Knowledge characteristics and the dynamics of technological alliances in Pharmaceuticals: Empirical evidence from Europe, US and Japan

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Knowledge characteristics and the dynamics of technological alliances in Pharmaceuticals: Empirical evidence from Europe, US and Japan[1]

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ABSTRACT. The paper investigates the co-evolutionary patterns of the dynamics of technological alliances and of the structure of the knowledge base in the pharmaceutical sector. The main hypothesis under scrutiny is that technological alliances represent a key resource for firms in knowledge intensive sectors to cope with dramatic changes in the knowledge base, marked by the introduction of discontinuities opening up new technological trajectories. By using patent information and data on technological alliances drawn from the CATI-MERIT database, we compare the evidence concerning the so-called triad, i.e. United States, Europe and Japan. The empirical results confirm the existence of a life cycle in biotechnology affecting the pharmaceutical industry. Furthermore, the dynamics of alliances is found to depend on (i) the phase of the biotechnology life cycle, (ii) the strength of the region in biotechnology and (iii) the general features of the economic environment of the region.

JEL Classification Codes: O33, L2

Keywords : Collective Knowledge, Technological alliances, Knowledge Variety, Knowledge Coherence, Evolutionary Economics

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[1] A preliminary version of this paper has been presented at the annual conference of the European Association for an Evolutionary Political Economy (EAEPE) held in Bordeaux, 28-30 November 2010. We wish to thank Alex Coad for his comments. The authors acknowledge the financial support of the European Union D.G. Research with the Grant number 266959 to the research project 'Policy Incentives for the Creation of Knowledge: Methods and Evidence' (PICK-ME), within the context Cooperation Program / Theme 8 / Socio-economic Sciences and Humanities (SSH).

1 Introduction

During the 1980s and the 1990s the phenomenon of cooperative agreements among firms has received increasing attention in the economic and management literature, both from a theoretical and an empirical viewpoint. In the field of the economics of the firm, Oliver Williamson (1985), following the tracks opened by Coase (1937) and also by Richardson (1960, 1972), is now recognized as the economic scholar having framed the problem within a transaction-cost heuristic framework. In that perspective, many efforts have been produced at understanding the rationale behind firms choices between vertical integration pursed by means of mergers and acquisitions and more flexible organizational forms consisting in the establishment of cooperation schemes with other firms. Within the industrial organization and strategic management literature, the choice between M&As and alliances was understood with respect to main firms' objectives like market entry, the increase of market power and the development of synergies to the access to foreign markets, enlarging the scale of production processes, and hence the search for scale and scope economies (King et al., 2004; Mukherjee et al., 2004). This literature contributed to shift the focus on cooperative alliances as a stable form of organization, clearly distinguishable from the firm and the market.

More recently the role of innovation as an incentive for M&As or alliances has been recognized of growing importance (Duysters, 2001; Lipton, 2006; Moeller and Brady, 2007). Out of generic strategic alliances, technological alliances have been therefore defined as those "modes of inter-firm cooperation for which a combined innovative activity or an exchange of technology is at least part of the agreement" (Hagerdoorn and Duysters, 2002: p. 168). A wide body of empirical literature has then emerged focusing on the analysis of the relationships between strategic alliances and innovation, above all in correspondence with the gradual relaxing of the linear approach to knowledge creation in favor of theories emphasizing the interactive and collective nature of the processes of knowledge creation and exploitation (Lundvall, 1992; Nelson, 1993; Foray, 2004).

The changing focus in the analysis of strategic alliances and the increasing attention towards their links with the creation of new technological knowledge allowed to going beyond the traditional transaction costs framework by grafting the insights of the resource based theory of the firm (Penrose, 1959). The choice between looser or tighter organizational forms is not only influenced by the nature of interactions between supposed partners or the completeness degree of contracts. Technological alliances differ from traditional cooperation schemes as they involve important assets stemming from learning dynamics and knowledge transfer (Mayer and Teece, 2008). Within the resource based perspective, each firm can be considered as a bundle of skills and competences which are developed through learning dynamics and intentional efforts in R&D. In this direction, firms' incentives to establish strategic alliances focused on the exchange of knowledge or on its collective development may be due to the inability of firms to undertake the innovation efforts on their own in the technological domain covered by the alliance (Teece, 1986; Gomes-Casseres et al., 2006).

Therefore, technological alliances appear to be strategic for firms as they help their internal learning as well as the knowledge transfer processes. For this reason, the investigation of the relationships between the dynamics of technological alliances and innovation seems to be particularly relevant. A wide body of the literature has devoted attention to the importance of sector specificities in shaping the choice between alliances and integration. Strategic alliances have proven to be the most effective governance scheme in presence of fast rates of change (Brusoni et al., 2001; Langlois and Robertson, 1995; Langlois, 2003). In this direction, due also to their higher degree of flexibility, they are mostly used in high-tech sectors, when the research activity involves technological fields that are distant from the core competences of the company seeking for an alliance. Moreover, the more the research activity is related to new and uncertain technological trajectories, the more firms are willing to rely on technological alliances to go through it (Duysters and de Man, 2003; Hagerdoorn and Duysters, 2002; Tether, 2002). Thus alliances are not only stable forms of organization, they also appear as a key form of organization for the development of innovation.

These studies shed an interesting and important light to gain a better understanding of technological alliances, and in particular of its relationships with different patterns of innovation. However, they are mostly focused in the analysis of a specific sector in a given period or at the comparison of different sectors in correspondence of specific phases of their lifecycle.

In this paper we try and provide an assessment of the co-evolutionary patterns of technological alliances and knowledge creation by focusing our analysis on the pharmaceutical sector in a lifecycle perspective. To this purpose we compare the evidence of Europe, US and Japan since 1980 to 2003. The main argument is that the dynamics of alliances change not only across different sectors, but also in the same sector across different stages of its technology lifecycle. We will adopt an approach to technological knowledge emphasizing its collective and recombinant nature, as well the key properties able to characterize the technology lifecycle with respect to random screening *versus* organized search innovation strategies (Krafft, Quatraro and Saviotti, 2009). While this approach has been successfully implemented in the analysis of productivity performances at different levels (Nesta, 2008; Quatraro, 2010; Antonelli, Krafft, Quatraro, 2010), there are no contributions yet in the literature that have used it in the investigation of technological alliances. This paper also aims at contributing to the debate on the relationships between innovation, industrial dynamics and industry evolution, by analyzing the links between the knowledge-base of the pharmaceutical sector and the patterns of collaboration for innovation (Malerba, 2007).

The rest of the paper is organized as follow. Section 2 will provide the basic theoretical background and articulate our working hypotheses. In Section 3 we will provide an outline of the evolution of the pharmaceutical sector, by emphasizing the fit with the phenomenon we want to investigate. Section 4 will describe the data and the methodology. In Section 5 we present and discuss the results of the analysis. Section 6 will conclude.

2 Theoretical background

One of the merits of the evolutionary approach developed in economics in the early 1980s is the rejuvenation of Schumpeter's contribution to the understanding of the dynamics by which firms introduce and exploit technological innovations (Nelson and Winter, 1982). The behavior of economic agents began to be framed more and more in out of equilibrium contexts, in which a constant pressure to change could be devised. This endless tension towards mutation is, according to Schumpeter, an intrinsic characteristic of capitalistic systems, whereby creative destruction is the process through which novelty is brought about into the economy (Schumpeter, 1942).

Schumpter's legacy has also influenced the investigation and the understanding of industrial dynamics. Indeed, his *Business Cycles* represent a key reference in the long-run analysis of industry evolution, along with the seminal contribution by Simon Kuznets published in the same period (Schumpeter, 1939; Kuznets, 1930). New industries emerge as a consequence of the introduction of radical technological changes, and evolve following an S-shaped dynamics characterized by an initial explosion, maturity and then saturation. This has paved the way to the elaboration of life-cycle theories of product innovation (Abernathy and Utterback, 1978) and, more recently, to the elaboration of the concept of industry lifecycle (Klepper, 1997).

As Malerba and Orsenigo (1997) point out, the concept of industry lifecycle is useful in that it allows to devise different innovative behaviors not only when one compares two different sectors, but also when one looks at one single sector from a diachronic viewpoint. They propose the well-known distinction between Mark I and Mark II Schumpeterian patterns of innovation. ‘Creative destruction’ is a distinctive feature of the Schumpeter Mark I. In particular such pattern is also characterized by ease of entry, the appearance of new firms based on business opportunities, which challenge incumbents and continuously disrupt the current ways of production, organization and distribution. On the contrary, the Mark II pattern is characterized by ‘Creative accumulation’, the relevance of industrial R&D labs and the key role of large firms. They also label the two patterns as ‘widening’ and ‘deepening’. The former is related to an innovative base which is continuously growing, while the latter are characterized by accumulation strategies based on the existing technological premises (Malerba and Orsenigo, 1995). This distinction has been mostly used to characterize different sectors, but has remained rather unexploited in the analysis of the different stages of the evolution of a given industry.

In this paper we focus on a technology lifecycle which occurs due to the presence of knowledge discontinuities. The lifecycle begins with the emergence of the knowledge discontinuity and proceeds by the gradual transformation of such discontinuity into a routine. This lifecycle is in principle distinct from product or industry lifecycles. However, as it will turn out, this technology lifecycle can induce corresponding changes in industrial organization. In particular, as we will show, it is capable of affecting the formation and behavior of strategic alliances.

In this direction, the grafting of the lifecycle perspective into the analysis of strategic alliances is likely to be far reaching in that it allows to contributing both of the perspectives. Indeed, we have already emphasized that the analysis of strategic alliances focusing on the development and transfer of new technologies is quite recent. However, most of the empirical studies in the field look like a sort of comparative statics, whereby firms in different sectors are likely to show different attitudes towards technological alliances according to idiosyncratic features of the sector and of the technology they are working on. When long-run analyses have been conducted, these have been mostly directed towards the understanding of the changing structure of cooperation networks, rather than to emphasizing the links between the evolutionary patterns of technological change and the choice to look for a technological alliance.

