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Competencies, Technological Change, and Network Dynamics. The Case of the Bio-Pharmaceutical Industry

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Competencies, Technological Change and Network Dynamics

The case of the bio-pharmaceutical industry

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1. Introduction

This paper is a study on the organizational mechanisms guiding the search and exploitation of technological competencies. It focuses on a specific organization form, namely networks of collaborative relationships among firms, in a specific technology, pharmaceutical biotechnology. There are several reasons why we believe this subject is interesting and relevant to the broader Dynacom project.

First, networks of collaborative relationships among firms have attracted a great deal of attention in recent times among sociologists, organizational theorists and industrial economists, as it is now widely recognized that collaborative relationships are an important form of organization of innovative activities, especially (but not only) in high technology industries. It is therefore crucial to understand their logic, the processes that guide their emergence and subsequent evolution and their implications for the performance of individual companies and industries. In this paper, we focus only on a subset of these questions. We examine in particular the dynamics of networks and derive only some very preliminary implications in terms of the performance of firms, industries and countries. \ These issues will be the subject of a companion paper, which will be focused on the analysis of the role and performance of European companies within the global network

Second, biotechnology is a major new technological paradigm which has been deeply transforming the nature of the relevant competencies and of the learning processes in various industries, particularly in pharmaceuticals. The pharmaceutical industry used to be - and to a large extent still is - one of the sectors where Europe enjoyed relative and in some cases absolute technological and competitive advantages. However, over the past two decades these advantages have been partly eroded. US companies have clearly taken the lead in innovation and sales. Within Europe, British firms have shown a remarkable performance, whilst the position of the German industry - which has been an absolute world leader for almost a century - has been deteriorating. Whilst there is a considerable debate about the reasons and the extent of this decline, a wide consensus appears to exist on the consideration that this (partial) decline is linked to the joint working of two main factors: \ a series of big technological shocks and a series of large institutional shocks (ranging from the introduction of tighter regulations in the process of approval of drugs, to policies of cost containment of health expenditures, etc.). Thus, it is certainly relevant to explore in some detail how these shocks have impacted on different firms and national industries.

In this paper, we focus on technological shocks. It has been argued (see, for example Henderson, 1994, Gambardella 1995, Henderson, Orsenigo and Pisano, 1999, Pammolli, 1997) that the emergence of a new knowledge base in the pharmaceutical industry, based on biology rather than on chemistry, has led to profound transformations in the procedures underlying drug

discovery and in the organisation of the innovative process within firms and among firms and other institutions (like University laboratories). The different response of both individual corporations and national industries to these changes is certainly a major part of the explanation of the aggregate trends of competitiveness in this sector. For the specific purposes of this paper, two issues stand out as particularly challenging.

First, the new knowledge base has a distinct scientific nature and therefore it is, in principle, abstract, codified and - absent the establishment of intellectual property rights- immediately accessible by everybody. \ This makes the case of pharmaceuticals largely different from most of the cases on which the empirical literature about organizational transformations is based, which deals mainly with engineering knowledge. Moreover, there might be somewhat of a puzzle here. Given these properties, how is it that firms and national industries reacted so differently to the "molecular biology revolution"? Second, a distinct feature of the recent evolution of the pharmaceutical industry has been the emergence of a dense network of collaborative relations between various types of firms (new specialized entrants, large established corporations, universities, etc.). What does explain this "organizational innovation" and what are the variables driving the dynamics of the network over time?

One can find in the literature widely different interpretations of the nature, motivations, structure and functions of these networks, ranging from more sociologically oriented approaches to economic explanations based on (various mixes of) alternative theoretical backgrounds, e.g. transaction costs, contract theories, game theory and competence-based accounts of firms' organization. In turn, these interpretations generate widely different predictions about the evolution of collaborative relationships over time (Barley, Freeman and Hybels; 1992; Arora and Gambardella, 1994; Gambardella 1995; Powell, Doput and Smith-Doerr, 1996; Orsenigo et al., 1998)..

For example, with reference to the case of biotechnology, collaborative relations have been often considered as a transient phenomenon, bound to decrease in scale and scope as the technology matures and as higher degrees of vertical integration are established in the industry (Pisano, 1991).

In a rather different perspective, the role played by scientific knowledge in pharmaceutical research is stressed and the nature and properties of the learning processes fuel the emergence and evolution of networks. In this vein, collaborations represent a new form of organization of innovative activities, which are emerging in response to the increasingly codified and abstract nature of the knowledge bases on which innovations draw (Arora and Gambardella,1994, Gambardella, 1995). To be sure, substantial market failures exist in the exchange of a commodity like information. However, the abstract and codified nature of science makes it possible, in principle, to separate the innovative process in different vertical stages.

According to this perspective, a key factor in reducing the importance of this constraint to division of innovative labor is the growth in physical, biological and engineering sciences. This provides the opportunity of comprehending in new ways what is already known, abstracting from the idiosyncratic and contextual features of specific applications, so that what is known can be generalized to encompass several applications. Abstract and general knowledge tends to be better articulated and easier to codify in useful ways. In recent years, the growth of computing capabilities, both hardware and software, is assumed to have given a big boost to the growth of such general and abstract knowledge. In turn, this has made possible a greater separation between the production of general-purpose knowledge -- of general and abstract knowledge -- and the use of such knowledge.

Thus, according to this approach, the innovative process can be adequately represented as a sequence going downstream from science to marketing, in which division of labor can occur at any stage of the process. Different types of institutions tend to specialize in the stage of the innovative process in which they are more efficient: universities in the first stage, small firms in the second, big established firms in the third. In this view, then, a network of ties between these agents can provide the necessary coordination of the innovative process. Collaborations are likely to be a permanent feature of the industry, with a large (and possibly continuously expanding) number of entities interacting with an equally large number of other entities, generating an intricate network within which each subject specializes in particular technological areas or stages of the innovative process getting benefits from an increasing division of innovative labor.

Finally, according to some more radical interpretations, the complex and interdisciplinary nature of relevant knowledge bases in pharmaceutical R\&D tends to make technological innovations the outcome of interactions and cooperation among different types of agents commanding differentiated competencies and complementary resources (Orsenigo, 1989; Pisano, 1991; Orsenigo et al., 1998). In this perspective, it has also been suggested that the locus of innovation (and the proper unit of analysis) is no longer a firm, but a network of differentiated agents (see Powell, Koput, Smith-Doerr, 1996). In this case, the direction of causation is reversed. It is the structure of the network and the position of agents within it that fundamentally determine agents' access to relevant sources of scientific and technological knowledge and, therefore, innovative activities and performances (see also Kogut et al. 1994; Walker et al., 1997).

However, albeit with some notable exceptions (see Powell, Doput and Smith-Doerr, 1996, Walker, Kogut and Shan, 1997; Orsenigo et al., 1998), it has proved very difficult to provide strong empirical evidence in support or against these different accounts. In fact, while the natural test bed of these different interpretations should be based on the observation of network dynamics over time, most of the analyses are static in nature or perform comparative statics

exercises. On the contrary, very little has been done, at the empirical level, on the dynamics of collaborative relationships, i.e. how are they formed, how do they change over time, to which sort of configuration do they converge at, if any.

We do not review here this rapidly expanding and complex literature. However, it is possible to observe that despite their differences, most of these approaches and explanations seem to agree in principle that, particularly in high growth, technology intensive industries, networks of collaborative relationships have to be analyzed as organizational devices for the coordination of heterogeneous learning processes by agents endowed by different skills, competencies, access to information and assets.

Thus, learning ought to be a central concern in the analysis of collaborative relationships. Beyond a rather generic agreement, though, available empirical analyses do not address the specific nature and properties of the underlying knowledge bases and search activities that should be used as explanatory constructs. Consequently, it becomes hard to understand clearly what are the implied relationships (if any) between the structure and functions of the network and its evolution on the one hand, and the fundamental features of the relevant learning processes on the other.

Against this background, this paper aims to move a step forward in the direction of establishing a closer connection between the structure and evolution of knowledge and the structure and evolution of organizational forms in innovative activities.

As compared to the existing literature on network of collaborative agreements, this paper is characterized by an explicit focus on the technological and cognitive determinants of the structure and dynamics of relevant industrial variables (see Dosi, 1982).

The nature and evolution of underlying technological conditions are explored in order to identify major boundaries to the range of possible structural configurations which the structure of the network can assume over time.

We rediscover the mathematical language of the theory of directed graphs moving back from concepts, measures, and explanations developed in the field of social network analysis, in order to explain how scientific and technological knowledge induce distinguishable patterns of change at the macro level of industry structure and evolution .

By means of graph theory, we develop a set of indicators that have not been exploited in the field of social network analysis. In particular, graph theory appears to be very useful to unravel the complex properties of empirical objects such diverse as technological and industrial structures, revealing the existence of basic technological determinants of network structure and evolution.

First, we describe some basic features of research strategies and heuristics underlying the evolution of relevant knowledge bases in the field of analysis. Second, the relevant features of\ the structure and evolution of the industry network are examined.

We come to demonstrate that a mapping exists that goes from decompositions and research heuristics observed in scientific and technological research to the patterns of structural evolution at the macro level of the industry network.

In other words, the specific nature of relevant problem solving strategies and learning processes turns out to be a fundamental determinant of the structure and dynamics of the network of collaborative agreements.

The paper is organized as follows.

Section 2 briefly highlights the nature and goals of some fundamental 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 particular, a fundamental distinction is captured between co-specialized and transversal research technologies/strategies; that is, between heuristics/research techniques that tend to be specific to particular domains, and heuristics/research techniques that are both generic and, at the same time, complementary to co-specialized ones.

In Section 3, we highlight some implications of the nature of these heuristics and research strategies on the organization of innovative activities and on patterns of evolution of the network of R&D collaborative relationships.

In Section 4 we turn to the empirical analysis of the evolution of the network. Graph theory and numerical representations of networks are introduced, coming to show the existence of a striking homomorphic relationship with the structure and evolution of most recurrent research hypotheses and techniques used in problem solving activities. We refer to the notion of Canonical Decomposition of a graph in order to disentangle two major drivers/components of the structural evolution of the net, i.e., co-specialized and transversal actors that rely on co-specialized and transversal research techniques.

