Clusters and clustering in biotechnology: stylised facts, issues and theories

Book Section

Clusters and Clustering in Biotechnology: Stylised Facts (?), Issues and Theories.
From Clusters to network structures and their dynamics

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1. **Introduction**

This paper provides a critical review of the literature on innovative clusters in biotechnology. It examines the main contributions on this subject, trying to identify some robust stylised facts, the main puzzles and unresolved questions concerning the ingredients and the dynamics of the geography of innovation in this industry.

Clusters of production and innovation have become in the last two decades a major focus of attention for social scientists and policy makers. Theoretically, the observation that production and innovative activities tend in many cases to concentrate in specific geographic areas obviously raises the questions about the relevance of space in shaping economic activities and about the nature of the mechanisms and processes that lead to agglomeration.

Clusters have become also important in terms of policy-making, as they have been increasingly considered as drivers of economic growth and innovation, on the basis of the assumption that there are advantages to economic agents located in a cluster and that innovation is more likely to occur in clusters. The Silicon Valley at one extreme, Italian industrial districts on the other have become a sort of "influential methaphysics" guiding academic analysis and policy making (see e.g. Special Issues of Regional Studies (33/4; 1999) and World Development (27/9; 1999). Cluster policies have been adopted in both advanced and developing countries and, in some cases, these have been considered drivers of national economic growth (UNCTAD, 1998; Porter, 1998; OECD, 1999; 2001).

The notion of clusters has spawned an enormous literature, wich includes a variety of approaches and methodologies, ranging from case-studies, comparative case studies, econometric analyses and theoretical models- having either a formalised or appreciative structure. The literature on clusters traces its origins in trade theory, regional economics and economic geography, but it has been increasingly overlapping with other streams of literature, including innovation studies, industrial dynamics, small firms, entrepreneurship, networks, etc...

While these contributions have significantly improved our knowledge of the factors that lead to the clustering, several fundamental issues remain controversial and poorly understood. Among them:

- the relative role of alternative mechanisms that have been proposed as possible explanations of the observed concentration of productive and innovative activities, in particular as it concerns the nature of what are now commonly defined "local knowledge spillovers" (LKS);
- even more important, the nature of the dynamic processes – as distinct from or overlapping with the "ingredients" – that might produce clustering.

Rather than addressing the whole literature on clusters, this paper takes a much more narrow focus. It concentrates on the relationships between clusters and innovation; and looks at one particular industry (or technology), i.e. biotechnology.

Biotechnology is a particularly challenging case within this stream of literature, for a variety of reasons, but mainly because it is an extreme case which provides more puzzles than answers.

First of all, biotechnology is a highly innovation – intensive industry where spatial agglomeration appears indeed to be quite a prominent characteristic of its development. Yet, it has become increasingly questioned how precisely space influences innovation in this field and what are the specific mechanisms leading to agglomeration, even coming to the conclusion in some cases that the role of geography might have been vastly exaggerated. So, this case provides an intriguing opportunity for discussing the mechanisms and processes that generate geographical concentration of innovative activities.

Rather than trying to provide definite answers, the main aim of this this paper consists in flagging out puzzles and unresolved problems. In particular:

i) to what extent is clustering a necessary feature of innovative processes in this industry?

ii) in what way is space really important in determining innovation in biotechnology?

iii) Can one identify specific ingredients and specific processes that lead to emergence and development of clusters? Can on meaningfully distinguish between "ingredients" and "processes"?

iv) What are the factors that might explain the genesis of clusters and what are the factors that sustain clusters once they have emerged? Do they coincide or are they different?

v) Among the processes that create innovative clusters, what is the role of various forms of agglomeration factors?

vi) What are, if any, the specific properties of the technology and of the related innovative activities that favour processes of clusterisation in the biotech industry and sustain specific agglomeration forces?

vii) More generally, are clusters producing innovation or is it innovation that creates clusters?

Against this background, an excessively provocative, but perhaps useful, way of framing the paper is to take the devil's advocate position and putting forward the "null hypotheses":

i) innovative activities in biotechnology are less concentrated than it meets the eye;

ii) space as such is not a fundamentally important determinant of innovation in this technology / industry

iii) what matters in triggering agglomeration processes are networks of relations which have only partially a clear spatial dimension;

iv) in particular, localised knowledge spillovers are not important drivers of agglomeration; rather, concentration of innovative activities is linked primarily to pre-exisiting and self-reproducing bodies of previously accumulated knowledge, thick labour markets for highly skilled labour and - in general – to more formal and formalised mechanisms of transmission of knowledge, many of which are not specifically spatially constrained.

After the review of the literature, I'll come to a much more nuanced position that acknowledges:

a) the relevance of the spatial dimension, but mainly as a reflection of the spatial concentration of cutting edge research in selected universities and public research organisations, and mainly at the level of research groups ;
b) the relevance of localised processes of creation and transmission of knowlege, which are however only partialy linked to knowledge spillovers and have more to do with active processes of construction of supporting institutions;
c) the importance of markets for technology and of attempts at privately appropriate the economic benefits stemming from academic research but also of other less formal mechanisms for the creation, diffusion and economic exploitation of knowledge.

The paper is organised as follows. Section 2 provides a broad, but brief, overview of some key issues in the literature of clusters that set the stage for the subsequent discussion of the case of biotechnology (Section 3). In particular, paragrah 3.1 proceeds to review briefly the evidence about agglomeration in biotechnology; paragraph 3.2 examines the ingredients of biotechnology clusters; paragraph 3.3 discusses what is known about the processes of spatial agglomeration in biotech, especially as it concerns local knowledge spillovers and other mechanisms based on increasing returns. Section 4 concludes the paper.

2. Clusters of innovative activities: some basic questions and open problems

2.1 The Spatial Embeddness of Innovation

The observation that economic activities are spatially embedded has a long history in economic analysis, that goes back at least to to Von Thunen and Marshall and constitutes the starting point of sub-disciplines like regional economics, economic geography, trade. In more recent years, a variety of intertwining factors have focused attention on the more specific phenomenon of clusters of innovation, as distinct from clusters of production activities.

A first reason is the increasing recognition of the role of innovation (and more generally of learning) as an engine of economic growth, at various levels of spatial disaggregation. Thus, "regional economists"and "economic geographers " – as well as policy makers - have started to thoroughly consider how innovation can be generated and sustained in specific geographic areas and regions.