A key finding in this respect concerns the higher propensity of firms to undertake a strategic alliance focused on the development of technological knowledge as the fields in which the research activity is focused move far away from their core competences (Duysters and de Man, 2003; Hagerdoorn and Duysters, 2002; Tether, 2002). In this direction the introduction of a discontinuity by means of a radical innovation within a given sector is likely to create a serious threat to incumbent firms, which are not able to command the necessary technological capabilities to run the competitive race in the economic arena (see also Langlois and Roberston, 1995; Langlois, 2003). Therefore, to resort to strategic alliances with new firms mastering the new technology represents one of the main tools to address the challenge.

If one thinks about technological innovation as the outcome of a search behavior conducted in the knowledge landscape, one can maintain that firms well localized in a given point of such a landscape are more likely to look for a technological alliance the more the knowledge base of the sector in which they operate moves far from that point. Indeed, this is where the issues of the dynamics of technological alliances and the processes of creation of new knowledge closely interact.

It seems necessary at this point to add another element to the picture. Indeed, most of the empirical analyses of innovation processes, even within the alliances framework, have been conducted by using a knowledge production function approach, which in turn implies a view of knowledge as a black box, i.e. as an homogeneous good, while the interactive dynamics of its creation are left completely unexplored (Ahuja and Katila, 2001; Cloodt, Hagedoorn, and Van Kranenburg 2006).

In order to take into account its internal properties an approach starting from a representation of knowledge as a structure seems more appropriate. Such an approach can be constructed from two properties of knowledge, those of being (a) a co-relational structure and (b) a retrieval-interpretative structure (Saviotti, 2004, 2007). According to knowledge establishes generalizations by finding relations, or connections, between variables and concepts. According to (b) the probability for any human being or organization to learn new knowledge falls with the dissimilarity, or distance, between the knowledge previously held and the external knowledge to be learned. According to (a) the whole space of human knowledge can in principle be represented as a network the nodes of which are either variables or concepts and the links of which are the connections between different variables or concepts. Both the number of nodes and the number of links of such a knowledge network can be expected to change in the course of time as new concepts and variables are discovered and as new links are created between previously unconnected variables or concepts. The overall network of human knowledge can never be expected to be fully connected as the rate of addition of new nodes and that of creation of new links are unlikely to be identical at all times. Thus, the density or connectivity of the network of knowledge can be expected to fluctuate in the course of time, rising or falling depending on whether the rate of creation of new links or the rate of creation of new nodes prevails. Such fluctuations are not in general random but are likely to be related to the phases of a technological life cycle or of a technological paradigm.

Our representation of knowledge is very similar to the recombinant knowledge approach (Weitzmann, 1998; Kauffman, 1993), but goes a step ahead. According to this recombinant knowledge approach the creation of new knowledge is represented as a search process across a set of alternative components that can be combined one another. A crucial role is played here by the cognitive mechanisms underlying the search process aimed at exploring the knowledge space so as to identify the pieces that might possibly be combined together. The set of potentially combinable pieces turns out to be a subset of the whole knowledge space. Search is supposed to be local rather than global, while the degree of localness appears to be the outcome of cognitive, social and technological influences. The ability to engage in a search process within spaces that are distant from the original starting point is likely to generate breakthroughs stemming from the combination of brand new components (Nightingale, 1998; Fleming, 2001).

The network corresponding to the recombinant knowledge approach would have a constant number of nodes and a growing number of links. The step ahead with our approach is that the network of knowledge has a variable number of nodes and a variable number of links. Our approach encompasses the recombinant knowledge approach (creation of links between pre-existing nodes) but in addition allows the emergence of radically new concepts (introduction of new nodes).

As a consequence, the knowledge base of a sector can be represented by the network including both the nodes corresponding to newly acquired components of knowledge and the relations occurring between the different pieces of knowledge that are combined with one another. Some of the key properties that are based on the process of creative discovery and recombination are the following:

- Variety measures the technological differentiation within the knowledge base. We can further distinguish unrelated variety, which is likely to be affected by radically new type of knowledge, from related variety, which is likely to be affected by incremental recombination of already existing types of knowledge.
- Coherence can be defined as the extent to which the pieces of knowledge that agents within the sector combine to create new knowledge are complementary with respect to one another.
- Similarity (alternatively dissimilarity) refers to the extent to which the pieces of knowledge used in the sector are close one another in the technology space.

The dynamics of technological knowledge can therefore be understood as the patterns of change in these properties, i.e. in the patterns of recombination across the elements in the knowledge space. This allows for qualifying both the cumulative character of knowledge creation, as well as for linking them to the relative stage of development of a technological trajectory (Dosi, 1982; Saviotti, 2004 and 2007; Krafft, Quatraro and Saviotti, 2009).

Such representation enables the investigation of the patterns of change of knowledge structure in relation to the dynamics of industry lifecycles, especially in that it allows to better detecting the introduction of a discontinuity in the sector knowledge base. Discontinuities occur in the production of knowledge when entirely new concepts and theories non comparable to pre-existing ones emerge. They are therefore signaled by increasing levels of dissimilarity and decreasing levels of coherence, as well as by the predominance of unrelated over related variety.

In sum, the evolution of knowledge intensive industries is punctuated by the introduction of major discontinuities in the knowledge base by means of radical innovations, which mark the shift to a new technological paradigm. In correspondence of the introduction of such discontinuities, search strategies are more likely to rely on exploration rather than exploitation (March, 1991). Technological alliances are therefore expected to increase, as incumbent firms are no longer able to manage the discovery process in domains of the knowledge space that are so different from their established competences. As the technological paradigm moves towards the exploitation phase, the knowledge base of the sector stabilizes and the strategic role of technological alliances becomes less and less important. Consequently, the predominance of technological alliances dedicated to develop and sustain the creation of new knowledge, i.e. the expansion of the knowledge base, should also decrease over time in a phase of maturity or exploitation of the technological paradigm.

In view of the arguments elaborated so far, we are now able to spell out our main working hypotheses. The characterization of the knowledge base of sectors in terms of their knowledge properties (variety, coherence, similarity) provides a set of useful tools to capture the transition in technology lifecycles from exploration to exploitation phases. The intra-paradigmatic lifecycle followed by knowledge is likely to have an impact on industrial organization. The representation of knowledge we propose will allow us to study with greater analytical depth the relationship between knowledge and industrial dynamics, based on the following two propositions.

Proposition 1: Discontinuities in the generation of knowledge can be better characterized by the consideration of key properties of the knowledge base (coherence, similarity and variety).

- The emergence of a discontinuity in a type of knowledge suitable to become the future knowledge base of a sector occurs according to a sequence of two periods, the former random search occurring in the exploitation phase, and the latter of organized search occurring later in the exploitation phase;

- During the exploration phase knowledge variety rises, coherence decreases and the similarity with previous knowledge existing in the sector decreases. During the exploitation phase, the rate of growth of variety decreases, knowledge coherence increases and the technological similarity between the previous knowledge existing in the sector and the new emerging knowledge rises as well.
- Moving from the exploration to the exploitation phase knowledge variety tends to shift from unrelated to related, as the pattern of differentiation changes from adding completely new elements of knowledge to differentiating around the most promising ones.

Proposition 2: Discontinuities in the generation of new knowledge affect the probability and propensity of firms to develop technological alliances.

- During the exploration phase, the probability of forming an alliance is rising while the propensity may be decreasing either because of the increasing number of new firms, or because of the difficulty to form an alliance between firms with highly different knowledge bases.
- During the exploitation phase, the probability is still rising, and the propensity starts increasing with knowledge bases being more similar and more coherent, the issue for firms being now predominantly to recombine already existing pieces of knowledge.

These predictions seem to imply that there is a one to one mapping between the properties of the knowledge base of a sector and more qualitative concepts such as paradigms or exploration and exploitation. In reality not only such a precise correspondence does not exist but multiple possible patterns of change can correspond to a technological paradigm or to each of the phases of exploration and exploitation. For example, the transition from exploration to exploitation can occur for very different ratios unrelated to related knowledge variety. Thus, the properties of the knowledge base we introduce not only allow us to quantify the different phases of the technology life cycle but can reveal a considerable diversity of behaviour in correspondence to each of those phases.

3 The Empirical Context

This paper analyses the relationships between the patterns of change of knowledge structure and the dynamics of technology alliances in a lifecycle perspective. The focus on the pharmaceutical sector is particularly appropriate for this purpose for two sets of different and yet related arguments.

First of all, there is a wide body of literature dealing with the history of the pharmaceutical sector, which provides a somewhat converging picture (Orsenigo, 1989; Gambardella, 1995; Galambos and Sturchio, 1996 and 1998; Henderson et al. 1999). According to these contributions, the evolution of the technologies and of the knowledge base of pharmaceuticals has been interested by three main discontinuities, which determined a dramatic change in the process of drug discovery.

Following Lee (2003), the first major source of modern drug discovery had its origins in chemical research. At the end of the XIX century the core of research in the field was carried out in Germany, in laboratories which were able to routinely synthesize and screen chemical compounds in search of new drugs. The first discontinuity is represented by the emergence of biology as a source of drug discovery. Fleming's discovery of penicillin in 1928 is viewed as the key event in this respect, although its exploitation came only in the 1940s. It is the antibiotic revolution, based on microbial biochemistry and enzymology.

The origins of the second discontinuity can be rooted in the discovery of the technique of recombinant DNA (r-DNA), which was invented by Cohen and Boyer in 1973 on the basis of Watson, Crick and Franklin hypothesis concerning the double-helix model of DNA. This marks the entry of molecular biologists in an industrial knowledge regime that was mainly dominated by synthetic and organic chemistry (Quéré, 2003). While these achievements appeared in the early 1970s, they began to be integrated into the pharmaceutical industry only in the 1980s, when a large number of biotechnology firms started entering the pharmaceuticals markets (Gottinger and Umali, 2008).