The presentation of the main findings and the discussion of some implications for the analysis of organization and industrial dynamics close the paper.

2. The growth of scientific and technological knowledge in pharmaceutical R&D

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; Henderson, Orsenigo, Pisano, 1999).

In fact, the so-called "*molecularization*" of physiology, pathology and pharmacology, corresponds to a principle according to which for the development of new powerful and selective drugs search has to penetrate deeply into the human organism to unravel the biochemical interactions at the cellular, infra-cellular and, most importantly, molecular levels.

According to the molecular biology paradigm, the route to understanding of human organism (nature) is through the dissection of the system in its constituent parts, followed by the study of these parts. The properties of the whole – and hence its behavior – are the sum of the properties of the parts, while pathologies are analyzed in terms of specific alterations of the molecules that constitute the human organism. This philosophy has had profound effect on the methods of inquiry, leading scientists to pursue the pattern: "study: dissect, identify, classify, and dissect further" (Testa, Meyer, 1995, p. 6).

In this perspective, the development of new drugs rests on the ability to generate more general theories that yield an increasingly "deeper" explanation of processes that take place at higher levels of organization of matter inside the human organism.

Notably, with reference to the range of possibilities for therapeutic intervention, the convergence at the level of scientific explanations generated by the progress of fundamental knowledge corresponds to the identification of longer and more complex chains of causal events. In fact, for almost all the more complex pathologies, the inner dynamics of knowledge has been leading to a proliferation of a priori hypotheses on plausible research trajectories. Whilst new scientific explanations and discoveries can lead to deeper knowledge and, moreover, more fundamental explanations of the nature of processes that happen in the human organism can focus search at a given level of analysis, the very same achievements generate new hierarchies of sub-hypotheses.

This dynamics creates a dilemma: by definition, more fundamental theories explain more but, simultaneously, they multiply the number of points of entry for the discovery and the development of new therapeutic treatments.

In other words, the very process of convergence at the level of scientific explanations can lead to a process of divergence in research strategies generated along the hierarchy of increasingly specific sub-hypotheses, with an increase in the number of alternative routes for intervening in the disease process.

To put it differently, scientific progress certainly "simplifies" the search space, eliminating certain alternatives that are proven to be wrong (Nelson 1959; Arrow, 1962). However, at the same time, scientific discoveries generate a deformation and an expansion of the search space, by suggesting new competing hierarchies of sub-hypotheses as well as previously unconceivable opportunities of discovery. Moreover, many research techniques and biological targets tend to be typically characterized by high degrees of co-specialization. That is to say, research techniques tend to be relatively specific to particular fields of application. Thus, a proliferation is observed in the number of trajectories, techniques, and ex ante conceivable exploration strategies.

Moreover, technologies such as genomics, gene sequencing, transgenic animals, and molecular biology have started to supply the industry with a huge number of novel biological targets thought to be relevant to a vast array of diseases defined at the molecular level and developing highly sensitive assays incorporating these targets.

The substantial growth of biological knowledge on the human organism at the cellular, molecular and genetic levels notwithstanding, the discovery and development of drugs continues to be a lengthy, expensive and often unsuccessful process. Within this context, the increasing number of plausible targets has generated severe bottlenecks in the drug discovery process, associated with the difficulty of quickly and cheaply analyzing function and disease relevance of newly discovered targets and matching related compounds (see Vos, 1991).

Against this background, during the Eighties and Nineties new developments in solution phase and solid phase chemistries, high-throughput screening technologies (HTS), information technologies, and combinatorial chemistry have led to the development of research technologies that allow to achieve a higher breadth of applications, measured in terms of the number of disease areas and biological targets to which the technology may be applied.

In extreme synthesis, while several thousand genetic targets could not have been addressed with the methods of conventional medicinal chemistry, the development of combinatorial chemistry libraries, together with new techniques for high-throughput screening and ever-improving bio-informatics tools, has gradually made it possible to test a large number of potential drug targets against an even larger number of chemical entities[1].

[1] *Combinatorial chemistry enables rapid and systematic assembling of a variety of molecular entities, or building blocks, in many different combinations to create tens of thousands of diverse*

More generally, during the Nineties a set of generic research technologies has been developed, from *Polymerize Chain Reaction* to protein structure modeling, rapid computer based drug assay and testing, recombinant chemistry techniques, drug delivery systems, chemical separation and purification techniques that allow researchers to screen thousands of potentially promising compounds.

On the whole, the recent evolution of research strategies and heuristics in pharmaceutical R&D can be characterized by discerning between two main search regimes, that coexist within the industry. The first regime is essentially based on research techniques that tend to be specific to given fields of application (co-specialized technologies) while the second regime is characterized by the emergence of new generic tools (transversal technologies).

In the case of co-specialized research technologies, the design and experimentation of each new drug tends to require individual analysis, while lessons learned from the design and experimentation of one therapeutic cannot be immediately transferred to the development of other classes of drugs. Conversely, transversal technologies are in principle applicable to multiple biological targets and diseases. However, since pharmaceutical R&D "deals with a system – the human body – far more complicated than any mechanical or electronic system" (Gambardella, 1995, p. 16), co-specialized and transversal techniques remain coupled to each other, in the context of research projects and development activities carried out under conditions of strong uncertainty[2].

3. From growth of knowledge to network dynamics

So far, we have identified some properties of the processes of scientific discovery underpinning research activities in the pharmaceutical industry. An extensive literature has documented some of the consequences that the advent of molecular biology has produced on the

compounds that can be tested in drug discovery screening assays to identify potential lead compounds. Large libraries are available to be tested against both established and novel targets to yield potential lead compounds for new medicines. Such vast numbers of compounds have been introducing a substantial challenge to the drug discovery process and have created a need for faster and more efficient screening. High-throughput screening (HTS) methods make it possible to screen vast populations of compounds via automated instrumentation: that is, complex workstations capable of performing several functions with the help of mechanical arms or simpler automated dilution devices.

[2] *For example, new technologies including high-throughput methods for sequencing genes, for monitoring and comparing their expression in different situations, and following their inheritance in families prone to particular diseases, depend crucially on the integration of molecular biology with robotics, and analytical instrumentation. The integration of these disciplines has started to provide powerful capabilities for generating and analyzing large volumes of data about genes and their expression, making it possible for the first time to mount a systematic search effort to discover and characterize the genes and biochemical pathways which underlie human diseases.*

organization of innovative activities, at the firm level and at the industry level (Henderson, 1994; McKelvey, 1995; Gambardella, 1995; Orsenigo, 1989; Galambos and Sturchio, 1998; Henderson et al., 1999). In particular, it has been emphasized that the emergence of a dense network 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.

In this section, we examine in more detail if and how the specific properties of the processes of scientific discovery in molecular biology influence the patterns of evolution of the network of collaborative relationships. Our main claim is that these basic properties ought to be preserved in the dynamics of the network, if such a form of organization of innovative activities has (at least partly) to be understood as an adaptive response to the structural cognitive features of the dynamics of search activities. That is, if the specific properties of learning processes influence and constrain the possible forms of organization of innovative activities.

Let us briefly summarize the basic properties of the dynamics of knowledge discussed in the previous Section. First, a process of fast expansion of biological knowledge in the fields of biochemistry, physiology and pathology has been surging within the industry. Secondly, such growth of knowledge has taken the form of a branching process, in which general hypothesis gives origin to a variety of 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 hierarchical nature. Fourth, the overall process is highly cumulative, since it is based on a dynamics that introduces progressive specifications of biological hypotheses at each level of the hierarchy. Fifth, this 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 the appearance of transversal technologies for the production and screening of new molecular structures has introduced a new dimension in the evolution of the relevant knowledge bases.

According to our conjectures, these basic properties ought to be reflected in the network of collaborative relationships. We address only indirectly the question why collaborative agreements have become such an important form of organization of innovative activities. This would imply the specification of a fully-fledged model of how cognitive structures influence organization forms (for a first attempt, see Pammolli and Riccaboni, 1999). We advance some rather specific hypotheses on how the structure of the network should look like and treat the empirical evidence as a sort of reduced form of a well-specified structural model.

It is important to notice that the task of specifying the linkages between the properties of the dynamics of knowledge and the structural evolution of the network is somewhat facilitated

by the very special nature of the pharmaceutical-biotechnology industry, as a strongly science-based sector. Differently from other industries or technologies, in this case, scientific research has had (and continues to have) a direct and immediate relevance for innovative activities. The proliferation of new companies specialized in the production of new techniques and products directly derived by cutting edge academic scientific research and the development of a dense network of collaborative relations among firms are – as it is well known – prominent features of the industry.

In the following empirical analysis, a research hypothesis/technique is associated to a specific R&D project embedded in a firm/institution. Every firm/institution is defined by the collection of its research projects over time, while agreements are conceived as organizational devices through which hypotheses/techniques are combined and in which an *Originator* can be distinguished from a *Developer* (see Appendix 1 for technicalities).

On these bases, we can advance the following testable "predictions".

First, as projects correspond to research hypotheses/techniques, and provided that the latter proliferate over time, originated by an increasing number of firms, we would expect to observe an expansion of the network over time. This growth may take place both through the entry of new firms and by means of an increase in the number of agreements between existing agents. Secondly, the hierarchical structure of growth of knowledge should result in a process of hierarchization of the network, with the emergence of a core of firms/institutions who are able to manage general hypotheses/projects. Third, given the cumulative nature of the growth of knowledge, earlier (later) entrants in the network should embody more general and stable (specific and unstable) hypotheses. Thus, we would expect to observe the development of a stable core in the network – composed mainly by earlier entrants – linking with an expanding turbulent fringe of later, more co-specialized, entrants. Fourth, this structure would be perturbed by the entry of new agents embodying either new "general" hypothesis, a wide portfolio of specialized techniques, or "transversal" techniques. In such a circumstance, one would observe a reduction of the degree of hierarchization of the network, as these agents are in principle able to link with many other actors and – in the case of transversal techniques – they would also induce a shift in the profile of relationships between earlier and later entrants.

Please note that we are not making any assumptions about the role of firm size, degree of diversification and propensity to enter into collaborative relationships. These are clearly important firms characteristics that ought to be controlled for and that might induce dynamic patterns in the network similar to those described above. We shall discuss these issues in the concluding section.

