.

[26] Orsenigo, L., Pammolli, F., Riccaboni, 1998, "The Evolution of Knowledge and the Dynamics of an Industry Network", *Journal of Management and Governance*, 1, 2, 147 - 175.

[27] Orsenigo, L., Pammolli, F., Riccaboni, M., 1999, "Technological Change and Network Dynamics. The Case of the Bio-Pharmaceutical Industry", *Research Policy,* forthcoming.

[28] Palmer E. M., *Graphical Evolution*, Wiley, New York.

[29] Pattison P., Wasserman S., 1997, "Logit Models and Logistic Regression for Social Networks: II. Multivariate Relations", *British Journal of Mathematical and Statistical Psychology.*

[30] Powell K., Koput K., Smith-Doerr L., 1996, "Interorganizational Collaboration and the Locus of Innovation: Networks of Learning in Biotechnology", *Administrative Science Quarterly*, 41.

[31] Richardson G. B., 1972, "The Organization of Industry", *The Economic Journal*, 82, 883 - 896.

[32] Simon H.A., 1962, "The architecture of complexity", *Proceedings of the American Philosophical Society*, 106, 467 - 482.

[33] Simon H. A., Ando A., 1961, "Aggregation of Variables in Dynamic System", *Econometrica*, 29, 111 - 138.

[34] Slepian P., 1968, *Mathematical Foundations of Network Analysis*, Springer-Verlag, Berlin.

[35] Strauss D., Ikeda T., 1990, "Pseudolikelihood Estimation for Social Networks", *Journal of the American Statistical Association*, 85, 204 - 212.

[36] Sutton J., 1998, *Technology and Market Structure*, MIT Press, Cambridge, MA.

[37] Wasserman S., Pattison P., 1996, "Logit Models and Logistic Regressions for Social Networks: I. An Introduction to Markov Graphs and p*, *Psychometrika*, 60, 401 - 426.

[38] Winter S., 1984, "Schumpeterian Competition in Alternative Technological Regimes", *Journal of Economic Behavior and Organization*, 5, 287-320.