The third discontinuity is instead related to the so-called genomics revolution in the 1990s, characterized by the spread of gene sequencing activity and the rise of bio-informatics. As compared with the previous wave of technological innovations, the pharmaceutical knowledge base in this phase appears to be more inter-disciplinary, and shows the features of a general purpose technology suitable to be applied in a wide range of contexts.

Besides the evolutionary dynamics of its knowledge base, the different phases or 'epochs' characterizing the pharmaceuticals are also featured by related changes in the organization of innovation activities and in market structures. These are due on the one hand to the kind of search strategy made possible by the technologies underlying the different paradigms. Malerba and Orsenigo (2002) indeed stress that in the first phase firms were characterized by a kind of 'random screening' behavior, as the techniques typical of organic chemistry did not allow for targeted search, while the advent of r-DNA made it possible 'guided drug discovery', i.e. the rise of significantly more effective ways to screen compounds.

On the other hand, when radical technological changes determined a discontinuity in the knowledge base incumbent firms had to face competitive pressures such that they were forced to adapt their innovation strategies. In particular moving from organic chemistry to genomics through r-DNA, the role of technology alliances has become more and more important. Large incumbents were indeed hardly able to command the knowledge base underlying the new paradigms, and hence needed to resort to the so-called dedicated biotechnology firms (DBFs), mostly run by academic researchers, in order to run effective R&D activities. On the opposite, DBFs did not possess the necessary competences and resources to industrialize and commercialize new discovered drugs. Such a symbiotic relationship made the practice of establishing alliances between large incumbents and small start-ups a persistent feature of pharmaceutical industry in the last decades (Galambos and Sturchio, 1998). As noted by Quéré (2003) and Philippen and Riccaboni (2007), the structure and function of innovation networks were slightly different in the epoch of r-DNA and in that of genomics. In the former technological reasons were amplified by financial difficulties of new start-ups, and the structure of the network was characterized by links occurring mostly intra-disease areas. In the latter instead, the higher degree of complexity of the knowledge base made uncertainty and limited technological capabilities the main reasons underlying the establishment of network. Given the general purpose nature of the knowledge base, the structure of network is featured by links occurring across different disease areas.

In conclusion, the pharmaceutical sector provides the ideal setting to investigate the dynamics of knowledge structure and its relationships with the evolution of technological alliances. The data we use cover the period between 1980 and 2001, i.e. the decades characterized by the establishment of the r-DNA and the genomics revolution.

4 Data and Methodology

4.1 The Data

In order to analyze the relationships between the dynamics of technological alliances and the evolutionary patterns of knowledge base in the pharmaceutical sectors gather information contained in two different databases, the CATI-MERIT database on technological alliances and the Espacenet database on patent applications[2] provided by the European Patent Office.

CATI-MERIT contains data on nearly 13.000 cooperative technology agreements involving about 5.000 parent companies. Since 1987 data on inter-firm alliances has been systematically collected, including a retrospective search, and the database currently covers the period between 1970 and 1993. The most important data sources are a large number of international and specialized trade and technology journals for each sector of industry and many fields of technology. These journals cover in particular companies from North America, Europe and Asia. Companies' annual reports, the Financial Times' Industrial Companies Yearbooks and Dun and Bradstreet's Who Owns Whom provided information about dissolved equity ventures and investments, as well as ventures that we did not register when surveying alliances. Cooperative agreements are defined as the establishment of common interests between independent (industrial) partners which are not connected through (majority) ownership. The transfer of technology or the undertaking of joint research is considered as crucial to these arrangements. Examples in this respect are joint research pacts and joint development agreements. In addition data are collected on joint ventures with technology sharing or with a

[2] The limits of patent statistics as indicators of technological activities are well known. The main drawbacks can be summarized in their sector-specificity, the existence of non patentable innovations and the fact that they are not the only protecting tool. Moreover the propensity to patent tends to vary over time as a function of the cost of patenting, and it is more likely to feature large firms (Pavitt, 1985; Griliches, 1990). Nevertheless, previous studies highlighted the usefulness of patents as measures of production of new knowledge (Acs et al., 2002). Besides the debate about patents as an output rather than an input of innovation activities, empirical analyses showed that patents and R&D are dominated by a contemporaneous relationship, providing further support to the use of patents as a good proxy of technological activities (Hall et al., 1986). Moreover, it is worth stressing that our analysis focuses on the dynamics of technological alliances, wherein the use of patent to proxy innovation has been found less noisy than any other indicator (Ahuja and Katila, 2001; Cloodt, Hagedoorn, and Van Kranenburg 2006).

joint R&D program. Mere production or marketing joint ventures are excluded. R&D oriented joint ventures and jointly-owned research corporations are seen as joint ventures, joint development agreements, joint research pacts and research contracts are taken together as contractual agreements. Within the CATI database there are 65 classifications with respect to sectors and fields of technology. A major distinction is made between new core technologies (information technologies, biotechnology, new materials) and other industrial sectors. Additional information on this data bank can be found in Hagedoorn (1993) and Hagedoorn and Schakenraad (1994).

The information concerning patent applications required to test our working hypotheses has been obtained from the Espacenet data base provided by the European Patent Office. The initial dataset consisted of 2,659,301 items, including both EU and Worldwide applications, over the period 1978 – 2005. The analysis thus focuses on a subset of patent applications concerning the pharmaceutical sector.

The assignment of patent applications to the sector has been carried out by starting from the CATI-MERIT database. As already mentioned, such dataset already reports the sector classifications of each alliance. Pharmaceuticals are sharply identified therein, while some difficulties apply to define the boundaries of the sector as far as patents are concerned. To this purpose, we use the MERIT concordance table between industrial classification (ISIC) and international patent classification (IPC) (Verspagen et al., 1994). In such table the pharmaceutical sector corresponds to the ISIC (rev. 2) 3522 and to thirteen IPC classes (see Table 1). Our search strategy then consisted in submitting queries reporting the IPC classes that define the knowledge intensive sector under study.

>>> INSERT TABLE 1 ABOUT HERE <<<

4.2 Methodology

We propose a way of describing the emergence of alliances by adopting a network-based approach to the representation of technological alliances. The representation as a network enables us to better appreciate the dynamics of technological alliances by monitoring the changes in nodes and links. We allow the nodes to represent each individual firm and the links to represent the interactions between firms forming technological alliances. The dynamics of technological alliances can thus better be appraised by considering the number of firms and the number of technological classes (observed or potentially formed). Let n and l be respectively the number of firms and the number of links observed in country j in the sector i, we then propose the two following measures (time subscripts are omitted for the sake of clarity):

- **Probability to observe an alliance** (relative frequency measure) can be defined as the **s**ectoral share of observed alliances weighted by firms number:

$$P(A)_{ij} = \frac{l_{ij}}{\sum_i l_{ij}} \quad (1)$$

- **Propensity to establish an alliance** (density measure) can be defined as ratio between observed alliances and all possible alliances one can form:

$$C(A)_{ij} = \frac{l_{ij}}{n_{ij}(n_{ij}-1)/2} \quad (2)$$

When a discontinuity is likely to occur in the knowledge base then this should affect both propensity and probability. Probability should be increased in most cases, while propensity should only increase when the interactions between firms is higher than the number of firms. When the discontinuity emerges, the number of new firms able to create new knowledge may jump, but not necessarily the number of interactions which depends on the ability of firms to develop alliances between them. This ability ultimately depends on the knowledge properties in terms of coherence, similarity, and variety of firms involved in the sector and willing to form an alliance.

The general properties of the knowledge base we described in the section 2, i.e. coherence, similarity and variety, can be implemented by means of different methodologies, like social network analysis or the calculation of indicators based on co-occurrence matrixes in which the elements of rows and columns are bits of knowledge, while each cell reports the frequency with which each pair of technologies is observed. Moreover, in order to provide an operational translation of such concepts one needs to identify both a proxy of the bits of knowledge and a proxy of the elements that make their structure. For example one could take as a proxy of knowledge scientific publications, and look either at keywords or at scientific classification (like the JEL code for economists) for the constituting elements of the knowledge structure. Alternatively, one may consider patents as a proxy of knowledge, and look at technological classes to which patents are assigned as the constituting elements of its structure.

In this paper we use patent statistics to derive measures drawing upon co-occurrence matrices. Each technological class *i* is linked to another class *j* when the same patent is assigned to both of them. The higher is the number of patents jointly assigned to class *i* and *j*, the stronger is this link. Since the technological classes attributed to patents are reported in the patent document, we will refer to the link between *i* and *j* as the co-occurrence of both of them within the same patent document[3].

On this basis we calculated the following three key characteristics of the knowledge base of pharmaceuticals (see the appendix A for the methodological details):

a) Knowledge variety (KV) measures the degree of technological diversification of the knowledge base. It is based on the information entropy index, and it can be decomposed in related knowledge variety (RKV) and unrelated knowledge variety (UKV).
b) Knowledge coherence (COH) measures the degree of complementarity among technologies.
c) Cognitive distance (CD) expresses the dissimilarities amongst different types of knowledge.

This set of indicators provides us with useful measures to investigate the evolutionary patterns of knowledge structure and compare them with the dynamics of technological alliances in the pharmaceutical sector. The next section will present the results of our calculation and provide interpretation in the light of the working hypotheses spelled out in Section 2.

5 Results

5.1 General evidence

[3] It must be stressed that to compensate for intrinsic volatility of patenting behaviour, each patent application is made last five years.