The importance of the technological determinants of the structural evolution of the network of collaborative agreements can be appreciated, at a first glance, by looking at Figure 1.

Figure 1 is based on a 3D graphical representation of the network by means of level curves. Columns correspond to the *x*-axis (*Originators*), while rows to the y-axis (*Developers*). Levels $z(x,y) = b_{ij}$ indicate the cumulated number of agreements between firms *i* and *j*, classified according to year of entry into the network, with darker regions representing areas of higher relational intensity.

Figure 1 shows that:

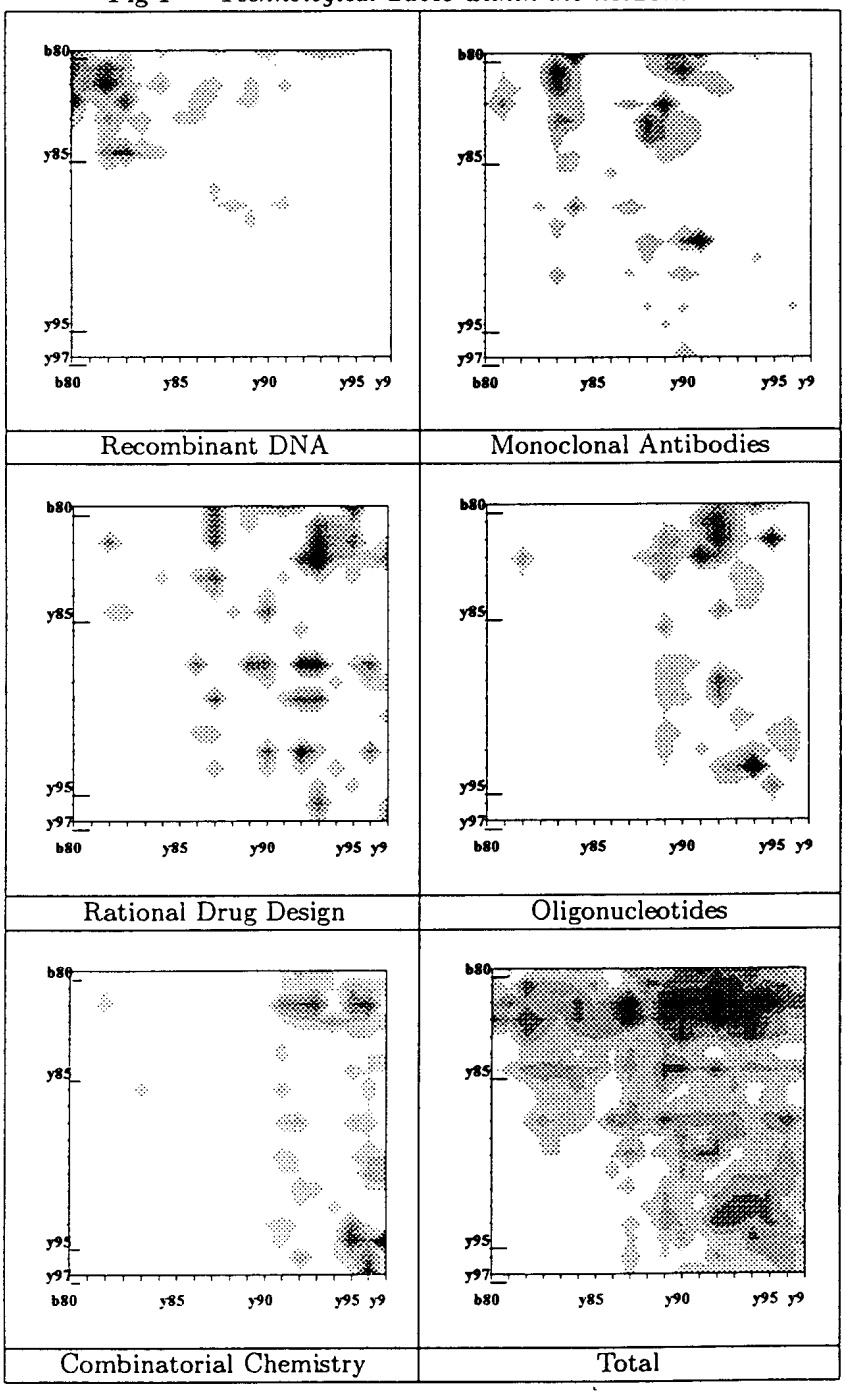
i) *Originators* have entered the network by introducing successive waves of new research technologies, which shape the overall evolution of the network;

ii) Firms already active within the network have not played a major role as *Originators* in the new technological trajectories that have emerged after their entry;

iii) Rather, earlier entrants have gained access to the new technological trajectories mainly as *Developers*.

iv) As times goes by, the rate of entry in any given technological trajectory has been slowing down. That is to say, entrants are closely linked to the generation of new technological trajectories.

Fig 1 — *Technological waves within the network*



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 with the following properties. Major new technological breakthroughs initially induce the entry of new Firms/Institutions, which act 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.

v) After 1992, the emergence of *transversal technologies* like combinatorial chemistry has been perturbing the structure of the network. New entrants based on the new transversal technologies and acting as *Originators* make more agreements than *Developers* because they establish relations with a large variety of Firms/Institutions, irrespective of age.

4. The evolution of the industry network

This section analyzes in detail the transformations occurred in the organization of innovative activities within the international pharmaceutical industry during the period between 1978 and 1997.

Several graph theoretical measures are applied to investigate the evolution of the inter-organizational R&D activity that has characterized the pharmaceutical industry after the emergence of molecular biology.

The analysis is based on a unique data set obtained by integrating several fonts. In particular, we merged a *proprietary database* on more than 14.000 pharmaceutical R&D projects with information about collaborative agreements drawn from a handful of well-known sector-specific databases (*Bioscan*, *Recombinant Capital*, *IBI*). Finally, we updated the resulting database by means of annual reports (*SEC files*), and specialized press (*Scrip*, *Spectrum*).

Tab. 1 - *The collaborative agreement data set*

Type of contacts	
License	3039
Research	1359
Development	1641
Equity	860
Collaboration	818
Supply	453

Technology	
Miscellanea	958
Drug Delivery	650
Monoclonals	489
Screening	463
Recombinant DNA	405
Synthetics	364

Option	445	Oligonucleotides	348
Distribution	388	Combinatorial Chem.	217
Marketing/Promotion	326	Gene Sequencing	207
M&A	321	Gene Expression	193
Joint Venture	226	Rational Drug Design	127
Asset Purchase	186	Transcription Factors	107
Manufacturing	169	Cell Therapy S.C.F.	103
Warrant	108	Phototherapy	36
Loan	93	No Information	389
n.a.	26	Total	5056

On the whole, the *collaborative agreement data set* considered for this paper covers 5056 agreements and 9785 research projects carried out by 2297 firms and institutions (*F/Is* from now on). Among them, 651 units have been classified as "Incumbent Firms" (*INC*: firms founded before 1973); 1372 units have been classified as "New Biotechnology Firms" (*NBF*: firms founded after 1973) and 274 units have been considered to be "Institutions" (*INST*: Universities, Hospitals, Public/Private Research Institutions). Merger and acquisitions have been taken into account by collapsing information relative to the firms engaged in consolidation deals starting from the date of subscription[3]. With regard to collaborative agreements, the data set provides detailed information about the typology, the technological content and the date of signing (on a monthly basis)[4]. Table 1 synthesizes the broad characteristics of the overall dataset.

Starting from the complete database, the subset consisting only of the R&D agreements has been selected. A total of 3973 agreements signed by 1709 *F/Is* have been extracted. The *R&D agreement data* set contains information on 349 *INCs*, 1112 *NBFs* and 248 *INSTs*.

Table 2 classifies agreements according to their stage of signing. Interestingly, more than 88% out of the total number of collaborations were subscribed before the starting of the development stage. Furthermore, more than 76% of the total number of R&D agreements include a licensing contract.

[3] *It is worth nothing that, especially in the Nineties, M\&A activities strongly contributed to the process of hierarchization of the net.*

[4] *Every agreement may include different contract typologies at the same time. The information on the technological content is available for each agreement as it refers to the underlying discovering technology.*

Tab. 2 - *Classification of R&D agreements according to the stage of signing*

Phase	%
Discovery	47.08
Lead molecule	17.09
Formulation	15.89
Preclinical	8.49
Clinical I	3.72
Clinical II	4.74
Clinical III	2.99

In Appendix 1 the network of R&D collaborative agreements is rigorously defined in graph theoretical terms and the formal apparatus required for the analysis of its structural evolution is highlighted. In particular, the overall network is referred to as a digraph (Harary, 1969; Harary et al., 1975). More specifically, the digraph is identified according to a time *orientation*. That is to say, for any given R&D project, we identified the F/I which acts as the *Originator* (*o*) from the one that acts as the *Developer* (*d*). In addition, the digraph has been *ordered* on the basis of time of F/I entry within the network. To put it differently, each node of the graph has been labeled by the date of signing of the first agreement. In synthesis, two distinct time dimensions have been identified: the first one is defined at a micro level (the distinction project *Originator/Developer*); the second is singled out at a macro level (the emergence of the overall industry network as a product of F/Is entry and new agreements).

In what follows, the digraph is analyzed in order to explain its main structural properties in terms of both determinants of structural inertia and persistence, and drivers of structural instability and change. To accomplish this goal four major steps will be undertaken in the following sections:

1. Some generic properties of the evolution of the graph are analyzed. In particular, we observe that the graph expands almost exponentially over time and that such growth is

essentially driven by the entry of new firms/institutions, while the density of the graph slightly decreases;

2. Some permanent structural properties of the digraph are identified. Despite the steady rate of growth of the overall network, we find high levels of structural stability, both in terms of degree of asymmetry, intransitiveness, and hierarchization. Moreover, the digraph is shown to be "time reverse", as time *order* and time *orientation* are inversely related.