On the other hand, it has been observed that innovative activities are often geographically concentrated. As such, this observation might not necessarily be a shattering new discovery. After all, it has been a well known fact to historians and economists studying technological change that not only innovation has been historically strongly concentrated in few countries; but also that the club of innovators has remained quite small with few notable exceptions (often linked to major technological revolutions); and that countries tend to exhibit stable patterns of technological specialisation (Dosi et al., 1994; Cantwell, 1989). These observations are indeed a fundamental building block of the various forms of the "national systems of innovation" approaches (Nelson, 1991; Edquist 1997), whereby these phenomena are essentially explained on the basis of some key characteristics of technical knolwedge, like its tacit and cumulative nature, coupled with the recognition of the systemic nature of innvative activities, which involve diverse interactions between different agents, competencies, institutions.

However, three further findings have sparked new research in the field of the geography of innovation. First, it has been observed that innovation is more spatially concentrated than production activities (Audretsch and Feldman, 1996). Second, concentration of innovative activities occurs at spatial dimensions much smaller than nation states, i. e. regions, areas, cities, etc.. Third, firms located in innovative clusters tend to be systematically more innovative than firms located elsewhere. Jointly, these observations have led to the notion that innovative processes are intimatley embedded is space and and have opened a set of questions concerning the specific characteristics of particular areas that make them conducive to innovation.

A review of this enormous body of literature goes far beyond the scope of this paper. Suffice it to say here – in a heroic simplification – that research into the spatial dimension of innovative activities has basically reformulated in a new setting the main questions that have been addressed for more than a century by social scientists interested in the spatial dimension of economic activities. Quoting Bottazzi et al, 2002:

(i) Why and when can one observe persistent spatial patterns that cannot be explained by resorting to pre-existing heterogeneity in agents and locations (i.e. by some kind of "comparative advantage theory" alone) ?

(ii) What are the agglomeration and dispersion forces that generate spatial concentration (and possibly its destabilization) ?

(iii) What is the role of mere “chance” in the observed spatial concentration of economic activities ?

(iv) How and when emerging spatial structures of production and innovation tend to become self-sustained over time ? (And, conversely, what make them wither away ?)

2.2 Endownments, agglomeration forces and localised knowledge spillovers

It is fair to say that, despite the staggering amount of empirical work that has been produced, the answers to all these questions remain highly controversial.

As it concerns point (i) and (ii), there seems to be a wide consensus that clustering in innovative activities cannot be simply explained by some sort of given and immobile “endownments”, but that powerful agglomeration forces must be at work in order to produce geographical concentration. However, what these forces are precisely and what is their relative explanatory role remains unclear. And, in some cases, the doubt can legitimately arise that perhaps some of these agglomeration mechanisms could be interpreted more simply as “endownments” or viceversa, as it will be argued at more length later on.

In fact, the development of the geography of innovation have concentrated their explanations to these questions essentially on various reformulations of the fundamental sources of agglomeration externalities originally suggested by Marshall (see Henderson (1986) and Krugman (1991) among others):

a) Economies of intra-industry specialisation: a localised industry can support a greater number of specialised local suppliers of industry-specific intermediate inputs and services, thus obtaining a greater variety at a lower cost.

b) Labour market economies: a localised industry attracts and creates a pool of workers with similar skills, which benefits both the workers and their employers.

c) Ease of communication among firms: information about new technologies, goods and processes seem to flow more easily among agents located within the same area, thanks to social bonds that foster reciprocal trust and frequent face-to-face contacts. Therefore adoption, diffusion and innovation seem faster and more intense in geographical clusters than in scattered locations. That is, some ‘knowledge spillovers’ exist, which are geographically bounded.

A significant fraction of the theoretical literature on clusters explains different spatial agglomeration patterns (from concentration of economic activities in few locations to hierarchical structures) as the solution of static trade-offs between agglomeration and dispersion forces, particularly combinations of static externalities, transport costs and economies of scale (Papageorgiou and Smith (1983) and Fujita (1988, 1989, Henderson (1974). The “New Economic Geography” (Krugman (1998, (1991a, 1991b, 1991c, 1993), Krugman and Venables (1995, 1995a, 1996), Venables (1996), Ottaviano and Thisse (1998), Fujita, Krugman and Venables (1999), Puga and Venables (1996), Ottaviano and Puga (1998), Fujita and Thisse (1996) focuses instead on various forms of increasing returns to scale (or indivisibilities) at the level of individual agents as the main mechanisms leading to agglomeration and to ist persistence..

However, and perhaps not too surprisingly given that innovation is the subject of the analysis of this stream of research, the role of knowledge spillovers has attracted the attention of scholars. The localised nature of such spillovers is usually associated to the tacit nature of knowledge. Thus, communication occurs more easily through face-to-face contacts and interactions.

Different types of methodologies (estimation of knowledge production functions as in Jaffee (1989), Acs et al (1992 and 1994), Audretsch and Feldman (1996), Feldman and Audretsch (1999), Feldman and Florida (1994); use of patent citations to track direct knowledge flows from academic research into corporate R&D (Jaffee et al (1993), Almeida and Kogut (1997)); and an immense set of empirical case studies and narratives confirm that indeed important localisation effects exist in innovative activities.

The notion of knowledge spillovers has taken a central role not only in scientific analysis but also in policy-making, where the a key emphasis has been attributed to the idea that interventions should be directed primarily towards the attempt at facilititating such knowledge flows and spillovers, through, e.g., offices for technology transfer, all kind of measures for strengthening university-industry relations, etc..

However, it has become increasingly acknowledged that the evidence supporting the role of knowledge spillovers is largery indirect and that it is quite difficult to clearly separate knowledge spillovers for other types of pecuniary extenalities and more generally between Marshallian externalities and more classic urbanisation externalities or even natural endownments (Glaeser et al., 1992, Ellison and Glaeser (1999), Henderson (1999)).

In particular, as forcefully argued by Breschi and Lissoni (2001), it is has proven hard to precisely show how knowledge spillovers actually work and even whether they can legitimately interpreted as spillovers. To begin with, in econometric studies spillovers are often identified as a sort of a residual, rather than directly. But that residual might actually include many different processes that do not necessarily coincide with knowledge spillovers. Thus, for instance, in diverse instances, the pool of of knowledge that should constitute the very origin of knowledge spillovers seems to be embodied in specific people and/or in a pool of specialised workforce, as argued for example by Zucker et al. (1998, 1998a) and Almeida and Kogut (1999).