Figs 1a,b,c and d show the results of our calculations for the whole data base, including the USA, Japan and Europe. In Fig 1a we can see that the probability of creation of alliances increases while the propensity to form alliances falls during the whole period of observation. This behavior is understandable considering that the probability of alliance formation can be expected to increase when the number of potential partners grows – in this case the potential partners were DBFs (dedicated biotechnology firms), the number of which has clearly risen. Given that, as explained before, the propensity to form alliances is essentially a measure of density of the innovation networks formed by LDFs (Large diversified firms), DBFs (dedicated biotechnology firms) and by PROs (public research organizations), the observed fall in propensity could be explained if the rate of creation of DBFs was higher than the rate of creation of alliances. A fall in network density due to a rate of creation of DBFs higher than the rate of alliance formation can be expected to occur during periods in which a knowledge discontinuity is emerging (Saviotti and Catherine, 2008). It is to be noticed that the rate of growth of the probability to form alliances was initially very low and started to rise only after 1983.

Fig 1b shows that the knowledge coherence goes through two cycles, within each of which coherence rises first, then reaches a maximum and finally falls. Each of these cycles was started by a knowledge discontinuity which sharply reduced knowledge coherence and was continued by the subsequent rise in coherence due to the normalization or maturation of the once new knowledge type as the absorption capacity of it has increased. The first of these knowledge discontinuities coincides with the emergence of r-DNA and the second with that of genomics (Saviotti and Catherine, 2008). Cognitive distance shows an overall decreasing trend after an initial rise, with several oscillations superimposed upon the trend. This behavior can be explained by the impact of the initial discontinuity constituted by r-DNA followed by a gradual process of absorption of the new technology by most pharmaceutical firms.

The oscillations superimposed upon the trend could be due to the emergence of 'smaller' discontinuities and by their subsequent absorption. However, this explanation seems to be incompatible with the presence of two knowledge discontinuities indicated in Fig 1b. Related knowledge variety (RKV) is always considerably greater than unrelated knowledge variety (UKV) (Fig 1d). RKV remains almost constant with some small fluctuations while UKV keeps increasing during the whole period of observation. Overall knowledge variety shows a clearly overall increasing trend with sharper rises in the initial and final parts of the period. These two rises in overall variety correspond approximately to the two discontinuities shown by the curve of knowledge coherence.

>>>INSERT FIGURE 1 ABOUT HERE<<<

Some features of the evolution of biotechnology within the pharmaceutical industry, such as the initial rise and the subsequent fall in cognitive distance, correspond to the pattern of behavior to be expected by a technological life cycle. However, other features of these figures do not correspond to the simplest possible representation of a technology life cycle. Thus, there are not one but two discontinuities, as shown by the evolution of knowledge coherence.

Furthermore, the evolution of both cognitive distance and of knowledge variety seems to indicate that each of these two discontinuities does not follow a smooth pattern going from high to low cognitive distance and from low to high knowledge variety. Each of the two generations of biotechnology giving rise to the cycles in knowledge coherence seems to have an internal structure, as shown by the intra-generation peaks and troughs of cognitive distance and of knowledge variety. For the moment the interpretation of the intra-generation peaks is not completely clear. To proceed we have to bear in mind that the results examined so far do not correspond to a homogeneous sample within which the only possible variations could be due to the evolution of biotechnology. On the contrary, the data set used contains information about three different geographical regions within which the evolution of technology and of industrial organization could have differed considerably. For example, we know that the rate of creation of DBFs during the 1980s was much higher in the USA than in Europe and even more so than in Japan (Escourrou, 1992; Walsh et al, 1995; Senker and Sharp, 1997). As a consequence, the results displayed in Figs 1a-1d are not due only to the intrinsic dynamics of knowledge and to its impact on industrial organization but also to the aggregation of samples of firms and research organizations belonging to different regions. In order to try and understand the mechanisms underlying the relative dynamics of knowledge in these different regions we now turn to the analysis of Figs 3a-3f.

5.2 Cross country comparison

The probability of formation of alliances increased in all three regions during the period considered. This means that in all three regions the pharmaceutical sector increased its share of alliances with respect to other sectors. In all three regions the factors which tend to favor alliances, such as new discoveries of potential economic applicability, must have become particularly abundant in pharmaceuticals. In this sense the observed behavior of the three regions is very similar. The only very slight difference is that the probability starts rising later in the USA with respect to the EU or to Japan. The propensity to form alliances is always higher in Japan than in the EU, and in the EU than in the USA. In the USA it declines all the time while it falls initially and then recovers for the EU and Japan.

>>>INSERT FIGURE 2 ABOUT HERE<<<

Thus, propensity (Fig 2a) differs by value and by trend amongst the three regions. Bearing in mind that according to its definition propensity measures the density of the innovation networks formed by the partners DBFs, LDFs and PROs, we can say that the density of pharmaceutical innovation networks was systematically higher in Japan than in Europe and in Europe than in the USA. Furthermore, propensity falls all the time in the USA while it first falls and then rises in Europe and in Japan. Considering that network density measures the fraction of all possible links which are used at a given time, we can expect network density to depend on the balance between the rates of growth of links and of nodes. In our case new links are formed by new alliances while new nodes are mostly formed by new DBFs. In general we can expect the density of innovation networks to bear a systematic relationship to the phases of a technology lifecycle. Thus, during the paradigm emergence, or exploitation phase, we can expect to observe a higher rate of growth of nodes than of links, leading to a falling network density. Conversely, during the paradigm consolidation, or exploitation phase, we can expect a higher rate of growth of links than of nodes (Saviotti, 2009). Such a relationship has been empirically observed for the first and second generations of biotechnology (Saviotti and Catherine, 2008). For what concerns the comparison of propensity to form alliances, a lower propensity, corresponding to a lower network density, need not be interpreted as a competitive disadvantage. On the contrary, a higher network density could simply indicate an economic environment where the rate of creation of DBFs is very low and where, as a consequence, new alliances can absorb a higher percentage of possible links. This is likely to be the explanation of the higher propensity to form alliances of

Japan relative to the USA. Thus, a lower network density could indicate a more creative economic environment, and a growing network density an economic environment which is rather consolidating than creative. Always referring to the propensity to form alliances, Japan shows a cyclical trend in the dynamics of nodes and links in contrast to the almost continuous one observed for the USA or the EU (Figs. 2 b, 2c, 2d). The reason for this difference is likely to be found in the relative lack of success of the early policies aimed at creating DBFs in Japan. (Odagiri, 2006)

The picture emerging from Fig 3a is of (i) the USA being the dominant power in the creation of DBFs and in the formation of alliances in pharmaceuticals during the whole period, (ii) in spite of the growing number of DBFs created in Europe, and somewhat less so in Japan since the 1990s, the rate of formation of alliances in both regions is likely to have remained lower than in the USA. The interpretation we propose, a faster rise in R_{DBFs} than in R_{All} for both the EU and Japan from the second half of the 1990s, is one of those which could have led to an increase in the propensity to form alliances but not the only possible one. Our choice of this interpretation is not based uniquely on these results but it has benefited from the use of research findings about the relative rates of creation of DBFs in the three regions.

>>> INSERT FIGURE 3 ABOUT HERE <<<

Knowledge coherence is always higher for the USA than for the EU or for Japan (Fig 3b) and this advantage of the USA tends to increase with time. Knowledge coherence for the USA not only increases with time but shows two peaks – beginning in the early 1980s and in the mid 1990s – and corresponding to the two generations of biotechnology. Knowledge coherence for the EU and for Japan is always lower than that of the USA and falls gently in the course of time. Even for the EU and for Japan we can detect two barely perceptible peaks corresponding to the two generations of biotechnology. Bearing in mind that knowledge coherence measures the capability of firms to combine different pieces of knowledge, old and new, the advantage of the USA has been based not only on the ability to learn new knowledge but also on that to integrate different pieces of knowledge. Given that knowledge coherence has been found to be a determinant of the technological and of the stock market performance of pharmaceutical firms (Nesta and Saviotti, 2005, 2006) we can interpret Fig 3a as showing that the USA has been gaining a growing competitive advantage with respect to the EU and to

Japan during the period studied. As far as the EU is concerned, this corresponds to the observed diminished capacity of EU pharmaceutical firms to create new drugs.

Cognitive distance (CD) was initially much higher for Japan than for the USA and for the EU but it has been falling for the three regions (Fig 3c). At the end of the period Japan has almost caught up with the USA and the EU and the three regions have similar values of CD. The CD curves of three regions show two peaks, once more corresponding to the two generations of biotechnology. Such peaks are much more pronounced for Japan than for the USA or the EU, but are still visible for the last two regions. In particular, the USA has a higher CD than the EU for the first peak but a lower one for the second peak. CD is expected to rise at the emergence of a discontinuity, for example of a new technological paradigm, and to fall as the discontinuity is absorbed into the KB of incumbent firms. The high values of CD at the beginning of the period show the existence of a corresponding barrier to learning. The subsequent fall in CD shows that pharmaceutical firms in the three regions have gradually acquired an absorption capacity for the new biotechnological knowledge. The relative values of CD also show that at the beginning of the period Japan had a much lower absorption capacity than either the USA or the EU. The CDs of the USA and of the EU were very similar during the whole period although their relative positions underwent a reversal. At the beginning and during the first generation of biotechnology the USA had a slightly higher CD while during the second generation the EU had a slightly higher CD. These subtle differences are more difficult to explain but they could be due to the different rates at which pharmaceutical firms internalized the new knowledge, higher for USA firms in the 1st generation and for EU firms in the second generation. This could be explained if EU firms and research institutions were more capable of learning knowledge of the r-DNA generation than of the genomics generation. By the end of the period Japan has a very similar, although still slightly higher, CD than both the EU and the USA.

Total technological variety (TKV) shows a tendency to increase for the three regions (Fig 3d), but with considerable differences amongst them. Japan, which at the beginning of the period had a much lower technological variety than both the USA and the EU, by the end of the period, has caught up with both of them and in fact it has overcome the EU. The differences in the relative behavior of the three regions are even more evident when we differentiate between related (RKV) and unrelated technological variety (UKV) (Figs 3e, 3f). The advantage of the USA is more pronounced in RKV than in UKV. Furthermore, Fig 3e shows that the advantage of Japan in TKV is exclusively based on RKV. By the end of the period the three regions have very similar levels of UKV (Fig. 3f). The curves for RKV, UKV and TKV show two peaks corresponding to the two generations of biotechnology. The second peak, corresponding to the emergence of genomics, shows a much faster rate of growth of RKV than the first one.