3. The degree and sources of structural instability within the graph are investigated. As a reference point (a sort of null hypothesis), we start hypothesizing a conservative process being in place. At any point in time, such an inertial process would reproduce the same invariant structural properties. If such a process captured the dynamics of the network, one would observe a smooth structural change, despite the intense growth of the network. In particular, given that the growth of the network is driven by flows of entry, structural inertia would be the effect of a cumulative, incremental technological dynamics. Moreover, given the time reversal phenomenon we mentioned above, it would be possible to locate the source of structural stability at the level of the process driving the entry of new *Originators*.

However, the empirical analysis carried out in order to test the structural inertia hypothesis has revealed two major sources of departure from such a conservative process. On the one hand, a strong first mover advantage is observed for firms that entered the network before 1981. On the other hand, some important destructuring patterns are identified for the years following the peak of entry of 1992.

4. The departures from the structural inertia hypothesis are examined using the notion of Canonical Decomposition of a bipartite graph (Dulmage Mendelsohn, 1958; 1959), which allows us to categorize F/Is according to the role they play in the dynamics of the network. Specifically we identify two groups of subjects; that is, a group of F/Is which interact locally with given types of partners, and another group whose interactions are de-localized, i.e. are not restricted to a particular category of partners. What is even more interesting, is that F/Is belonging to any one of these two categories are immediately identifiable by the nature of the competencies they embody. The formers are active in those technological sub-fields that are recognized to be co-specialized, while the others are active in transversal technologies.

In synthesis, our empirical analysis reveals that major changes in the network structure take place in correspondence with major shifts occurring at the level of the underlying scientific and technological bases.

In order to properly identify that relationships, we have built an original formal apparatus for the representation of the structural evolution of a network of interacting economic agents.

4.1 *Growth of the network and patterns of entry*

For the period of time from 1985 to 1997, Figure 2 shows the number of firms founded per year, the number of R&D projects started/ended per month and, finally, the one-year moving average of monthly-subscribed R&D agreements. Over time, the number of ties grows approximately in proportion to the number of firms within the network. As a consequence, we observe a steady decrease in the density of the net that moves from about one per cent at the beginning of the Eighties to less than 0.15 per cent in 1997. The analysis of patterns of firms entry in pharmaceutical industry reveals the existence of two peaks in 1988 and 1992. *Both R&D projects and collaborative agreements are driven by flows of entry*, with an average time lag of, respectively, two and three years (see also Oliver, 1993; Orsenigo et alii, 1998). It is worth noting that the number of collaborative agreements parallels the number of R&D projects over the whole time period but after 1992. Starting from 1992, two different patterns are detectable. From 1992 to 1994, it is possible to observe a higher growth in the number of R&D projects as compared to that of agreements; on the contrary, since 1994 an opposite pattern has been in place.

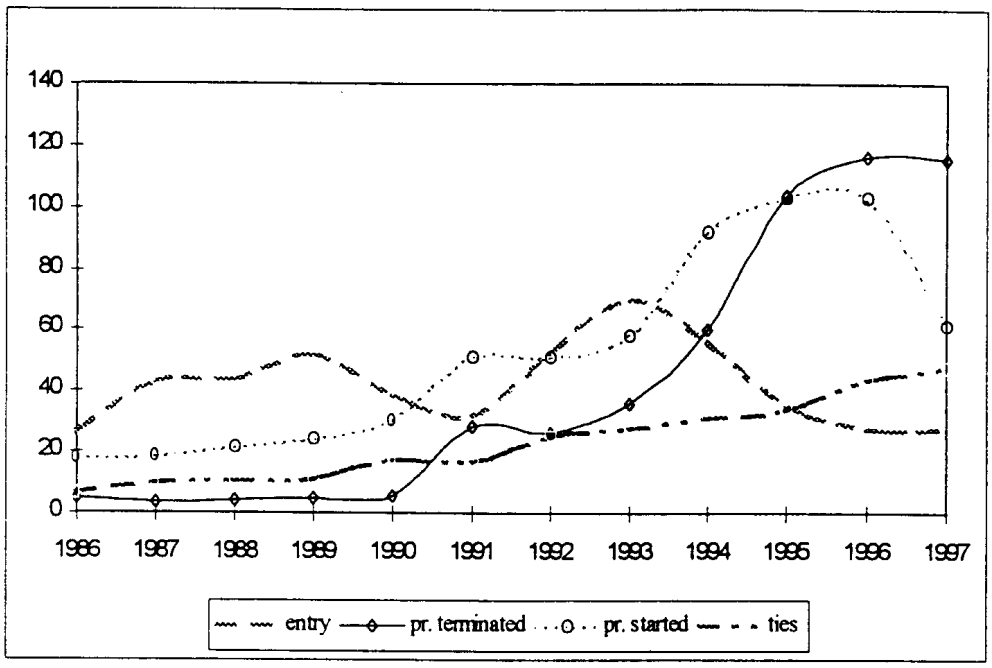


Fig. 2 — *Entrants, R&D projects, and R&D agreements*

4.2 *Structural properties of the graph*

The network of agreements at time *t* is represented as a digraph $G_t(E,V)$, whose vertices *V* and edges *E* consist, respectively, of F/Is active in pharmaceutical research and development (*V*) and of R&D formal collaborations among them (*E*) drawn up by time *t* .The digraph G_t can be univocally represented by an *adjacency matrix* $G_t \Leftrightarrow A(G)_t=[a_{do}]_t$. Matrix entry a_{do} is equal to 1 if an edge *e(d,o)* does exist at time *t*, while a_{do} is equal to 0 otherwise. Matrix rows consist of all the vertices V_d (*Developers*), while matrix columns consist of all the vertices V_o (*Originators*). Thus, rows and columns vectors define, respectively, the sets of projects for which each F/I has acted respectively as an Originator and a Developer until time *t*.

dDegree(*i*,*t*) and *oDegree*(*i*,*t*) of vertex *i* at time *t* are given by the sums of matrix entries over row and column *i*. The total *Degree*(*i*,*t*) equals the sum of *dDegree* and *oDegree*.

As mentioned already, the set of vertices can be ordered according to time of entry into the network. Consequently, it is possible to permute the adjacency matrix in order to obtain a matrix $A(G)_{\leq t} = [a_{do}]_{\leq t}$, where $d \in \{1,\ldots,n$, $o \in \{1,\ldots,m$, with $\{\varepsilon(1) \leq \ldots \leq \varepsilon(d) \leq \ldots \leq \varepsilon(n) \leq t$, and $\{\varepsilon(1) \leq \ldots \leq \varepsilon(o) \leq \ldots \leq \varepsilon(m) \leq t$, where ε is the month of entry into the network.

Afterwards, it is possible to pass from $A(G)_{\leq t}$ to $A(G)_{\leq (t+1)}$ by adding rows and columns corresponding to F/Is entering the network at time $(t+1)$ and updating the entries of the new matrix according to latest agreements.

Sometimes, we shall use a more concise representation of the digraph structure at time *t*, by considering the block matrix $B(G)_{\leq t(\theta)}$ obtained by collapsing rows and columns of matrix $A(G)_{\leq t}$ that correspond to F/Is belonging to a common cohort of entrants defined by the time period $\theta=[t, t+\theta)$ (Generation). Entries b_{ij} of $B(G)_{\leq t(\theta)}$ indicate the total number of agreements between *Generations i* (*Developers*) and *j* (*Originators*) at time *t* (see Table 3).

The analysis of the structural properties of the digraph has led to the following results:

A - *The digraph is asymmetric*

For almost all relationships $e(d,o)$, $\varepsilon(d) < \varepsilon(o)$ i.e., the *Originator* usually entered the network after the *Developer* does. Early entrants act mostly as *Developers*. Moreover, earlier generations of *Developers* establish a large number of agreements with a large number of later entrants, which act as *Originators*.

Data presented in Table 3 show that a large number of R&D agreements are associated with projects started by both younger firms and research institutions and developed by older firms. In other words, the graph is characterized by a strong prevalence of inter-generation agreements over intra-generation agreements.

Tab.3- *Intergeneration and intrageneration R&D agreements.*

O

D	ICN	NBF1	NBF2	NBF3	NBF4	INST
ICN	203	387	722	434	218	32
NBF1	12	23	55	25	14	17
NBF2	18	22	77	40	42	309
NBF3	13	10	41	38	35	246
NBF4	8	6	27	22	32	94
INST	1	4	7	3	5	8

INC= Firms founded before 1973

NBF1= Firms founded between 1973 and 1981

NBF2= Firms founded between 1982 and 1986

NBF3= Firms founded between 1987 and 1991

NBF4= Firms founded after 1992

INST= Research Institutions

This result is confirmed by two tests carried out on block matrix $B(G)_{\leq t(\theta)}$, according to different values of θ.

The first one is the *Conditional Symmetry Model* (McCullagh, 1978; Everitt, 1977) applied to the ordered data matrices. According to the model, the null hypothesis is:

$$H_0: P(b_{ij})=P(b_{ji}) \text{ for } i<j$$

that is to say $P(b_{ij})$, the probability of observing a given number of agreements between a generation *i* of *Developers* and *j* of *Originators* is equal to $P(b_{ji})$, i.e. there is no structural bias leading younger/older F/I to be more frequently Originators/Developers.

Within the model, the ratio between the frequency of values above and below the main diagonal is set constant and equal to δ:

$$\delta = F_{ij} / F_{ji} \ , \ i<j.$$

According to Agresti (1984), the estimators for the constant δ and the frequencies F_{ij}, F_{ji} are given by:

$$\hat{\delta} = \frac{\sum_{i \le j} b_{ij}}{\sum_{j \le i} b_{ij}}$$

$$E_{ij} = \frac{\hat{\delta}(b_{ij} + b_{ji})}{(\hat{\delta} + 1)}, \quad if \quad i \le j$$

$$E_{ij} = \frac{(b_{ij} + b_{ji})}{(\hat{\delta} + 1)}, \quad if \quad i \ge j$$

After running the model over our data for $B(G)_{\le t(12)}$ we found that δ =1,8163 the X^2 test being highly significant (p value <.01). This result confirms the insight gained by inspection of Table 3. In other words, one observes many more agreements between earlier generations of *Developers* and all the subsequent generations of *Originators*.