Similarly, knowledge within a clusters in many cases does not appear to simply "spill over". Rather, access to such knowledge seems to require deep involvement in the research process and bench-level scientific collaboration and the conscious investment of resources not simply to search for new knowledge, but to build the competencies to absorb the knowledge developed by others. Finally, in other cases, knowledge flows occur via (localised) mobility of researchers and of the workforce and are mediated by market transactions or other institutionalised or quasi-institutionalised mechanisms involving not simply mutual trust and face-to face contacts, but highly complex economic and social structures.

Thus, in a highly influential paper, Lamoreaux and Sokoloff (1997) have criticised the assumption that inventors and firms operating in a specific industry and in close spatial proximity to each other will be more innovative than those who are geographically isolated because of the greater likelihood that they will share (tacit) knowledge. Using historical patent data for the US, the authors tracked the career patterns of a number of inventors, in order to relate the production of inventions to regional manufacturing activities. Summarising, their results suggest that concentration of firms and production in a given area was not per se a necessary, let alone sufficient condition to determine high rates of innovative activity. To put in slightly different terms, static externalities related to the current scale or size of an industry in a given area did not necessarily generate better (local) information flows to the advantage of innovative activities. What seemed to matter more was the accumulated stock of knowledge (dynamic externalities) in a diversity of industries as well as the levels and types of human capital in a region.

These results may well reflect radically different patterns of organisation of industrial and innovative activities as compared to the ones prevailing now. However, other studies (e.g. Lyons 1995, Echeverri-Carroll and Brennan 1999 among others. See also Giuliani, 2004, for further results and a broader discussion of these issues) suggest that local sources of knowledge are key in determining success in the development of new products and processes only in areas with a large accumulation of knowledge (e.g. Silicon Valley). On the contrary, innovations in firms located in cities with a relatively small accumulation of knowledge depend on the relationships with universities and other high technology firms (suppliers and customers) located elsewhere, especially in higher-order urban centres.

The most dynamic and innovative firms look for knowledge embodied in engineers and scientists wherever they are available, and are not necessarily constrained in this by geographical barriers. Local knowledge sources are relatively less important for firms located in lower-order regions. For these firms, local universities are viewed as suppliers of skilled workforce, rather than loci of innovations or sources of product ideas or spillover effects. In order to sustain high rates of innovation they must develop linkages with actors (universities and other high-tech firms) located in higher-order regions.

2.3 Clusters and networks

The issue becomes even more tangled whenever the cluster is directly assimilated to the concept of networks. Indeed, almost all the available analyses of clusters rely – directly or metaphorically – on the idea that the agglomeration forces that keep innovative activities localised are expressions of networks of (localised) relationships among agents, be they different types of firms, venture capitalists, academic scientists, local institutions, policy makers, etc..

However, the meaning attributed to the concept of networks varies drastically. In some cases, for example, networks are considered as a specific new form of organisation of innovative activities, which is substituting the traditional model based on internal R&D (Powell, 1996). According to this kind of interpretations, innovative activites tend to cluster because such kind of networks exist: the cluster is the outcome of the existence and development of local networks, rather than networks emerging as a result of specific localisation factors.

Partly overlapping with these views, in other cases, the notion of networks is strictly associated to the notion of collaboration. According to this perspectives, cooperation in innovative activities and interactive learning are the distinct property that defines and identifies (successful) clusters (see for instance Cooke, 2002; Maskell, 2001). A network-like structure is a typical properties of clusters and networks should e viewed as the proper unit of analysis to investigate innovation: knowledge resides in the network and not simply in each of its constituent nodes. Within innovative clusters, firms learn through a variety of types of interactions, ranging from user-producer relationships, formal and informal collaborations, interfirm mobility of skilled workers and the spin-off of new firms from existing firms, universities and public research centres. Embeddeness of local firms in a thick network of knowledge sharing, supported by close social interactions and by (formal and informal) institutions that promote the development of trust among participants in the network.

However, the concepts of networks and clusters do not coincide. More important – and quite obviously - networks do not necessarily imply cooperation, trust and distributed knowledge. As such, networks are just a language (in this sense, having the same methodological status of game theory) to represent and analyse interactions among agents. And in its most developed form – social network analysis – this approach is firmly grounded in sociology, its main object of analysis being social relations. Thus, there are many different types of networks and many different principles that determine their structure and their evolution.

Thus, formal applications of network analysis to the study of innovative clusters as well as an exploding number of case studies have highlighted the extreme diversity in their structure, logic and dynamics. In some cases, highly hierarchical structures are observed (see for instance Orsenigo et al., 2001). More generally, these studies had the great merit to show that (different) clusters are characterised by (different) highly structured patterns of knowledge diffusion and generation, produced by the interaction of a host of overlapping social and economic relations. This observation further weakens any simplistic description of the advantages of co-localisation as the result of some kind of local externalities. If anything, the ability to tap into the local knowledge base and to exploit the other possible agglomeration externalities appears not to be unrestricted, but structured and mediated through specific social, organisational and economic mechanisms.Hence, clusters might emerge as the outcome – or as a specific sub-network – of sets of relations which are not necessarily based on spatial proximity, but on other forms or contiguity, like organisational proximity (Rallet and Torre, 1999), epistemic communities, communities of practice, etc.. Conversely, clusters might well result as the effect of the intersection and coalescence of different networks.

One particularly important result of this stream of literature is that (successful) clusters are much more open and outward-oriented than the conventional interpretations would suggest. Rather than simply leveraging the knowledge available within a cluster, the existence of weak and strong ties with agents located outside the cluster itself increasingly appears to be a crucial feature of the more innovative clusters (see Bresnahan, Gambardella and Saxenian (2001) for a discussion), As such, this finding does not imply by any means that local sources of knowledge are unimportant. On the contrary, it might be interpreted as confirming that the ability to tap external sources of knowledge - absorptive capacities (Cohen and Levinthal (1990) - is itself a function of the local technological capabilities.