The analysis of the evolution of the properties of the knowledge base of pharmaceutical firms in the three regions confirms the competitive advantage accumulated by the USA since the advent of 3rd generation biotechnology in the late 1970s (Figs 4, 5 and 6). Such advantage is shown by all the properties of the knowledge base we examined but not to the same extent. In particular, the advantage seems more limited for CD and UKV and much more pronounced for COH and RKV. Thus, it is quite likely that, in view of the very clear evidence for the growing share of new drugs accounted for by USA pharmaceutical firms (Mitchell, 2007), not all properties of the KB have the same impact on the economic performance of firms. It seems as if the impact of COH and RKV on firm performance is much more pronounced than that of CD and UKV. To try and understand such a result we return to the meaning of these properties.

>>> INSERT FIGURES 4, 5 AND 6 ABOUT HERE <<<

In previous papers we found that both COH and TKV are determinants of the technological (Nesta and Saviotti, 2005) and economic (Nesta and Saviotti, 2006) performance of firms. These findings are confirmed by the results of the present paper. However, those papers did not introduce the distinction between related and unrelated variety, while the distinction proved to be very fruitful in the analysis of the impact of output and of export variety on the economic growth of regions and of countries. Related output variety turned out to be a determinant of growth in the regions of the Netherlands (Frenken et al, 2007) and related export variety was found to be a determinant of the short run growth of OECD countries (Saviotti and Frenken, 2008). However, unrelated export variety is a determinant of longer run growth of OECD countries. In the last paper, related export variety was interpreted as measuring the extent of differentiation of exports in the neighborhood of the position previously occupied by the country in product and knowledge space. On the other hand, unrelated export variety involves a greater extent of differentiation, or equivalently, a greater distance in product and in knowledge space. Those results had been interpreted as implying that countries and regions need to differentiate their output and exports in order to grow but that in the short run they will obtain a higher pay-off by differentiating in the neighborhood of their previous products. However, growth can only be sustained in the longer run if countries and regions start preparing a more radical type of differentiation by attempting to move further away from their previous products. In the present paper, the distinction between related and unrelated variety has a similar interpretation when applied to knowledge, but its implications for the dynamics of knowledge are somewhat different.

RKV measures the extent of differentiation of the knowledge base at a lower level of aggregation than UKV. Thus, the differentiation measured by RKV is more local, or intra-group. If we could apply the same interpretation to the knowledge base of pharmaceutical firms as to the output of countries and regions, we should expect RKV to be a more effective determinant of the performance of firms in the short run while UKV would become a more important determinant of performance in the longer run. While that may be true, we have evidence that the evolution of technologies tends to proceed through a life cycle, beginning with a knowledge discontinuity which increases CD and reduces COH. The life cycle proceeds by differentiating the knowledge base of the firms adopting the new type of knowledge, by gradually reducing CD and by gradually raising COH. As this happens the search strategies of firms move away from exploring at random the new dimensions of knowledge space, what we called 'random search', and start focusing on the more promising findings which had so far emerged. During this second phase, which we called organized search, the process of differentiation of the knowledge base continues but in the neighborhood of the new findings, or at a more local level. Thus, in this phase we can expect the rate of growth of UKV to start falling and that of RKV to start increasing. In previous papers (Krafft, Quatraro, Saviotti, 2009) it is pointed out that the measurement of these properties of the KB can provide a more accurate and semi quantitative interpretation of concepts such as technological paradigms and technological trajectories or of the transition from exploration to exploitation. However, the ordered transition from high to low CD, from low to high COH, from high UKV to high RKV is unlikely to happen always in the same way and many variants and combinations are possible.

One of the implications of the existence of this life cycle is that the performance of firms could depend on different factors depending on the phases of the life cycle. Thus, RKV and UKV could differ in terms of their impact on performance not in different time horizons but in different phases of the technology life cycle. For example, during the very early phases following the emergence of a discontinuity UKV could be expected to be a more important determinant of firm performance while RKV could become more important in later phases. Our results here do not seem to indicate this dependence since RKV is always higher than UKV. Our findings here indicate some variant with respect to the most simplified version of the life cycle. Thus, each of the two generations of biotechnology has its own life cycle and the overall path we observe is the combination of two life cycles.

We can now turn back to explore the reasons for the different impact of KB properties on firm performance. COH can be expected to measure the ability of firms or organizations to combine different pieces of knowledge. The observed impact of COH on firm performance can be explained by the fact that no drug or new plant variety can be created by means of only one piece of knowledge. The creation of any industrial application requires the combination of many different pieces of knowledge. Furthermore, the ability of firms to combine different pieces of knowledge is expected to increase after the emergence of a discontinuity. Thus, it is understandable that an advantage in COH can lead to a competitive advantage in the economic performance of firms. That the importance of COH grows in the same conditions as that of RKV is also understandable based on the nature of RKV. RKV is expected to measure the extent of differentiation of the KB of firms after that, during the organized search phase of the technology life cycle, all firms have focused on a more restricted but more promising subset of the knowledge space as compared to the one explored during the random search phase. During the organized search phase the process of differentiation of the KB is more local, or intra-group, with the consequence that the expected average similarity between any possible pair of units of knowledge is likely to be greater than in the random search period. Thus, the more local is the level at which the process of differentiation of the KB occurs in knowledge space the easier we can expect it will be to combine different pieces of knowledge. Thus, high COH and high RKV are likely to exist simultaneously and firms acquiring an advantage in them are likely to acquire an overall competitive advantage.

We can finally observe that the analysis of the above properties of the KB provide us with the capacity to detect the emergence of knowledge discontinuities. In fact, such discontinuities are detected not as discrete events but as a sudden rise or fall in one or more of those properties. For example, CD is expected to rise rapidly at the emergence of a discontinuity and to fall subsequently as the new knowledge matures and becomes part of the routines of the economic system. However, one of the findings of this paper is that not all discontinuities are alike. Thus, at the end of the 1st generation of biotechnology, COH for the whole sample fell back to very low values before recovering during the second generation. On the other hand, for the USA at the end of the 1st generation, COH did not fall back to values as low as those prevailing at the beginning of the same generation, but only fell slightly and then started rising very rapidly. Obviously, the 2nd generation of biotechnology was not equally discontinuous for the USA as for the EU or Japan. The 2nd generation of biotechnology differs from the 1st for the advent of bioinformatics but shares with the 1st all the basic concepts introduced by molecular biology. For what concerns the pharmaceutical industry we can observe that for the USA the 2nd generation of biotech was less discontinuous than the 1st one while for the EU and Japan they were both equally discontinuous. This raises the very interesting question of whether a discontinuity is intrinsic to knowledge or whether it depends on the overall learning organization of a society, what is called social technology (Nelson 1993).

6 Summary and conclusions

The findings of this paper confirmed the hypothesis that technologies develop according to a life cycle following a predictable pattern beginning with the emergence of a knowledge discontinuity and proceeding with the gradual transformation of such discontinuity into a routine of the economic system. During this process a number of properties of the knowledge base of firms or of other knowledge using organizations undergo systematic changes following a lifecycle consisting of moving away from an initial phase of random search towards a final phase of organized search.

In general at the emergence of a discontinuity coherence falls, cognitive distance increases and knowledge differentiation starts growing. However, the study of individual cases shows that many variants can occur within the general framework of a technology life cycle. For example, while in general we can expect knowledge differentiation to start moving from unrelated (UKV) to related (RKV) there may be cases where this sequence is not followed. In other words, we can see that general concepts such as paradigms or trajectories can encompass a considerable diversity of situations. The quantitative framework we propose allows us to separate cases which could seem to be describable as paradigmatic transitions and to elucidate their differential implications for industrial dynamics. Thus, in this paper we can see that in the application of biotechnology to the pharmaceutical industry there have been not one but two technology life cycles corresponding to two generations of biotechnology. Each of these generations leads to a detectable change in some of the properties of the KB. Yet, the two generations of biotechnology do not seem to have the same impact on the pharmaceutical industries of the three regions studied. Thus, USA pharmaceutical firms seem to experience a lower extent of discontinuity with the advent of the 2nd generation of biotechnology than either EU or Japanese pharmaceutical firms. This raises the important question of whether a knowledge discontinuity is an intrinsic feature of particular types of knowledge or whether and to what extent it depends on the social organization of learning.

In this paper we not only investigated the dynamics of knowledge but started exploring the impact it can have on firm competiveness and on alliance formation. This can be done by measuring both properties of the knowledge base of the sector and properties of the alliance networks formed. Amongst the latter we measured the probability of alliance formation and the propensity to form alliances. It seems as if not all the properties of the KB have the same impact on firm performance in the pharmaceutical industry. In particular, COH and RKV seem to have a much more marked impact on firm performance than either CD or UKV. In the previous section we propose an explanation of why that should be the case. Furthermore, a high propensity to form alliances as defined in this paper does not necessarily lead to a better economic performance of the pharmaceutical industry. This can be explained by using a network approach to analyzing technological alliances. Since the propensity to form alliances is proportional to network density, a falling propensity can indicate a very creative economic environment in which so many new DBFs are created that the process of alliance formation cannot keep pace. In this sense we can explain why the USA, by far the strongest region biotechnology and in alliance formation, has a lower and falling propensity to form alliances than the EU or Japan. In interpreting the relationship between alliance formation and the properties of the knowledge base of pharmaceuticals it must be remembered that the two are related by a co-evolutionary pattern in which a 'good' knowledge base in one period leads to better alliances in the subsequent period, which in turn improves the knowledge base in the next period.