Secondly, a series of *Permutation Tests* (Tsuji, 1998) have been carried out on matrix $B(G)_{\le t(\theta)}$. According to the *Permutation Test* the mean degree of asymmetry is measured by the expression:

$$D = \frac{\left(\sum_i \sum_j \left| b_{ij} - b_{ji} \right| \right)}{n} \quad for \quad i \le j$$

where *n* is the number of blocks (generations) of the matrix. Then, the original matrix $B(G)_{\le t(\theta)}$ undergoes a large number of random permutations and, each time, the mean degree of asymmetry, *D(p),* is computed again. The fraction of permutations with *D(p)>D* is always minor than 0.01. That is to say, the probability that the observed degree of asymmetry is purely random is very low.

In sum, the network of agreements is shown to be highly asymmetric. Moreover, the output of the *Permutation Test* shows that the degree of asymmetry measured by the value of δ

in the *Conditional Symmetry Model* is actually the outcome of the time order of the matrix and not of other possible ways of ordering the matrix itself.

In a nutshell, the digraph can be said to be *time reverse*, as on average, time order and time orientation are inversely related.

B - *The digraph is intransitive*

A graph is transitive if it contains a relation *e(u,w)* for every couple of edges *e(u,v)* and *e(v,w)*. That is to say, the more each node can link indifferently with any other node in the network, then the more a graph is transitive. Transitivity is essential for several different structural hypotheses, and various indices have been proposed for measuring it (Frank, Harary, 1982). In fact, intransitiveness implies some form of hierarchisation of the structure of the agreements over multiple levels (Hummon, Fararo, 1995).

In order to demonstrate the existence of an high degree of intransitiveness, we first calculated the number of paths of length two (8666) present in our network. Paths of length one correspond to simple edges $u \rightarrow w$. Paths of length two (R^2) correspond to sequences of two agreements $u \rightarrow w \rightarrow v$. Then, we calculated the percentage of transitive triads upon the total number of paths of length two within the digraph (see Wasserman, Faust, 1994; Harary et al., 1965). In our data this percentage is very low and it equals to 0.00018. This result is highly significant even after taking into account the low graph density (d=0.00136)[5] unambiguously confirming that the digraph is significantly asymmetric.

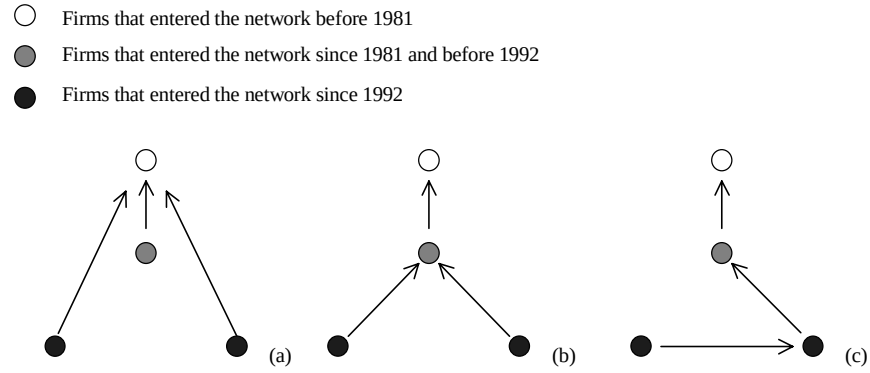
C - *The digraph has a hierarchical structure*

We now show that the observed degree of intransitiveness has to be interpreted as a result of the temporal structure of the network. To do that, we analyze the distributions of paths of length one (R) and two (R^2) according to the time of entry into the network. Specifically, we calculate the difference between the share of paths of length one and paths of length two ($\Delta = \%R^2 - \%R$) respectively for *Developers* who entered the network before and after 1981 and for *Originators* who entered the network before and after 1992[6]. Paths of length two identify a sequential structure where intermediate nodes exist who have an agreement as *Developers* with one agent and an agreement as *Originators* with another "terminal" agent. Computation of the

[5] *In fact, the ratio* $\frac{F(e(u,w),e(u,v),e(v,w))}{F(e(u,v),e(v,w))F(e(u,w))}$ *calculated over every triad of vertices u,v,w, equals to about only 0.13.*

values of Δ allows us to identify the relevance of these intermediate nodes. To fix ideas, compare the structures shown in Figure 3.

Fig. 3 - *Alternative structures of the network*



	R	R^2	Δ
<81	3	0	-3
≥81	0	0	0

	R	R^2	Δ
<81	1	2	1
≥81	2	0	-2

	R	R^2	Δ
<81	1	2	1
≥81	2	1	-1

The first structure (a) is a completely hierarchical one, with firms that entered the network before 1981 attracting all the agreements originated by younger generations. The second structure (b) is characterized by the upsurge of an intermediate layer, which is composed by firms that act as *Developers* in their linkages with younger generations and, at the same time, play as *Originators* with respect to the previous generation. Finally, the third elementary structure (c) is characterized by a reduction of the overall degree of hierarchization of the net driven by the emergence of intra-generation agreements.

Data presented in Table 4 show that the overall network is very similar to the second benchmark structure until 1992, while after 1992 it appears to be the result of the coexistence of structures of type (b) and (c).

[6] *We have done the same exercise using different dates. The years 1981 and 1992 however show much more clearly the patterns of hierachization of the network.*

In synthesis, not only the graph is intransitive, but it also has a distinct hierarchical structure, which is associated with the presence of different generations of firms, which play different roles within the network. Firms that entered the network before 1981 play a fundamental role in structuring it by linking as *Developers* to subsequent entrants. Later entrants perform a different role: they link both with older and younger generations, respectively as *Originators* and *Developers*.

Finally, however, it has to be noted that firms which have entered the net after 1992 have established a higher number of intragenerational agreements than firms of the previous generations. As a consequence, a lower value of Δ is observed for the agreements between orginators entered after 1992 and *Developers* entered after 1981.

Tab. 4 - *The value of according to date of entry into the network (t_ε)*

		O	
	Δ	$t_\varepsilon \leq 1992$	$T_\varepsilon > 1992$
D	$t_\varepsilon \leq 1981$	4.21	5.79
	$t_\varepsilon > 1981$	-8.28	-1.73

4.3 *The structural inertia hypothesis*

We now move to analyze the nature of the generative processes underlying the evolution of the net over time. In order to test our null hypothesis of a conservative process going on, let's suppose that the degree *Deg*(*i*,*t*), that is the total number of agreements of firms *i* at time *t*, depends upon how long it has been present within the network and on the number of potential partners active during the same period of time. In this case, *Deg*(*i*,*t*) may be expressed as a function of a value *t**, that is a measure of time weighted after considering the process of entry. In practice, we purify the observed values of *Deg* (*i*,*t*) from the effects of differences in periods of presence within the network and number of potential partners at any given time. Since the digraph is time reversal, *dDeg* (*i*,*t*), the number of agreements as a Developer of F/I *i* at time *t*, is distinguished from *oDeg* (*i*,*t*), the number of agreements as an Originator of the same F/I *i* at time *t*. Then, for each F/I belonging to the same generation $\bar{\varepsilon}$, two different *t** values, namely t_d * and t_o * have been calculated:

$$t_d^* = \sum_{t=\bar{\varepsilon}}^{\tau} n(\varepsilon_o = t);$$

$$t_o^* = \sum_{t=1}^{\bar{\varepsilon}} n(\varepsilon_d = t).$$

where $n(\varepsilon_o = t)$ and $n(\varepsilon_v = t)$ are respectively the number of firms entering the network as *Originators* and *Developers* at time *t* and τ is the last period of observation. In Figure 4, *dDeg*($\bar{\varepsilon}, t_d^*$) the degrees of *Developers* which entered the network during the same month $\bar{\varepsilon}$ are plotted as crosses, while the degrees of *Originators* o*Deg*($\bar{\varepsilon}, t_o^*$) are plotted as triangles.

The analysis of *dDeg*($\bar{\varepsilon}, t_d^*$) and o*Deg*($\bar{\varepsilon}, t_o^*$) indicates two major deviations from the structural inertia hypothesis:

i) Since *Deg*($\bar{\varepsilon}, t^*$)>*Deg*($\tilde{\varepsilon}, t^*$) for $\bar{\varepsilon}$ <1981≤$\tilde{\varepsilon}$, a persistent first mover advantage effect is present ;

ii) Since *dDeg*($\bar{\varepsilon}, t_d^*$)>o*Deg*($\bar{\varepsilon}, t_o^*$) for $\bar{\varepsilon}$ >1992, an inversion of the *Developer/Originator* profile can be detected after 1992.

That is to say, after controlling both for differences in time horizons and in the number of F/Is active inside the network in any period of time, earlier entrants tend to establish a larger number of agreements than later ones. Notably, the first mover advantage effect is stronger than it would have been under the conservative process hypothesis. Besides, firms which entered the net after 1992 established more agreements as *Developers* than expected according to the hypothesis of a conservative growth process being in place.