However, in more general terms, this observation links with the broader question concerning the existence an "ideal" knowledge network structure, which can be associated with high innovative performances. In some respects, the debate about the advantages of Silicon Valley vs. Route 128 might be considered as a particular version of this direction of research.In this respect increasing attention has been devoted to the studies of dense networks (Coleman 1988), to the importance of structural-holes (Burt, 1992) and to "small world" type of networks (Milgram, 1967; Watts, Strogatz, 1998). As discussed in Ahuja (2000) and Giuliani (2004), most likely an "optimal" network structure for innovation does not exist but, rather, different structures are likely to show different types of advantages and disadvantages. For example, dense networks tend to favour the formation of trust, which in turn limits opportunistic behaviour (Coleman, 1988) and encourage cooperation and diffusion of more high quality, fine-grained knowledge (Uzzi, 1997). Networks characterised by structural holes, instead, allow firms to expand the diversity of knowledge they can have access to (Ahuja, 2000) and reduce the probability of negative lock-ins (cf. Gargiulo, Benassi, 2000). Similarly, “small worlds” are considered a more efficient network structure as compared to a randomly interconnected one, to the extent that fewer but more distant linkages increase the probability of accessing diverse knowledge and allow efficiency gains in the processes of knowledge diffusion (Cowan, Jonard, 2004).

2.4 Forms of the organisation of the cluster and the nature of technology

In some respects, the debate about the advantages of Silicon Valley vs. Route 128 might be considered as a particular version of this discussion on the relative efficiency of different specific cluster or network structures. Annalee Saxenian (Saxenian, 1994) proposed the extremely influential argument that the superior performance of Silicon Valley was related to the particular form of organisation of innovative activities that had been developing over time, based indeed on network-like structures of interactions among entrepreneurial agents. On the contrary, Route 128 fared worse as a consequence of the dominance of a more traditional organisational structure, based on large vertically interated firms.

Kenney and Von Burg (2001) object to this interpretation that the main difference resided not so much in the organisational structure of the cluster as such, but in the nature of the relevant technology or set of technologies and related products that drive the cluster.

Without discussing the details of this debate, it is indeed important to notice that relatively little attention has been paid to the relationships between the structure and performance of a cluster and the nature of the knowledge base and of the market opportunities upon which the cluster is based. Yet, the properties of the relevant technology or technologies are likely to have an important role in shaping not only the critical resources or endownments that might determine the success or failure of clusters, but also the relative importance of alternative mechanisms of agglomeration and – of course – the relative efficiency of alternative network structures.

In fact, the debate on knowledge spillovers has concentrated on one particular property of knowledge, i.e. tacitness. However, while the crucial importance of tacitness can be hardly overemphasised, knowledge and technologies are characterised also by other dimensions that have a profound impact on the ways through which innovation takes place (Malerba and Orsenigo, 2000). As argued by Malerba and Orsenigo (1997) and Breschi, Malerba and Orsenigo (2000), the nature of technological regimes bears a close relationship with the patterns of innovative activities.

Thus, for example, the nature of technological opportunities and of the space in which search for new products and processes occurs implies specific incentives and possibilities for the entry of new innovators and more generally for the speed of technological change and for the organisation of innovative activities. High opportunities in technologies which offer ample possibilities of invention along diverse trajectories and over a wide range of products, processes and market segments are likely to associated not only to high rates of innovation, but also by a large and fastly changing population of innovators, who explore different avenues and open new market niches. Similarly, technologies which involve the access to and the mastery of differentiated fragments of knowledge open up possibilities for vertical and horizontal specialisation and the development of adequate organisational devices for the integration of the relevant knowledge. To some extent, the discussion about the role of specialisation vs. diversity, i.e. Marshallian vs. Jacobian externalities, might be interpreted also along these lines. Thus, Feldman and Audretsch (1999), for instance, support the view that diversity matters more than specialisation, finding that the number of innovations in sector i in state s owes more to tho the presence in the state of other industries whose science base is related to to that of industry i rather than to the specialisation in sector i. Henderson (1999) however comes to different conclusions. In a similar vein, Bresnahan, Gambardella and Saxenian (2001) suggest that clusters tend to form taking advantage of new technological and market opportunities that have not already been exploited.

The degree of cumulativeness and the appropriability conditions of technological advances are also likely to influence the structure of the cluster and the processes leading to (diverse structures of) the cluster. Strong cumulativeness and a tight appropriability regime make the circulation of knowledge more difficult and tend to strengthen and reproduce over time the advantages of early innovators. This might lead to stronger and persistent concentration of innovative activities in few firms, to more hierarchical network structures and – under some further conditions – to higher degrees and persistence of spatial concentration (Malerba and Orsenigo (1997), Breschi and Malerba (2001).

The combination of these and other properties of knowledge can therefore give rise to a large variety of different processes and structures of clusterisation (For some preliminary discussions and empirical evidence, see Bottazzi, Dosi and Fagiolo (2002)). In turn, alternative characteristics of the clusters – in terms of their endownments, patterns of internal interactions, mechanisms of agglomeration – may display different degrees of "fitness" with the relevant technological regime. At a higher level of aggregation – essentially the nation state - these relations have started to be explored, among others, by Hall and Soskice (2001), Casper and Kettler (2001) in the context of the literature on “national frameworks for innovation”. The contributions by P. Cooke (Cooke (2002)) on “regional innovation systems” partly share this orientation too. More systematic attempts to map and taxonomise the properties of technologies and the structures of clusters might turn out to be a very promising avenue for future research.

2.5 From static externalities to dynamic increasing returns: the genesis and evolution of clusters and the direction of causality between clusters and innovation

In a recent paper examining the reasons why Detroit emerged as the capital city of the automobile industry and maintained its leadership over time, Steven Klepper (Klepper, 2002) proposes and tests empirically the hypothesis that this process was the outcome of a combination of chance (the presence in Detroit of a few key individuals, who were not, however, closely related to each other) and processes of spinoffs of new firms by incumbent companies. On the basis of the key assumption that the “best” firms generate a larger number and more efficient of spin-offs, the model produces patterns of agglomeration without relying on any standard notions of externalities.

Irrespective of the merits or demerits of the specific argument and unduly generalising, Klepper’s approach is important because it highlights several crucial issues in the literature on clusters and innovation.