The paper shows the usefulness of measuring the above properties of the KB and the progress this entails with respect to concepts such as technological paradigms and trajectories or exploration and exploitation. Based on these properties of the KB we can show that more than one type of evolution can occur due to both the intrinsic characteristics of knowledge and to the relative effectiveness of different research and industrial systems.

While the dynamics of knowledge in biotechnology was the same all over the world, the translation of this new knowledge into industrial applications and the corresponding industrial dynamics has been quite different in the three regions we studied here. The leadership position of the USA appears quite clearly as well as the late start and the different rates of catching up of the EU and of Japan. Thus, the use of the above properties of the KB allows us both to give a clearer operational meaning to concepts such as technological paradigms and trajectories or exploration and exploitation and to better articulate them.

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A) Appendix A

A.1 Knowledge variety

We decided to measure technological variety by using the information entropy index. Entropy measures the degree of disorder or randomness of the system, so that systems characterized by high entropy will also be characterized by a high degree of uncertainty (Saviotti, 1988). Differently from common measures of variety and concentration, the information entropy has some interesting properties (Frenken and Nuvolari, 2004). An important feature of the entropy measure is its multidimensional extension. Consider a pair of events (X_l, Y_j), and the probability of co-occurrence of both of them p_{lj}. A two dimensional total variety (*TV*) measure can be expressed as follows:

$$KV \equiv H(X,Y) = \sum_{l}\sum_{j} p_{lj} \log_2\left(\frac{1}{p_{lj}}\right) \tag{A1}$$

If one considers p_{lj} to be the probability that two technological classes *l* and *j* co-occur within the same patent, then the measure of multidimensional entropy focuses on the variety of co-occurrences of technological classes within regional patents applications.

Moreover, the total index can be decomposed in a "within" and a "between" part anytime the events to be investigated can be aggregated into a smaller numbers of subsets. Within-entropy measures the average degree of disorder or variety within the subsets, while between-entropy focuses on the subsets measuring the variety across them. Frenken et al. (2007) refer to between- and within- group entropy respectively as unrelated and related variety.

It can be easily shown that the decomposition theorem holds also for the multidimensional case. Hence if one allows $l \in S_g$ and $j \in S_z$ (g = 1,…,G; z = 1,…, Z), we can rewrite *H(X,Y)* as follows:

$$KV = H_Q + \sum_{g=1}^{G}\sum_{z=1}^{Z} P_{gz} H_{gz} \tag{A2}$$

Where the first term of the right-hand-side is the between-entropy and the second term is the (weighted) within-entropy. In particular:

$$UKV \equiv H_Q = \sum_{g=1}^{G}\sum_{z=1}^{Z} P_{gz} \log_2 \frac{1}{P_{gz}} \qquad \text{(A3)}$$

$$RKV \equiv \sum_{g=1}^{G}\sum_{z=1}^{Z} P_{gz} H_{gz} \qquad \text{(A4)}$$

$$P_{gz} = \sum_{l \in S_g}\sum_{j \in S_Z} p_{lj}$$

$$H_{gz} = \sum_{l \in S_g}\sum_{j \in S_z} \frac{p_{lj}}{P_{gz}} \log_2\left(\frac{1}{p_{lj} / P_{gz}}\right)$$

We can therefore refer to between- and within-entropy respectively as *unrelated technological variety* (*UTV*) and *related technological variety* (*RTV*), while total information entropy is referred to as *general technological variety*.

A.2 Knowledge coherence

Knowledge coherence measures the degree of complementarity among technologies. We expect it to provide us with an indication of the difficulty, or cost, a firm has to face to learn a new type of knowledge. Typically a firm needs to combine, or integrate, many different pieces of knowledge to produce a marketable output. Thus, in order to be competitive a firm not only needs to learn new 'external' knowledge but it needs to learn to combine it with other, new and old, pieces of knowledge. We can say that a knowledge base in which different pieces of knowledge are well combined, or integrated, is a coherent knowledge base. The technologies contained in the knowledge base are by definition complementary in that they are jointly required to obtain a given outcome. For this reason, we turned to calculate the coherence of the knowledge base, defined as the average relatedness of any technology randomly chosen within the sector with respect to any other technology (Nesta and Saviotti, 2005 and 2006; Nesta, 2008).

To yield the knowledge coherence index, a number of steps are required. In what follows we will describe how to obtain the index at the sector level. First of all, one should calculate the weighted average relatedness WAR_l of technology l with respect to all other technologies present within the sector. Such a measure builds upon the measure of technological relatedness τ_{lj} (see Nesta and Saviotti, 2005, for details). Following Teece et al. (1994), WAR_l

is defined as the degree to which technology l is related to all other technologies $j \in l$ in the sector, weighted by patent count P_{jt}:

$$WAR_{lt} = \frac{\sum_{j \neq l} \tau_{lj} P_{jt}}{\sum_{j \neq l} P_{jt}} \tag{A5}$$

Finally the coherence of knowledge base within the sector is defined as weighted average of the WAR_{lt} measure:

$$COH_t = \sum_{l \neq j} WAR_{lt} \times \frac{P_{lt}}{\sum_l P_{lt}} \tag{A6}$$

It is worth stressing that such index implemented by analysing co-occurrences of technological classes within patent applications, measures the degree to which the services rendered by the co-occurring technologies are complementary to one another. The relatedness measure □ $_{lj}$ indicates indeed that the utilization of technology l implies that of technology j in order to perform specific functions that are not reducible to their independent use. This makes the coherence index appropriate for the purposes of this study.

A.3 Knowledge similarity and dissimilarity (cognitive distance)

We need a measure of cognitive distance (Nooteboom, 2000) able to express the dissimilarities amongst different types of knowledge. A useful index of distance can be derived from the measure of *technological proximity*. Originally proposed by Jaffe (1986 and 1989), who investigated the proximity of firms' technological portfolios. Subsequently Breschi et al. (2003) adapted the index in order to measure the proximity, or relatedness, between two technologies. The idea is that each firm is characterized by a vector V of the k technologies that occur in its patents. Knowledge similarity can first be calculated for a pair of technologies l and j as the angular separation or un-cented correlation of the vectors V_{lk} and V_{jk}. The similarity of technologies l and j can then be defined as follows:

$$S_{lj} = \frac{\sum_{k=1}^{n} V_{lk} V_{jk}}{\sqrt{\sum_{k=1}^{n} V_{lk}^2} \sqrt{\sum_{k=1}^{n} V_{jk}^2}} \tag{A7}$$

The idea underlying the calculation of this index is that two technologies j and l are similar to the extent that they co-occur with a third technology k. The cognitive distance between j and l is the complement of their index of the similarity:

$$d_{lj} = 1 - S_{lj} \tag{A8}$$

Once the index is calculated for all possible pairs, it needs to be aggregated at the industry level to obtain a synthetic index of technological distance. This can be done in two steps. First of all one can compute the weighted average distance of technology *l*, i.e. the average distance of *l* from all other technologies.

$$WAD_{lt} = \frac{\sum_{j \neq l} d_{lj} P_{jit}}{\sum_{j \neq l} P_{jit}} \tag{A9}$$

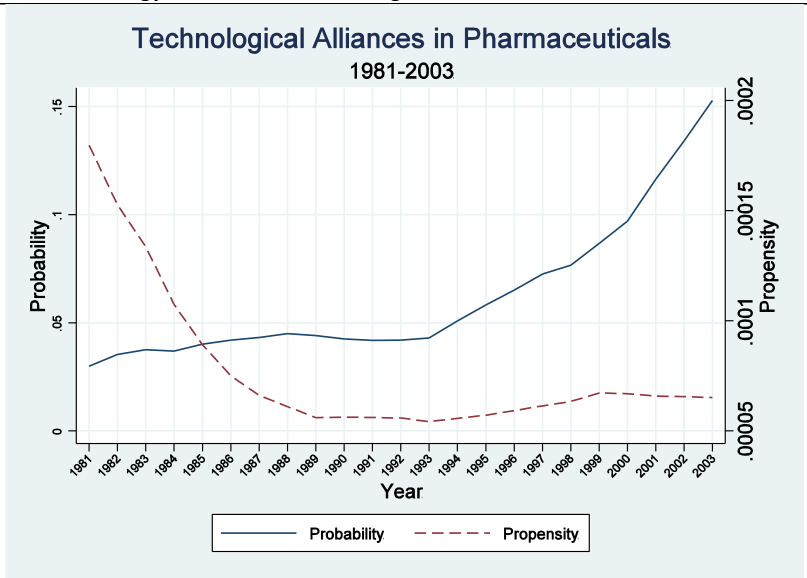
Where P_j is the number of patents in which the technology *j* is observed. Now the average cognitive distance at time *t* is obtained as follows:

$$CD_t = \sum_l WAD_{lit} \times \frac{P_{lit}}{\sum_l P_{lit}} \tag{A10}$$

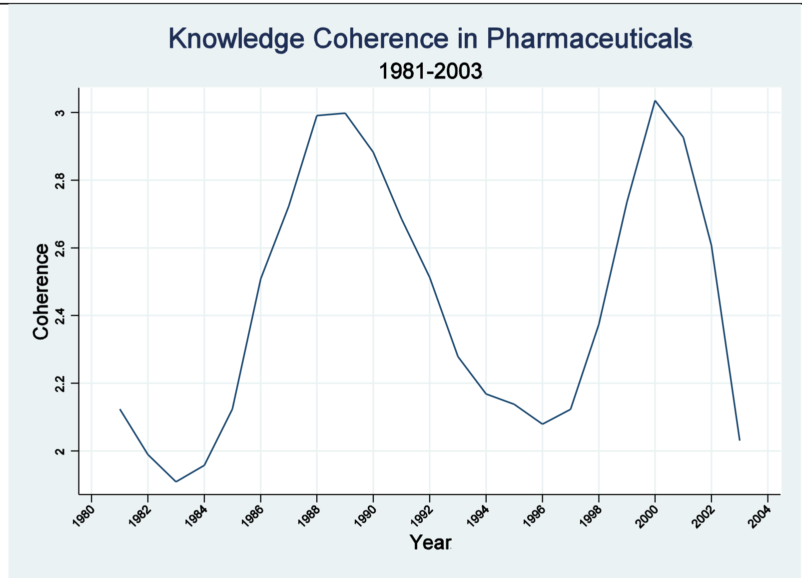
Table 1 - Concordance Table CATI-MERIT, ISIC and IPC