Fig. 4 – *Originators and Developers profiles*

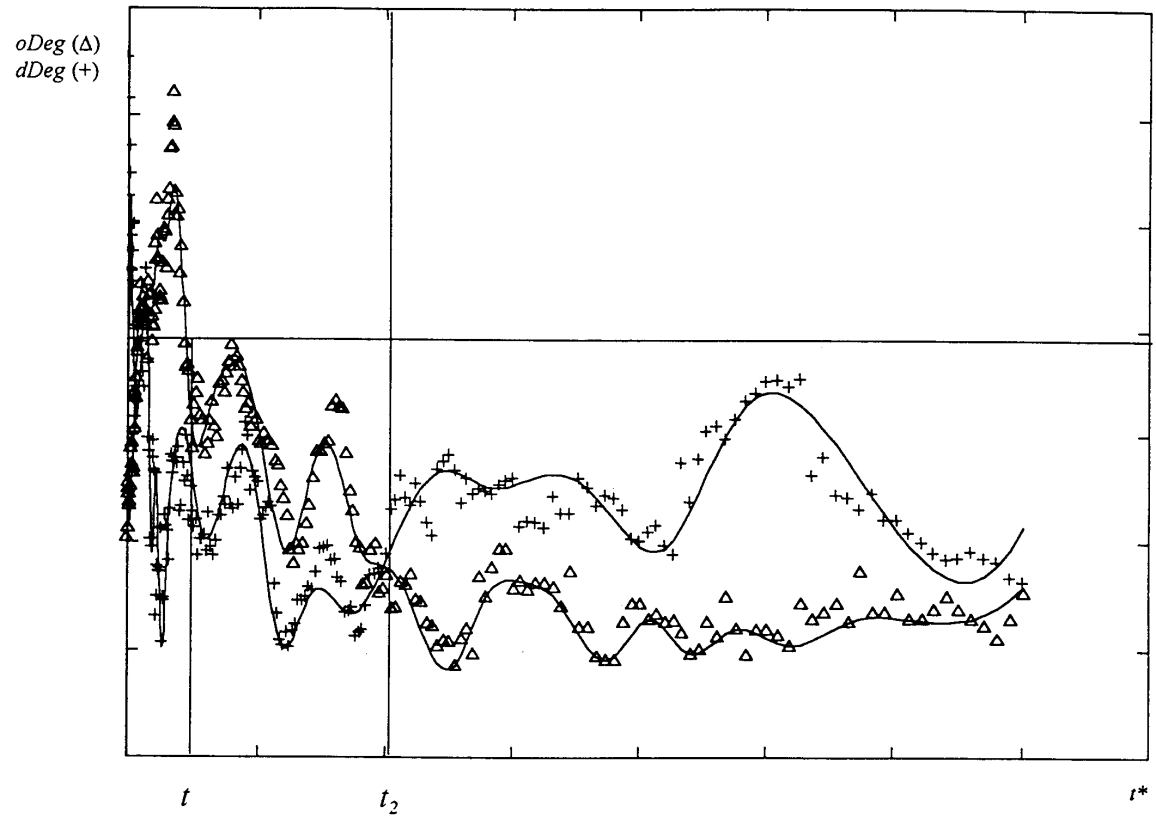
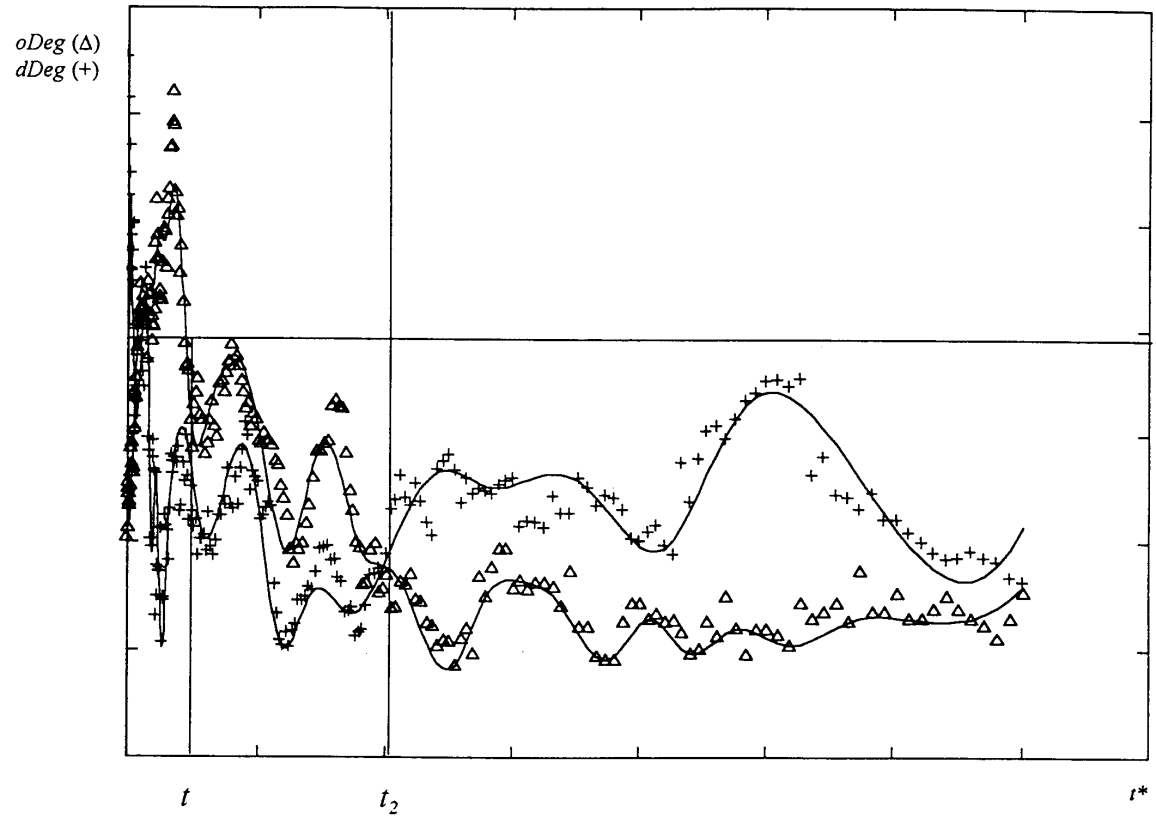


Fig. 4 – *Originators and Developers profiles*

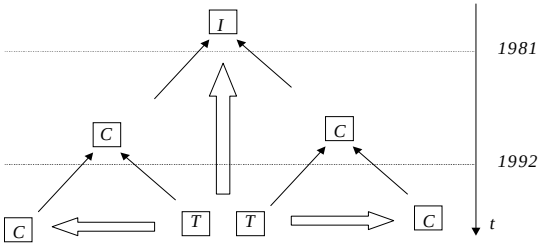


On the whole, the results presented so far on the structural properties of the graph in terms of patterns of growth, and degrees of hierarchization, asymmetry and intransitiveness in *t*, can be summarized by means of Figure 5.

Thin arrows give a stylized representation of the structural inertia hypothesis. Bold arrows are meant to capture the violations to that hypothesis. Let summarize them. First, we observe a first mover advantage effect (vertical bold arrow). Second, a change is detected in the Developer/Originator profile after 1992 (horizontal bold arrows).

In Figure 5, the orientation of the arrows reflects the time reversal phenomenon, i.e. the prevalence of inter-generation agreements over intra-generation agreements. *I* indicates firms that entered the network before 1981 and that benefit from a significant first mover advantage. *C* indicates firms that behave following the structural inertia hypothesis. *T* indicates firms that induce deviations from that pattern after 1992.

Fig. 5 - *Main structural properties of the network*



4.4 *Departures from the structural inertia hypothesis*

In this Section, we analyze in depth the nature and determinants of the relational roles played by the two types of firms/institutions *C* and *T* in Figure 5. First, we examine if firms of type *T* are a homogeneous group in terms of their relational profile. Secondly we advance and test the hypothesis that the major deviations in the structure of the network are related to the appearance of a new type of firms. Third, we show that these new firms embody what we called transversal technologies, which generate entirely different relational patterns than before. In synthesis, the observed structural changes in the graph are shown to be related to the emergence of a new class of transversal technologies.

As we already know, after 1992 a new dynamic process starts to interact with the conservative process discussed earlier to generate the structure of the network.

To test directly this conjecture, we now try to identify the relational role that different generations of firms and different firms within the same generation play in the network at different points in time (each year). In other words, we ask whether the graph can be meaningfully decomposed in specific subgraphs containing firms and institutions which play unambiguous relational roles. To do that, we analyze the nature and origins of deviations from a matching condition at different points in time. More precisely, we try to couple unambiguously individual *Originators* to individual *Developers*. If each specific Developer were coupled to a specific Originator we would obtain a perfect matching. However, we may find some *Developers* that are not linked only to a specific set of *Originators*, but attract a large number of different *Developers* and lead to a hierarchization of the network. We call them Transversal *Developers* (*TransDev*). Similarly, we might observe *Originators* who make agreements with

different agents. This would be the case of what we may call Transversal *Originators* (*TransOr*).

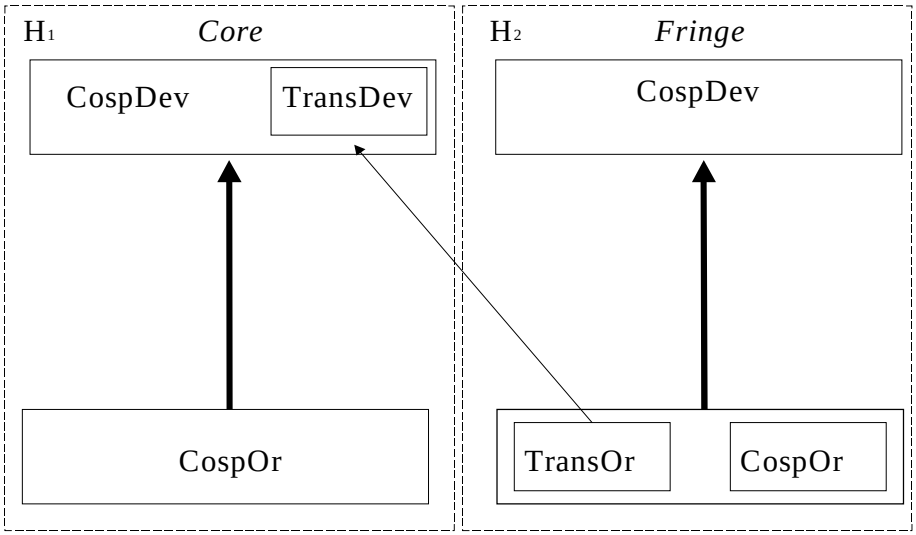
In order to identify firms that play different relational roles within the network, the Canonical Dulmage-Mendelsohn decomposition has been performed (see Appendix 2). The digraph has been transformed into a bipartite graph and each node has been classified only either as a *Developer* or as an *Originator*[7]. Figure 6 appropriately synthesizes the logic and the result of the Dulmage-Mendelsohn decomposition. Boxes H_1 ,H_2 represent the two non trivial subgraphs for which a matching can be found. In each box, we observe two subsets of *Developers* and *Originators*. Box H_1 contains the relational core of the network (approximately, the persistent relational component of the network: i.e. firms which have a large number of agreements and/or have entered the network early on), while box H_2 includes the relational fringe of the network. The matching in box H_1 captures the main structuring process of the network that we termed as the conservative process. Note however that we also identify a subset of *Developers* in box H_1 that link with a subset of *Originators* in box H_2. They correspond to what we defined above as Transversal *Developers* (*TransDev*) and Transversal *Originators* (*TransOr*).