First, Klepper’s argument does not rely on the standard notions of externalities, but introduces the idea that other forms of dynamic increasing returns might lead to clusterisation, in particular as it concerns the cumulativeness of innovative processes. Cumulativeness plays indeed a fundamental role in the explanation of the processes of concentration at the industry level (Dosi et al., (1995); Malerba et al (1999); Sutton, 1999) and constitutes a plausible further candidate explanatory variable for concentration at the spatial level. As long as innovation is cumulative, early innovators have a higher probability to continue to innovate in the future, at least until the emergence of new technological paradigms make the relevant knowledge and competencies obsolete. Shifting this argument from individual firms to clusters requires some additional assumptions about the mechanisms through which knowledge and competencies are replicated outside the boundaries of the original innovator(s). Spin-off processes from incumbent firms (or other organisations like universities) are certainly a plausible – but certainly not the only - mechanism, which does not necessarily rely on externalities. Several accounts of the rise of the Silicon Valley (Kenney and Von Burg, 2001 among others) emphasise, in a strikingly similar way, the role played by Fairchild and the Fairchildren. Furthermore, this type of argument suggests a further important and in principle testable implication concerning the relative role of new firms originated from within the clusters as compared to new firms (entrepreneurs) attracted to the cluster from outside, i.e. the relative importance of internal cumulativeness vs. attractiveness of the cluster itself.

Second, this approach somehow raises the question about the direction of causation between innovation and clusters. Whereas most of the literature discussed so far focuses on the conditions that make a particular area conducive to innovation, - i.e. on the idea that clusters promote innovation – the opposite nexus of causation might turn out to be at least equally important: it is an original innovation that creates clusters. Quite obviously, it remains necessary to specify the mechanisms that tend to keep subsequent innovations within the clusters rather than spreading outside. In this respect, the degree of overlapping between these two extreme approaches is very high and it might be difficult to meaningfully separate them.

Third, Klepper's argument suggest that perhaps more emphasis should be attributed to specific characterists of the firms and of the other key agents active within a cluster.

As Giuliani, (2004) argues, both cluster and network studies tend to consider the *meso*-level (i.e. a cluster or a network of firms) as the unit of analysis. And hence most of research has been undertaken to analyze the effects of meso-level characteristics (e.g. degree of inter-firm co-operation, presence of localized knowledge spillovers, structural features of the networks, etc.) on the innovativeness and performance of the cluster or network. Less research has instead been directed to the understanding of how the meso-level characteristics come into being or evolve as a results of micro-level, non-structural characteristics. In the domain of cluster studies, for example, only relatively few contributions have emphasised the relationships between firms characteristics and the innovative outputs of clusters or regionally bounded areas (see, Harrison et al., 1996; Beaudry and Breschi 2003). As suggested by Caniels and Romijn (2003),

> "the regional agglomeration studies emphasize the favorable impact of geographical proximity on regional economic performance; but the firms that constitute those agglomerations largely remain black boxes. In contrast studies dealing with technological learning explain economic performance at firm level without systematically taking accounts of the effects of geographical proximity" (Caniels, Romijn, 2003: 1253).

Similarly, in network studies, recent contributions have stressed that: "the bulk of network research has been concerned with the consequences of networks" (Borgatti, Foster, 2003: 1000) and that "…limited attention has been paid thus so far to how important nonstructural features – such as the characteristics of the organizations that represent nodes in a network, geographic location, or the institutional underpinnings of the larger structure – alter the character of information flows." (Owen-Smith, Powell, 2004: 5).

Finally, emphasis on the "reverse causation" has the merit to recast the issue in an explicit dynamic way and therefore to reframe the initial question about "endownments" and agglomeration forces in quite a different perspective: clusters may well emerge as a sheer outcome of chance (e.g. an innovation) and develop through the working of (a variety of) self-reinforcing processes, irrespective of any initially favourable endownment.

As Bresnahan, Gambardella and Saxenian (2001) put it, the literature on clusters is much better able to provide hypotheses about how a cluster keeps going than explaining the nature of the spark that generate the cluster itself. Focusing on the interplay between chance, initial conditions and subsequent self-reinforcing processes might help in posing the problem sharply and in understanding the subtleties involved in these distinctions.

Indeed, one does not necessarily rely on chance alone in order to explain the genesis and the development of clusters. In many cases, particular sets of initial conditions make the onset of clusters more likely. For example, Bresnahan, Gambardella and Saxenian (2001) suggest that emerging clusters tend to share some common features: existence of unexploited technological and market opportunities, highly educated skilled labour, firm- and market building capabilities by pioneering firms, connection to markets; and luck. Another recurrent factor is the availability and concentration of state-of the art knowledge in key agents.

Interestingly, variables like the presence of supporting institutions (e.g. venture capital) diffusion of particular social attitudes (e.g. entrepreneurship) appear to play a much lesser role in nascent clusters and if anyting they tend to develop later on as a product of the agents' activities. Thus, in a dynamic perspective, considering these initial conditions as "endownments" may be deeply misleading, insofar as they are not given, but they are themselves the result of previous processes of construction of competencies and institutions.

This interpretation resonates with all those – mainly appreciative - accounts which highlight how the development of clusters involved complex processes of construction of competencies, supporting institutions, organisational structures unfolding in time by heterogeneous agents who cannot perfectly understand the environment in which they act (Kenney and Von Burg (2001), Feldman, Bresnahan *et al.* (2001), among others). And a now significant stream of theoretical literature, building on the seminal work by Brian W. Arthur and Paul David, has been indeed attempting to analyze the nature of economies/diseconomies of agglomeration in a truly dynamic framework in which persistent spatio-temporal patterns are conceived as emerging out of direct interactions among boundedly-rational, heterogeneous economic agents (cf. Arthur, 1994; Ch. 4 and 6; David et al., 1998; Cowan and Cowan, 1998). In explicitly dynamic settings, it becomes possible to appreciate:

> "the complex trade-offs become more clear between purely random factors and more systematic, historical forces (or, put it differently, the issue of necessity vs. chance) underlying the emergence of spatially ordered structures". (Bottazzi *et al*., 2001, 9).

2. 6 Some preliminary conclusions

The debate on the nature of the externalities that generate and sustain clusters provides – as it often happens in economics – perhaps too many possible hypotheses for explaining the phenomenon under considerations, and it is intrinsically difficult to satisfactorily discriminate among them. To some extent, this should come as not too big a surprise, when one considers the high degree of heterogeneity in the structure of clusters and in the nature of the relevant technologies. Thus, it is perfectly plausible that different "endownments" and agglomeration forces may generate clusterisation under different circumstances. Clearly, this is not a particularly illuminating insight, to the extent that it dangerously borders the notion that "everything can happen".