CATI-MERIT Database	ISIC (rev. 2)	International Patent Classification
A3	3522	A61J, A61K, C07B, C07C, C07D, C07F, C07G, C07H, C07J, C07K, C12N, C12P, C12S.
Source: Verspagen et al. (1994)		

Figure 1 – Technology alliances and Knowledge Structure : overall evidence



a)



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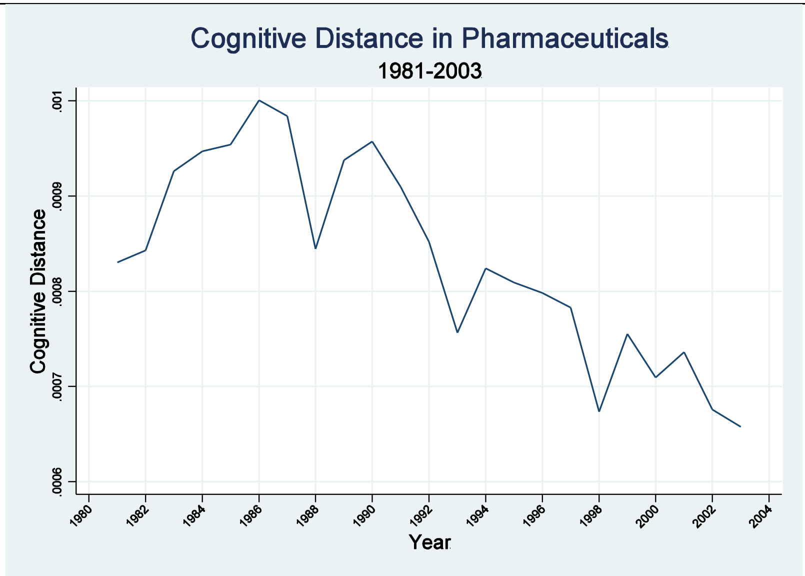

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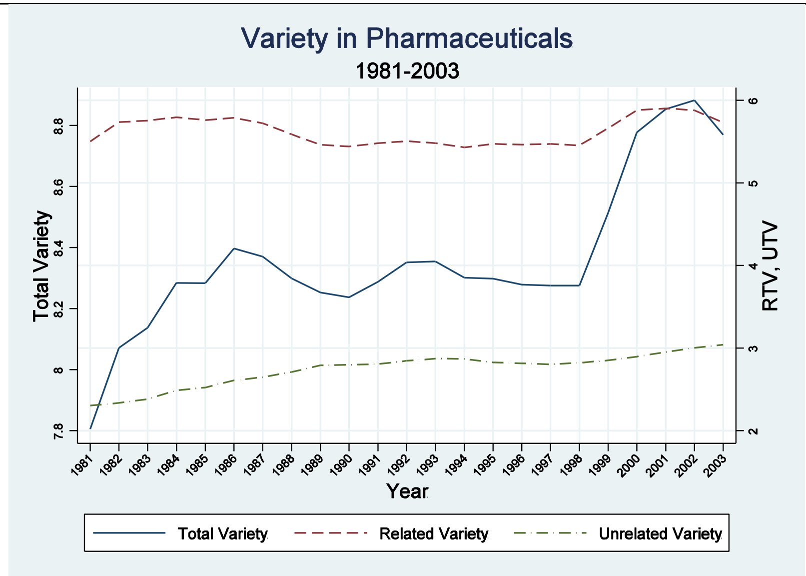

d)

Figure 2 – Alliances : nodes and links in the Pharmaceutical sector

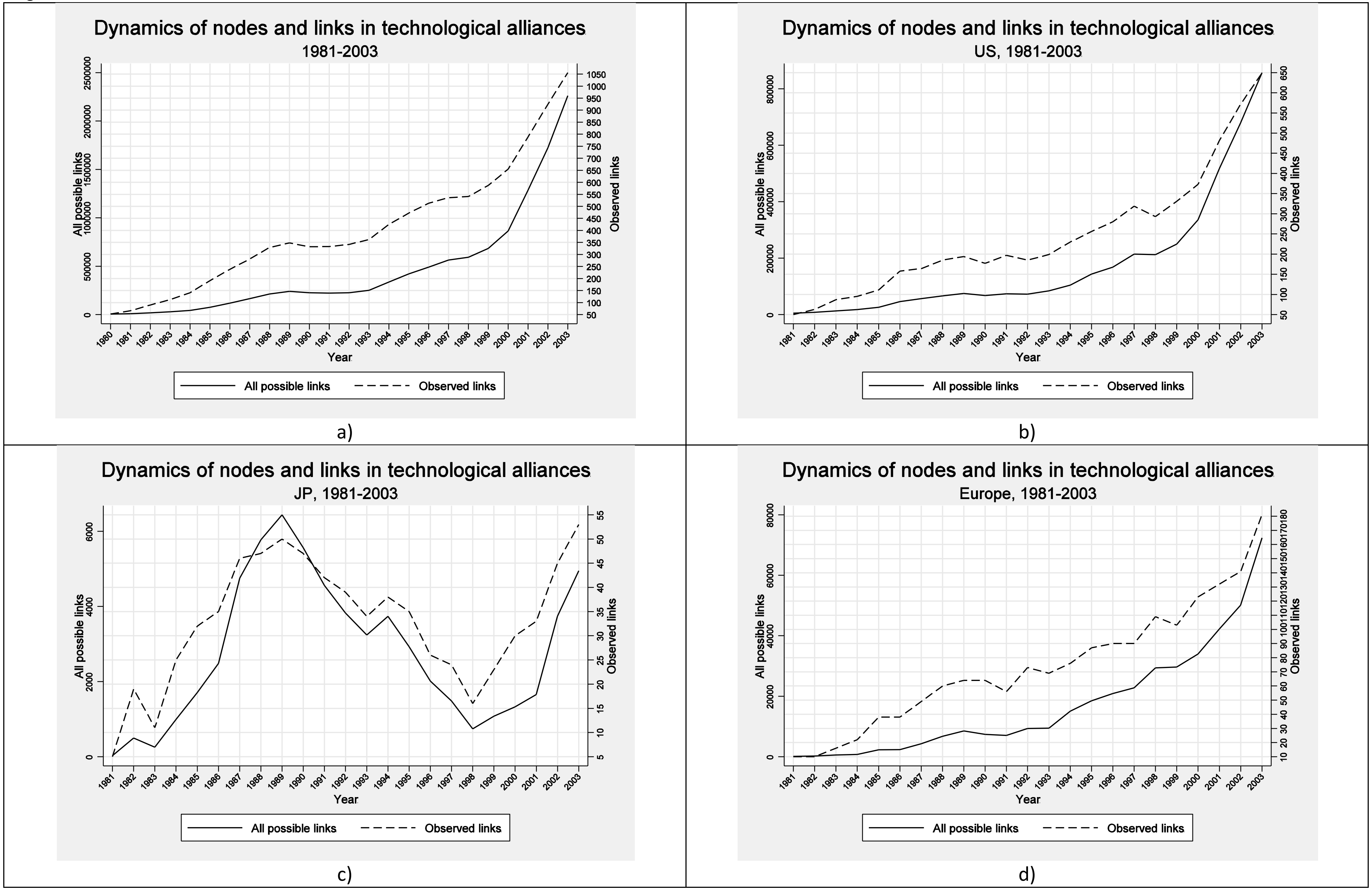

Figure 3 – Technology Alliances and Knowledge Structure : Cross-country Comparison