The two sets of firms/institutions denoted as *TransDev* and *TransOr* can be thought of as the structural attractors of the network, i.e. they attract most of the agreements in each period of time (technically, they are present in all the intersections among minimum coverage vertex sets, see Appendix 2).

TransDev and *TransOr* firms play a transversal role within the network, i.e. they cannot be assigned an unambiguous relational role. Transversal *Developers* (*TransDev*) establish several relationships with a wide variety of firms. On the other side, within the *Originators* group, a clear distinction can be drawn between a set of firms that are co-specialized in their relational behavior (*CospOr*), i.e. they are matched, and a set of firms that play a transversal role within the network (*TransOr*).

[7] *In a bipartite graph, the vertex set V(G) is partitioned into two sets V_1 and V_2 in such a way that no two vertices in the same subset are adjacent. In particular, to represent the pharmaceutical R&D network as a bipartite graph, the vertex set V has been partitioned into two subsets D and O. As a vertex is forbidden to be included at the same time in partitions D and O , vertices v_d and v_o (F/Is that act respectively as Developers and Originators) have to be treated independently. As for F/Is which operate at the same time as Developers and as Originators we consider for each of them two different vertices in set D and O respectively. As a result, we are allowed to consider the bipartite graph $bG_{\Delta\tau}((O, D),E)$, which represents the agreements drawn up during a given period $\Delta\tau$ among Developers on the one side and Originators on the other.*

Fig. 6 - *Transversal and Co-specialized nodes within the graph*



These results confirm that different kinds of relationships are present into the graph and hence that a conservative process cannot represent its whole structural evolution.

It is now possible to demonstrate that the relational 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.

On the Developer side, the core of the network is persistently composed by a relatively small group of firms. Table 5 classifies firms according to date of foundation and presents information on the cumulative number of R&D ties, on number of ongoing R&D projects, and on ranking in terms of worldwide pharmaceutical sales in December 1997. For the group of actors that compose the core of the network a strong positive correlation between the number of R&D agreements, R&D projects and market sales is clearly observable.

Tab. 5 - *First 20 Firms/Institutions by number of agreements according to:*

number and ranking of R&D projects, and worldwide sales ranking

Network Ranking	# Ties	Firms & Institutions	R&D Projects	Sales rank
1	145	*Novartis*	$224_{(2)}$	I_3
2	141	*Hoffmann - LaRoche*	$112_{(12)}$	I_6
3	88	*Smith Kline*	$152_{(7)}$	I_9
4	81	*Merck&Co*	$207_{(4)}$	I_2
5	77	*Bristol - Myers Squibb*	$209_{(3)}$	I_4
6	74	*American Home Products*	$124_{(10)}$	I_8
7	69	*Lilly*	$138_{(8)}$	I_{12}
8	62	*Abbott*	$93_{(13)}$	I_{18}
9	60	*Pfizer*	$77_{(19)}$	I_7
10	52	*Schering - Plough*	$113_{(11)}$	I_{15}
11	51	*Pharmacia & UpJohn*	$174_{(6)}$	I_{11}
12	46	*Glaxo Wellcome*	$204_{(5)}$	I_1
13	45	*Centocor*	$22_{(101)}$	*NBF*
14	43	*Genentech*	$45_{(33)}$	*NBF*
15	41	*Incyte*	$10_{(257)}$	*NBF*
16	40	*Bayer*	$44_{(35)}$	I_{16}
17	39	*Parke - Davis*	$88_{(16)}$	*I*
18	37	*Genetics Institute*	$19_{(123)}$	*NBF*
19	36	*NIH*	$131_{(9)}$	*P*
20	34	*Chiron*	$64_{(24)}$	*NBF*

As shown in Table 6, the set of firms playing a TransDev role is composed by the very same highly stable group of large R&D intensive pharmaceutical firms that entered the network early on and that have been playing a role of structural attractors during the whole history of

bio-pharmaceutical industry. Moreover, those firms that started to act as TransDev since the beginning of the Nineties were already part of the core of the network in the previous years.

Tab. 6 - *First 15 firms active as TransDev, 1981-1997*

TransDev Firms	Number of years
Hoffmann-La Roche*	7
Glaxo Wellcome*	6
Smith Kline*	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 *Cosp Dev* before 1992

Figure 7 plots the moving average of the number of firms classified according to relational categories in terms of co-specialization/transversality. It shows that a set of firms playing a transversal role within the network has taken off after 1992. At the same time, throughout the whole time period under observation, the number of firms that have been acting within the network as *CospOr* steadily increase. Correspondingly, from 1992 to 1997 the network has been characterized by the coexistence of both *CospOr* and *TransOr* firms.

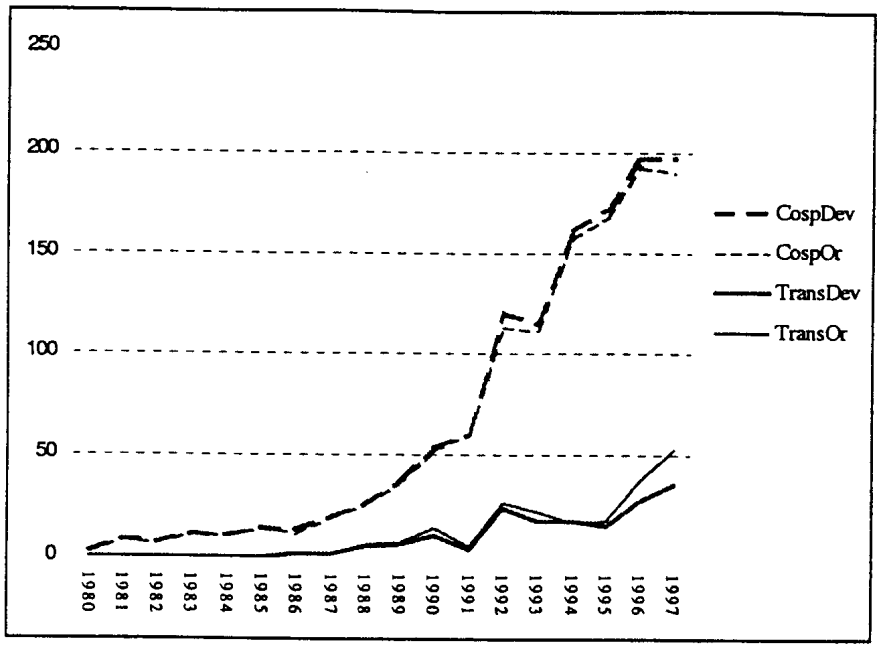


fig. 7 — Number of firms by relational category

On the Originator side, we already showed a correspondence existing between the emergence of transversal technologies and patterns of entry of new generations of *Originators*. We are now able to prove that technological transversality is a major determinant of relational transversality within the industry network.

More precisely, firms that have been identified as Transversal *Originators* into the graph by means of our analytical procedures embody Transversal Technologies .

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.

Transversal *Originators* are actually active in fields characterized by the presence of transversal research technologies, such as new drug delivery systems, combinatorial chemistry, genomics, genomic libraries, proteomics, highthroughput screening, and bioinformatics. In particular, Appendix 3 focuses on all most important firms which are active in the fields of genomics, genomic libraries, proteomics and combinatorial chemistry, reporting R&D projects

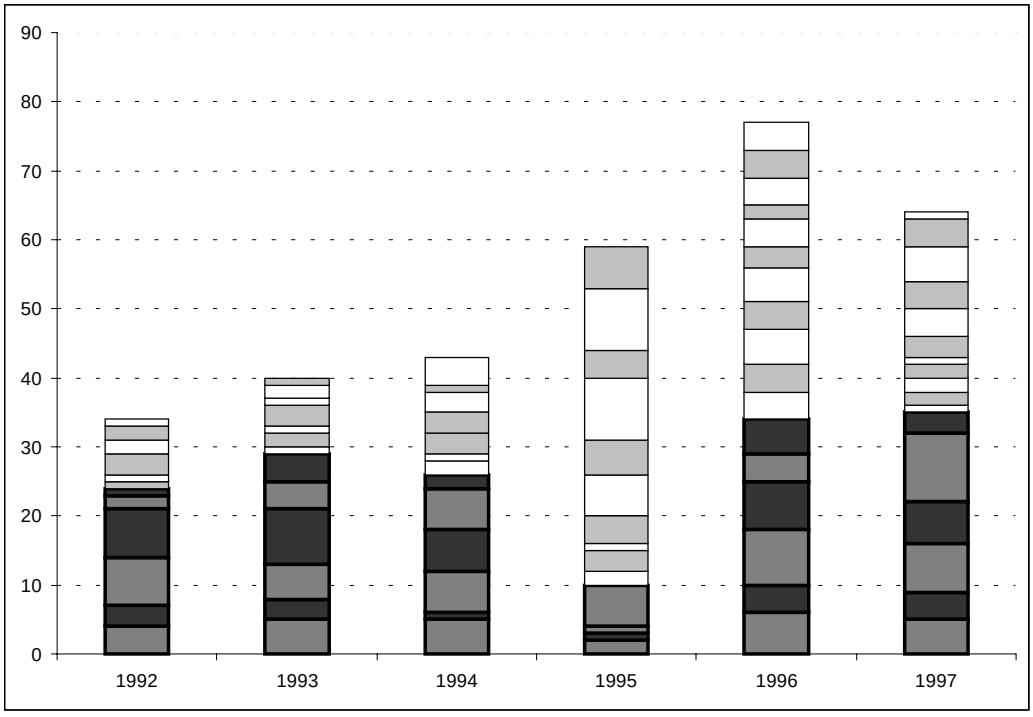
and agreements in the selected technological areas. Almost all the firms which were included in our R&D agreements data base have been categorized as Transversal *Originators* .

The insight we gained on the technological base of the changes in the structure of the network sheds additional light on the nature and determinants of the persistence by a core of established firms on the Developer side. Data presented in Figure 8 map the dynamics of the TransDev component after 1992. The core of the network initially expands, driven by flows of entry of new co-specialized firms and structured by the hierarchization of the network associated with the dominance of the regime of co-specialized technologies. Until about 1992 the relational core of the net was populated mostly by early entrants. After 1992, the underlying technological discontinuities induced by the emergence of the new transversal technologies induce a significant turnover in the core of the network on the Developer side.