In a slightly different perspective, the concept of clusters bears a worrying resemblance with other "stylised facts" which are found in industrial dynamics, like e.g. the persistence of skewed distribution of firms sizes. The "facts" are often what statisticians call "unconditional objects" (Brock, 1999), i.e. they can be generated by an enormous variety of alternative processes, so that empirical testing becomes exceedingly difficult. Under these circumstances, it becomes necessary to impose much stronger restrictions on both the type of phenomena that are to be explained and on the alternative theories. Thus, a theory should be able to account at the same time for a larger set of phenomena at the same time and these phenomena should be specified in much closer detail.

A final point deserves mention. The literature on clusters has certainly provided strong evidence that innovation often tends to be spatially localised and an extremely rich variety of explanations for this phenomenon. Yet, less attention appears to have been attributed to the exploration of the "null hypotheses":

- Are clusters a necessary characteristic of inovation processes?
- Are clusters unequivocally beneficial to innovation?

3. The case of biotechnology

As mentioned in in the introduction, the case of biotechnology is particularly interesting for a series of reasons.

First, it has been frequently noted that biotechnology is a strongly science-based industry (technology). As science should be in principle codified and public knowledge, a major motivation for clustering – i.e. local spillovers of tacit knowledge - would seem to be absent.

Moreover, biotechnology is characterised by a very particular form of industry structure, with a pronounced division of innovative labour between universities and other research organisations, specialised biotechnology firms and large corporations and the development of dense networks of relationships among these agents.

Thus, important questions arise concerning:

- how much are innovative activities actually spatially concentrated?
- what are the specific reasons for clusterisation?
- Are the agglomeration processes similar across different geographical areas?

3.1 Evidence of agglomeration

There is indeed strong evidence that innovative activities in biotechnology tend to cluster in specific geographical areas.

First of all, innovative activities are strongly concentrated in few countries and particularly in North America. In terms of patents the US are and continue to be the most important locus of innovation in biotechnology, with a share of around 50% (both as USPTO and EPO patents are concerned) followed by Japan, Germany, UK, and France, Canada and Australia. Spatial concentration has been increasing over time. From 1990 to 2000, the United States increased by 9 percentage points its share of all biotechnology patents granted by the USPTO. The share of Japan declined by 11 %. A modest ncrease occurred in the case of Denmark (+ 1.1%), while Germany lost a little ground (- 1.2%). The shares of all other European countries have remained relatively stable over the last decade. In Asia, new clusters are emerging in Singapore and Taiwan.The spatial concentration of innovative activities is even stronger in terms of patent citations. The share of citations to US patents is substantially higher (around 55%) than the share of simple counts and reaches around 65% for “highly cited” patents (i.e. patents receiving at least 10 citations in the period not counting self-citations) in the period 1978 – 1995 (with citations up to 1997) (Allandottir et al., 2001).

Second, innovative activities are strongly concentrated in specific regions within national States, in terms of patents and even more so in terms of number of firms, research institutions and employment. In the US, biotechnology has been characterised, historically, by a relatively high concentration of firms and employment in a restricted number of regions. In particular, the Bay Area and Boston established themselves as the main locations of the emergent biotechnology industry. Later on, as the industry developed, other regions have become important clusters: San Diego, New Jersey, New York metropolitan area, Maryland (between Baltimore and Washington DC), and Texas (Dallas and the Houston area in Texas) (see Owen Smith, Riccaboni, Pammolli, Powell, 2002; Zucker, Darby, *et al.* 1998).

In Canada, biotechnology activities are concentrated around a few large and medium-sized urban agglomerations, like Toronto, Montreal, Vancouver, Ottawa, Edmonton and Calgary, while more specialised clusters have also emerged around smaller cities (Niosi and Bas 2001)

Similarly, in Europe a relatively small number of local clusters are capturing a dominant majority of biotechnology firms and of public research organisations. Some of these clusters (i.e. Oxford, Cambridge, and Stockholm) are more consolidated and can rely upon sound research background and high international reputation, coupled with a critical mass of both young and established spin-off companies and international contacts. Other biotechnology clusters, like the German Bio-Regions (Munich, Rhine/Neckar and Rhineland), some French districts and, to a lesser extent, the Medicon Valley between Copenhagen and Lund, are younger, having taken off during the Nineties (Allansdottir *et al*, 2001).

In the UK, British DBFs are clustered in East Anglia (Cambridge), South East England (Oxfordshire, Great London, Surrey), and Central Scotland. A circle of 10 kilometres includes most of the activities around the Oxford and Cambridge Campuses, as well as within the City of London.

In Germany, German DBFs tend to be localised in Bayern, Baden-Württenberg, Rheinland-Pfalz, Nordrhein-Westfalen, and Berlin. In France, biotechnology firms are mainly concentrated in Paris, the second largest cluster in terms of number of DBFs in Europe after Cambridge. According to BID data, about 30% of French biotechnology firms are located in Paris trailed by a group of French regions (Auvergne, Loire, Rhone-Alpes and Midi Pyrennees) that have been catching up in the last five years (Allansdottir *et al*, 2001)

In Sweden , almost all biotechnology firms are located in four major regions: Stockholm-Uppsala, Skåne, which is the southern region including Lund and Malmö, Gothenburg and Umeå while in Denmark they are highly concentrated in the Sjælland Island. The southern region, (Øresund) is known as *Medicon Valley* (Horton, 1999). Medicon Valley has grown up between Copenhagen and Lund–Malmö, especially after the construction of the bridge between Denmark and Sweden. Other fast growing clusters are in Finland (Helsinki, Turku, Tampere, Kuopio, Oulu), in the Netherlands (Zuid-Holland Region), and in Lombardia (Milan) (Allansdottir *et al*, 2001).

In sum, the evidence in favour of clustering would seem to be overwhelming. Moreover, it is hard to find relevant examples of commercial biotechnology activities that do not occur in clusters. However, a few questions and caveats are in order here.

First, what are the properties of the dynamics of spatial concentration of biotechnology innovative activities over time? Is this concentration increasing or decreasing over time? Do the early clusters continue to dominate the industry or are they replaced by new clusters?