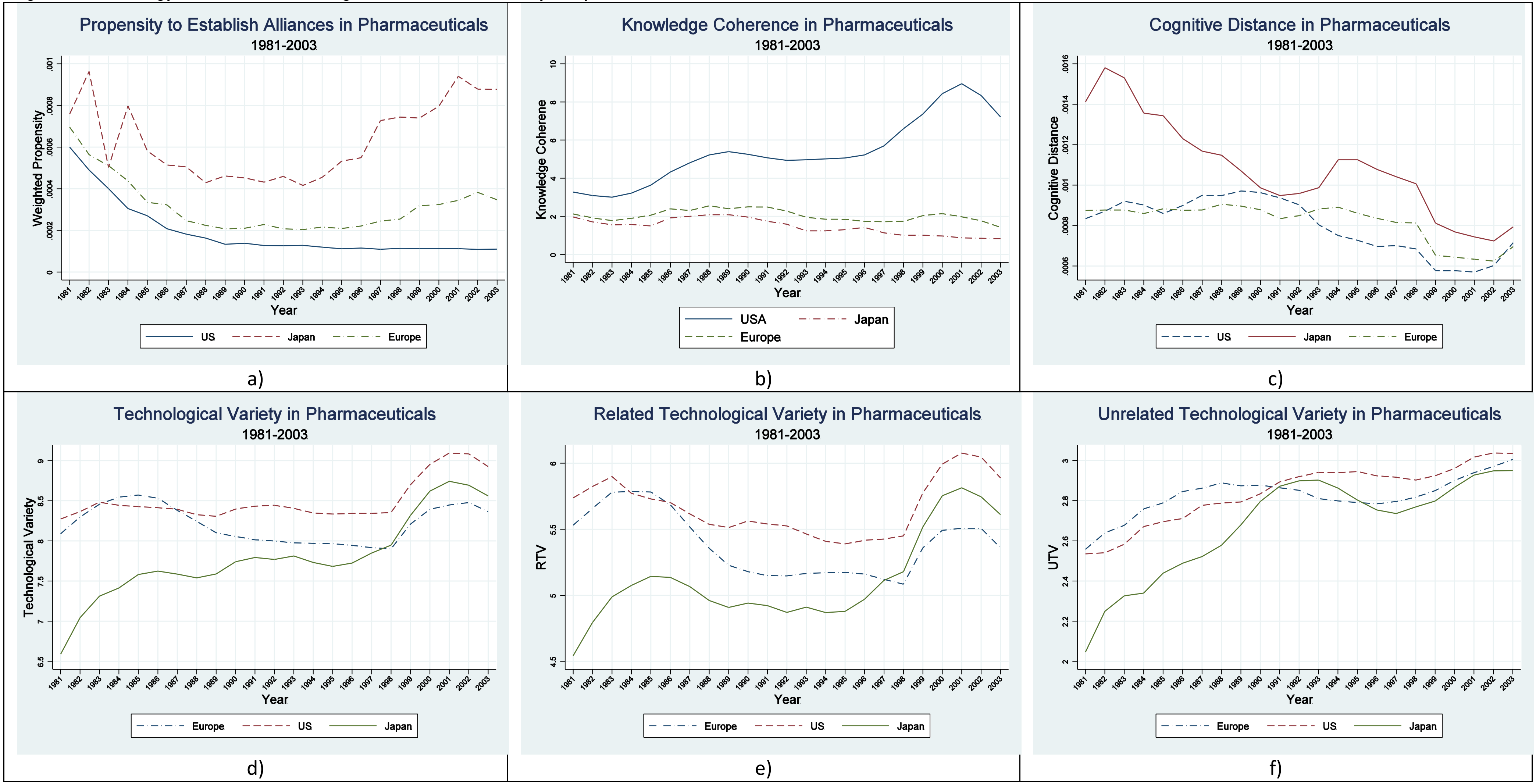

Figure 4 - Technology Alliances and Knowledge Structure : United States

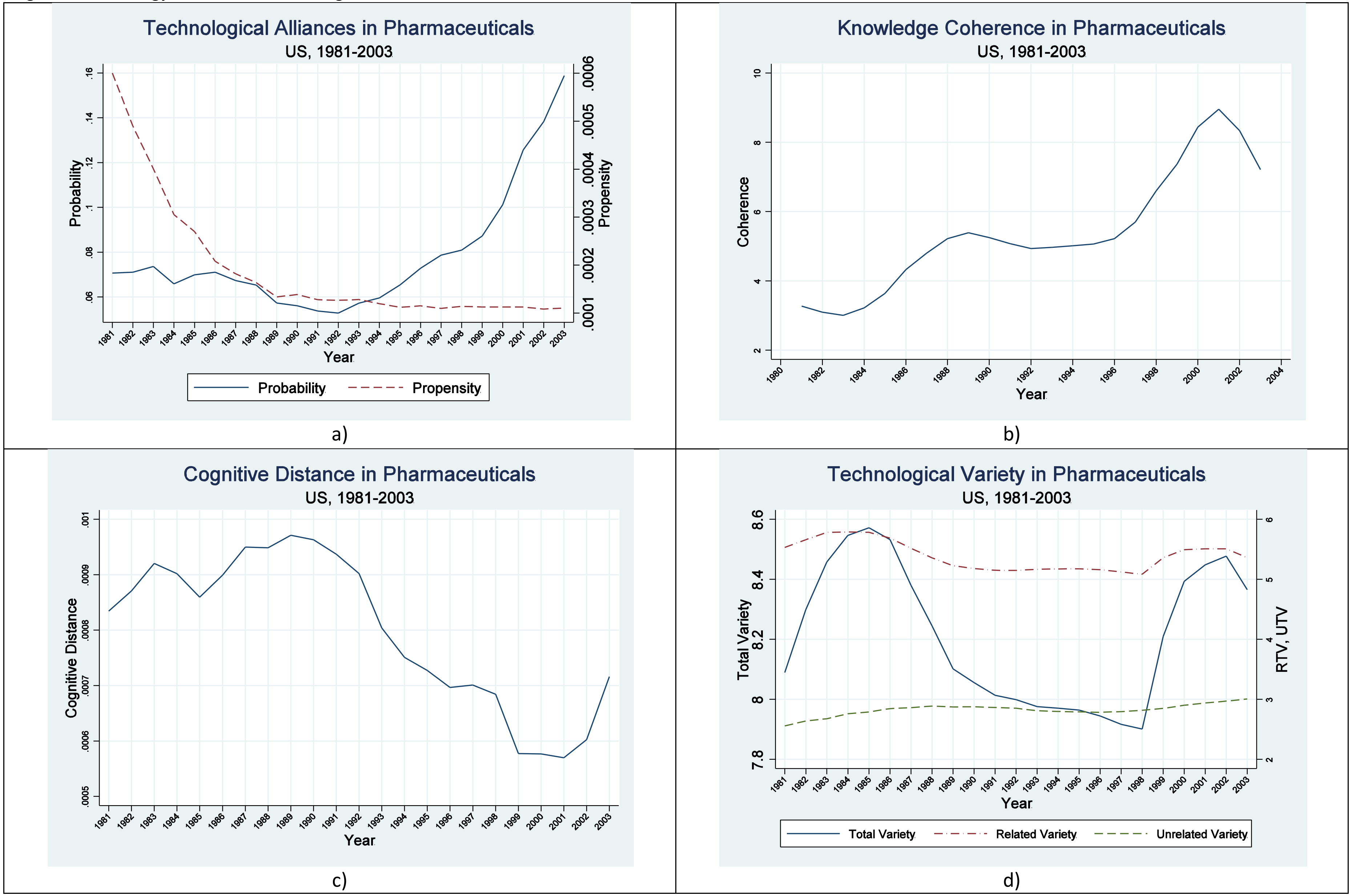

Figure 5 - Technology Alliances and Knowledge Structure: Japan

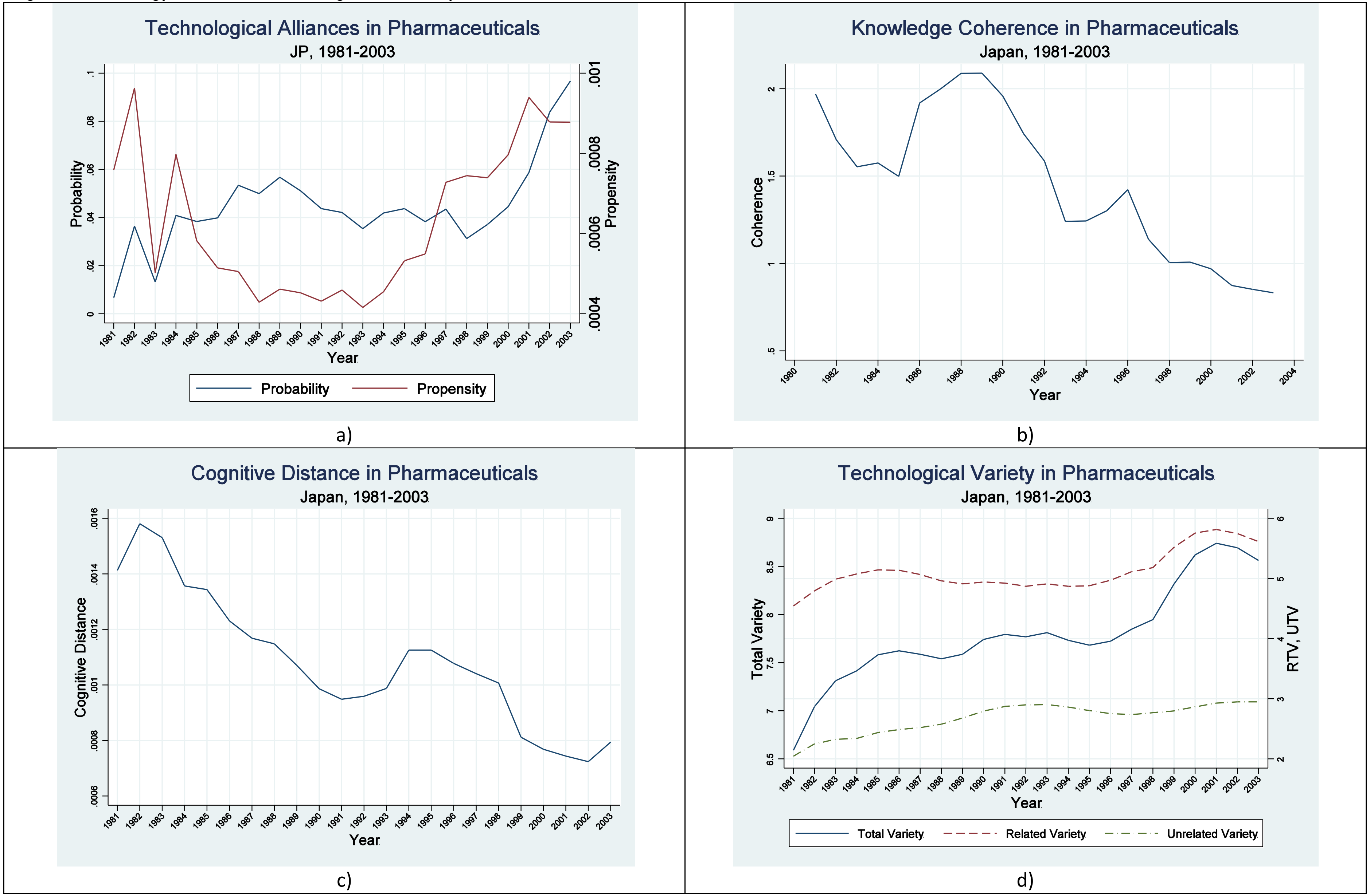

Figure 6 - Technology Alliances and Knowledge Structure: Europe