In other words, new transversal entrants have started to act as *Originators* not only in their relationships with early entrants, but also with young entrants lacking capabilities and knowledge bases in the fields of chemical diversity generation and screening.

However, in the following years, established firms active as *Developers* have regained very quickly their structural role in the evolution of the industry network. In a nutshell, the entry of new Transversal *Originators* and the correspondent shift at the level of relational behaviors did not deeply modify the overall core--periphery profile of the industry network.

Fig. 8 - *Number of TransDev firms by year of entry into the network*



5. Concluding discussion

In this paper we have analyzed the structural evolution of the network of collaborative agreements in pharmaceutical R&D in the last twenty years. Our results reveal that some fundamental properties of the processes of growth of relevant knowledge bases are preserved in the structural evolution of the net.

Specifically, both the growth of knowledge and the structural evolution of the network 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 at different levels of the hierarchy. Finally, major changes in the network structure have occurred in correspondence with the emergence of a new set of transversal technologies.

We think that our results, while specific to the pharmaceutical industry, might bear interesting implications for a variety of both empirical and conceptual issues.

First, our findings may contribute to the broad debate on the nature and motivations of the network of alliances. Secondly, they can contribute to the analysis of the relationships between science and technology, public research and industrial R&D and the like. More generally, they may have some implications for theories which aim at explaining the forms of organization of innovative activities, patterns of division of labour and industrial dynamics, particularly those which emphasize the relevance of the notions of competencies, and dynamics capabilities of firms.

In extreme synthesis, the main conclusion of this paper might be that the specific nature of technology and related learning processes matters in shaping (or, at least, in defining some boundaries to the possible) organizational forms of R&D, patterns of division of labour and industrial dynamics.

In our view, the formation and subsequent evolution of the network of R&D alliances can be interpreted primarily as an adaptive response to the emergence of a radically new knowledge base within the industry, that is molecular biology. Scientific progress, however, did not only simplify the search space by providing more general theories. It also led to an explosion of the search space, significantly deforming it. Firms – both large established companies and NBFs – could master at best only fragments of the relevant knowledge. The high rate of growth of knowledge, its branching into increasingly specific and uncertain directions and – especially after 1992 – the appearance of transversal technologies, have led to the generation of a wide variety of approaches and lines of research.

These properties of relevant knowledge bases and related learning processes have induced particular patterns of division of labour between different types of firms. In general, our results indicate that two different logics of exploration and technological advance have been coexisting and complementing each other in the process of network evolution. The first avenue has been following a trajectory of increasing specification of biological 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. In synthesis, several mechanisms 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 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. (Cohen, Levinthal, 1989; Henderson, 1994; Henderson, Cockburn, 1996; Granstrand, Patel, and Pavitt, 1997).

The evidence presented in this paper suggests also that firms have found serious difficulties in modifying their structural position within the network. 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 seems to have characterized the evolution of the network: 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.

First mover advantages, the asymmetry between “generalists” and specialists and – more broadly – the observed process of hierarchization of the network, 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 network is an “unconditional object”, which might have been generated by processes and influenced by different variables than those emphasized in this paper.

Indeed, controlling for variables like firm size, diversification, propensity to make agreements, etc., constitutes an important part of our future research agenda. It is worth noting, however, that an explanation based on conventional firms features is not in contrast with our interpretation. Moreover, the results we get support the potential value of an approach that emphasizes the relevance of the specific properties of relevant knowledge bases, learning, and technologies.

Finally, this paper might have further implications from a more technical perspective. The graph-theoretic techniques we have used proved useful in mapping major technological discontinuities on changes observed at the level of dominant organization forms. They might have applications in other domains, whenever the identification of structural breaks and homological relationships between technological and industrial spaces are important issues.

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Appendix 1. Graphs and digraphs

In order to define the notion of a digraph, we have to introduce a definition of what a network (net) is. A net is generally defined (see Harary et al., 1965; Slepian, 1968; Diersel, 1997) by the following axiom system:

1- A finite and non-empty set V of elements v called "vertices";

2- A finite set E of elements e called "edges";

3- A function f whose domain is E and whose range is contained in V;

4- A function s whose domain is E and whose range is contained in V;

A digraph (oriented graph) is a net which does not include neither loops ($f(e) \neq s(e) \forall e \in E$) nor parallel edges ($f(e_i) = f(e_j)$ and $s(e_i) = s(e_j) \Rightarrow e_i = e_j \ \forall e_i, e_j \in E$).

Within the context of this paper, the structural proprieties of the network of R&D agreements are investigate by interpreting sets V, E and functions f, s in the following way:

1- V: The set of Firms/Institutions (F/Is) that have at least one R&D project in their pipelines. In our case each firm is associated with a set of projects. In other words, v should be thought as the set of projects of F/I, while V should be thought as the collection of the project sets corresponding to each F/I;

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

3- $o(e)$: F/I that started an R&D project e. In addition, v_o denotes the subset of v projects originated by each F/I;

4- $d(e)$: F/I that develop an R&D project e. In this case, v_d denotes the subset of projects v developed by each F/I.

As a consequence of the above definitions, every edge e within the graph is an oriented edge defined by a couple (o,d). As far as our empirical analysis of the network structure is concerned, we take into account only the subset of the R&D projects for which $o \neq d$. That is to say, only projects associated to two or more F/Is are considered (no self loops). Moreover we treat multiple and repeated relationships among the same actors as a single edge (no parallel edges).

In order to study the dynamics of the digraph we define both a time orientation and a time order of the graph. As the development phase follows by definition the starting date of a project,

maps *o* and *d* substantiate a *time orientation* of the graph either. What we need now is a time order defined on the vertices according to the year of entering into the network. Formally:

- τ(e(*o*)): month in which project *e* is started by *o*;

- τ(e(*o*,*d*)): month in which F/I *d* start to cooperate with firm *o* to develop project *e*. By definition $\tau(\text{e}(o,d)) \geq \tau(\text{e}(o))$;

- $\varepsilon_o(v) : \min_{v_o} \tau(\text{e}(o,d))$ the month in which *v* signs its first agreement as an *Originator*;

- $\varepsilon_d(v) : \min_{v_d} \tau(\text{e}(o,d))$: the month in which *v* signs its first agreement as a *Developer*;

- $\varepsilon(v) = \min_{v} \tau(\text{e}(o,d)) = \min_{v}(\tau_o, \tau_d)$: date of entry within the network (the month in which *v* signs its first agreement).

In other words, with reference to the structural evolution of the pharmaceutical R&D network, a time ordering has been established according to both the year of foundation and the year of entry of any given F/I within the network. It is important to notice that both orderings are *complete*. On the contrary, the time-oriented graph generated by the distinction between *Originators* and *Developers* will be showed to correspond to a *partial* order set (see Asratian et al., 1998, Ch. 10) in particular to a time partially ordered set $\Gamma = (T, \text{f})$. According to ordered set theory, a non-empty subset $C = \{t_1, t_2, ..., t_k \subseteq T$ such that $t_1 \text{ f } t_2 \text{ f } \ldots \text{f } t_k$ is called a chain. If $C = T$, the time order is *complete*. Moreover, two elements of *T* are said to be comparable if they appear together in the same chain *C*. Conversely, non-empty set of pairwise incomparable elements is called an antichain. Finally, the partition of Γ into disjoint time chains corresponds to a time decomposition of the network.

Appendix 2. Dulmage - Mendelsohn decomposition

In order to identify the structure of the bipartite graph at different points in time ($bG_{\Delta t}$), a condensation procedure has been applied to the bipartite graph. This procedure generates a graph minor $bG_{\Delta t}[M]$ obtained by shrinking every strongly connected subgraph, replacing it with a vertex, and then substituting each set of parallel lines with single lines.

In the case of a bipartite graph, the concept of a strongly connected component is equivalent to that of a strong Hall component. Vertices in a Hall component are perfectly matchable, that is, there is a matching (a set of edges in which no two edges have a common end vertex) which covers every vertex within it (for further details, see Diersel, 1997).

The lines belonging to a matching are said to be admissible, while the remaining ones are called inadmissible[8]. Figure 6 represents graphically the outcome of the analytical procedure described so far.

The application of a Canonical Dulmage-Mendelsohn decomposition algorithm (see Dulmage, Mendelsohn, 1958, 1959; Lovasz, Plummer, 1986, Ch. 4, p. 137) to the bipartite graph $bG_{\Delta\tau}$ produces the following results:

(1) two subgraphs (non trivial) H_1 ,H_2 , which are the connected components of the induced subgraph $bG_{\Delta\tau}[M]$;

(2) H_1 ,H_2 are two elementary bipartite graphs;

(3) Since the number of connected components of $bG_{\Delta\tau}[M]$ is greater than one, by permuting rows and columns the corresponding bi-adjacency matrix $A(bG)_{\Delta\tau}$ can be put into the form:

$$\begin{bmatrix} A_1 & * \\ 0 & A_2 \end{bmatrix}$$

where matrices A_1 ,A_2 are the bi-adjacency matrices corresponding to the subgraphs H_1, H_2 while * represents the transversal ties between the two sub-matrices. As an example, Figure 9 depicts the matrix *A(bG)* for year 1997.

[8] *An edge e is inadmissible if and only if there exists a non-null minimum vertex covering – i.e., a covering consisting of as few elements as possible – $C_o \subseteq V_o$ of vertices in V_d (and vice versa) such that e belongs to that cover ($e \in E$ (G [C])) (see Lovasz, Plummer, 1986; Asratian et al., 1998).*

In the Canonical Dulmage-Mendelsohn decomposition we have applied, a major role is assigned to the interplay between maximum matching and minimum vertex cover. As transversal vertices are included in every minimum vertex covering of the graph, a greater proportion of such kind of vertices over the total number of *Originators* implies a higher number of time chains in which the graph can be decomposed. In other words, as the proportion of transversal nodes on the total number of vertices within the graph increases, a linear representation of the graph dynamics founded on a structural inertia hypothesis becomes less and less suitable.