Second, is spatial concentration in biotechnology innovative activities stronger or weaker as compared to other technologies or industries?

In both cases, there is little systematic evidence available. Casual empiricism seems to suggest that as innovative activities increase over time, new clusters are formed but they do not tend to replace the early leaders (See for instance Powell et al., (2002); Prevezer (2003)). On the contrary, they continue to maintain – and perhaps increase – their leadership. The overall effect on concentration is therefore ambiguous. Similarly, there is little evidence of phenomena of decline of clusters. If anything, new clusters may face difficulties in their growth but no significant shake-out appears to characterise industry evolution in its spatial dimension.

As it concerns the second question, there is even less direct evidence. Clearly, direct comparisons are inherently difficult given heterogeneity in data, measures, age and degree of development, etc.., but on the whole little is known about differences in spatial concentration in innovative activities across industries and technologies. In this respect it might be worthwhile mentioning the results obtained by Mariani (2001), according to whom biotechnology appears to be caracterised by lower degrees of spatial concentration – measured in terms of co-location of inventors as they appear in patent documents – as compared to other chemical – related patents.

These finding suggest a further interesting point. Innovative activities in biotechnology would seem to show lower degrees of concentration in terms of innovation – as measured by patents – as compared to other related technologies and above all than in terms of number of firms. Paradoxically, this observation would seem to reverse the now conventional stylised fact that innovation is more concentrated than production. Of course, this depends – in the case of biotech – on the role played as inventors by those research institutions and especially large firms which are located outside the cluster and on the very particular nature of industry structure in biotechnology. Thus, the criteria and the measures by which clusters are defined are likely to influence significantly the conclusions.

3.2 The ingredients of clusters

Almost all of the studies on biotechnology concentrate their attention on a set of ingredients that are usually thought to be important constituents of clusters:

a) the scientific base
b) entrepreneurship, venture capital and a favourable IPR regime
c) linkages with large firms and other industries
d) institutions, policies and other infrastructures that support and promote entrepreneurship.

3.2.1 The scientific base

There is little question that all biotechnology clusters are found in locations where there exists a strong concentration of scientific capabilities and institutions. Both case studies and econometric evidence (e.g. Prevezer (1997), (2001), (2203); Swann and Prevezer (1996); Swann, Prevezer and Stout (1998); Zucker, Darby and Brewer (1998); Audretsch and Stephan (1996)) strongly support this view.

However, beyond this observation, several further questions remain open. In particular, it is less clear what kind of institutions are important; what kind of sientific research is really important; and what exactly is the shape of the relation between the strength of the knowledge base and the (various measures of) performance of the cluster.

A strong academic base seems to be a recurrent ingredient. However, other types of research institutions are often mentioned to play a significant role: national laboratories, hospitals and medical schools, laboratories of large corporations. Indeed, one observes a significant variation in this respect. In the case of the US, for example, the leading clusters (the Bay Area and Boston) are not typically home of the labs of the large corporations. Viceversa, San Diego hosts mainly public and private research laboratories, but academic research is not as prominent as in the two previously mentioned clusters. The Capitol region is a different case again, characterised by the presence of the NIH and other public institutions (e.g. Walter Reed Army Institute for Research and the FDA), but less advanced university-based research (Feldman, 2001). In the case of Canada, Niosi and Bas (2003) report that government laboratories do not emerge as important factors in explaining clustering: if anything, their research capabilities – as measured by by patents) appears to be negatively correlated with with variables like the number of patents held by DBFs, number of DBFs, number of patenting DBFs.

As far as Europe – especially Continental Europe - is concerned, the situation is similar, although the role of research organisations different from universities appears to be relatively more prominent. Indeed, most of the leading European clusters include a variegated set of public and private research organisations. This might reflect, especially in Continental Europe, different patterns of organisation of research: in countries like Germany and France, for example, public laboratories like the Max Planck Gesellschaft or the Institute Pasteur rather than universities have been traditionally the main performers of basic research.

Rather than the specific nature of the relevant research organisations, what might turn out to be more important is the absolute level of excellency in research, the degree of variety in research and the interactions among organisations. Thus, Zucker and Darby (1995; Zucker *et al.*,1998) show that academic research as such explains little of new firms formation and their performance, but it is rather the presence of star scientists that leads to start-ups and agglomeration. Audretsch and Stephan (1996) confirm this finding, by showing that geographic proximity does not play an important role for for links between biotechnology companies and scientists in general, but it becomes crucial when linkages between scientists who are founders of a start-up - as distinct from scientists serving as members of the Scientific Advisory Board are considered.

Second, variety and diversification of scientific research within the cluster appears to play a significant role. Owen-Smith *et al* (2001), by analysing the co-location of innovative activities on the grounds of two different patent, data sets and two research collaboration data sets, show that American clusters are characterised by a larger number of different typologies of research organisations, operating in a wide spectrum of scientific areas and with substantial integration along the various stages of the processes of drug discovery and development. In contrast, laggard European clusters appear to be much more specialised and less integrated, both along the horizontal and the vertical dimension.

Similarly, Audretsch and Feldman (1999) stress that diversity of the science base at a location supports innovative activities to a greater extent than specialisation: the presence of of diverse industries within the same science base in a city leads to increased innovation. Along the same lines, Prevezer (2003) and Swann and Prevezer (1996) show that the links between science base and companies are supplemented by links between a number of industrial sectors. Primarily, therapeutics exerts a strong pull for the entry of new firms in diagnostics, agricultural and equipment , while activity in one's own sector serves a mild deterrent to entry. In general, firms with complementary, rather than similar specialisations are attracted to each other and tend to enter a cluster together. Partially different results are obtained however by Aharonson, Baum and Feldman (2004), who provide evidence that firms located in clusters that were strong in their technological specialization applied for patents at more than twice the rate of firms located in clusters that were strong in another specialization. Moreover, they show that new entrants in a cluster tend to locate near incumbent firms that engage in innovative activities close to the entrants' own technological specialization when those firms spend more on R&D, but also that stronger innovative activity of firms in other specializations results in a denser co-location to firms in the same specializations: as another specialization becomes more important in the cluster, entrepreneurs appear to seek out firms that are similar to themselves.

3.2.2 Entrepreneurship and incentives for the exploitation of academic research

Finally, as it is clear that a strong scientific base is a fundamental ingredient of clustering, it is also clear that it is not a sufficient condition. Examples abound of cases of areas where a strong scientific base has failed to spawn dynamic clusters (see Audretsch (2001); Orsenigo (2001)). Other factors, linked to the willingness and ability to exploit such knowledge for economic purposes, have been consistently identified as crucial ingredients of the clustering process.

As a general proposition, this assumption is dangerously close to a truism: if a cluster is defined in terms of agglomeration of economic activities, then it obvious that economic considerations are crucial for the explanation. The proposition becomes much more interesting and controversial as soon as the specific factors leading to and/or allowing for the decision to commercially exploit knowledge are examined.

Entrepreneurship is again quite obviously a fundamental characteristic. Yet, as such the notion of entrepreneurship explains little in the case of biotechnology. In many instances, the propensity to entrepreneurship is considered as a psychological and/or a social characteristic. Especially in this second interpretation, the explanation of differentials in entrepreneurial attitudes across space plays a significant role in the debate. Clusters are indeed often defined and explained as geographical areas where entrepreneurial attitudes are particularly developed, for various historical reasons, and are continuously reproduced by the cluster itself (see Becattini (1990) and Saxenian (1994) among others). Without denying the crucial relevance of these factors, a discussion of the notion of entrepreneurship falls quite obiously beyond the scope of this paper. It might be just worthwhile mentioning – with specific reference to the case of biotechnology – that attitudes towards entrepreneurship cannot account as such for the underdevelopment of biotechnology in Italy, a country which exhibits very high rates of new formation but in sectors quite different form biotechnology.

In a more subtle interpretation, entrepreneurship is not considered simply as a psychological and social attitude, but as a specific form of organisation of innovative activities, typically contrasted with the traditional picture of vertically and horizontally integrated large corporations (e.g. Saxenian (1994)). This is indeed an important argument and it plays undoubtedly a crucial role in the case of biotechnology, especially as it concerns the differences between the performance of the USA vs.

Europe. In any case, it is perhaps more fruitful to concentrate attention first on the factors that might facilitate or hinder entrepreneurship and the development of decentralised, network-like forms of organisation of innovative activities, assuming for the sake of discussion – that individual and social propensities are evenly distributed across space.

Rules governing academic involvement in commercial activities, IPRs and venture capital are in fact commonly referred to as essential factors that might account for the differential performance of the USA as compared to Europe and Japan.

In fact, the development of the biotechnology industry in the USA rested on the concomitant growth of series of supporting organizations and institutions which are now perceived as defining the distinct character of the "American way" to innovation, at least in high-tech industries and especially in biotechnology. This system is typically described as being based on three interconnected pillars: university-industry interactions, a strong intellectual property rights regime (which favours the commercialisation of scientific research) and venture capital.

The key role of scientific knowledge for technological innovation in biotechnology (and in other industries) has indeed manifested itself in an unprecedented intensification of both industry-university ties and in the direct involvement of academic institutions and scientists in commercial activities. Both phenomena are certainly not new in the USA (Rosenberg and Nelson (1993), Mowery et al (2001)). However, since the mid-Seventies and over the whole evolution of the biotechology industry, the drive towards an increasing commercialization of the results of research accelerated dramatically. Universities' patenting and licencing activities started to soar. The creation of academic spin-offs has become a distinct and crucial phenomenon of the American academic system and of the biotechnology industry..

The emergence of the entrepreneurial university and the specific forms this process took in the USA are strictly linked to some basic characteristics of the US academic system. American universities had been traditionally highly responsive to the needs of the local communities and industries. Also the organization of research and teaching had characteristics that facilitated both the production of high quality research and high degrees of mobility between academia and the commercial world.

Specifically, as shown by sociologists of academia (Ben-David (1977), Clark (1995)), in the USA (and in Great Britain) departments have long been the main organizational entities as opposed to the European institutes, dominated by a single professor, far less interdisciplinary in nature and with feudal-like career paths. Moreover, in the USA high degrees of integration between teaching and learning have been achieved through the sharp separation between undergraduate and post-graduate levels. The creation of research-oriented post-graduate studies entailed, in fact, a number of important consequences. In particular, post-graduate students are typically exposed and trained to the practice of scientific research within research teams composed by students and professors within departmental organizations. This arrangement does not only tend to free resources for scientific research, but provides also a fundamental experience in participating to and managing relatively complex organizations. In other words, it constitutes an essential source for the development of organizational capabilities. Moreover, the career of young research scientists after graduate studies has – under various perspectives - entrepreneurial characteristics. For instance, post-docs have to raise funds for their own research in a highly competitive environment, where performance is judged on the basis of a track record and the ability to set an independent research agenda (Gittelman, 1999). Finally, graduate students joining the industrial world after the completion of their studies constitute an essential source of skilled demand for academic research.

In Continental Europe, the integration of teaching with research has progressed far less than in the USA (and to some extent than in the UK). Clearly, enormous differences in education systems, especially on the higher education level, exist across Continental European countries and they certainly should not be overlooked. For example, as it was mentioned previously, in France, universities have never been the main center of both scientific research - which has been essentially conducted within the national laboratories and co-ordinated by the CNRS (National Center for Scientific Research) - and the education of the elites - monopolized by the system of the *grandes écoles*. In Germany, the "institute" – dominated by an individual professor – has been the main organizational unit co-ordinating teaching and research.

Despite these enormous differences, the structure of the academic systems of many European countries shares some important common features, as compared to the Anglo-Saxon systems. Ph.Ds are a relatively recent innovation in many Continental European countries and they remain far less professionally orientated than in the U.S.A. Departmental structures are also relatively new and in many cases institutes continue to be a very important organizational entity. In general, research has tended to be far more removed from teaching than in the USA. And in fact, in many Continental European countries, research has been to a large extent separated from universities and concentrated in specialized institutions (Ben- David (1977), Clark (1995)). At the cost of oversimplification, in Europe a model has been emerging based on high degrees of division of labor and specialization between teaching and research institutions, whereas in the USA the dominant model has been an integrated one (Bruno and Orsenigo, (2003).

It is possible to speculate that this separation might have had negative effects on both the quality of research and on the ability of academic institutions to interact with industry. Integration of research and teaching and collaboration with industry has been relatively more developed and frequent in the case of engineering schools (the Continental European polytechnics) and in some selected disciplines in particular countries (chemistry in Germany). In the 1960-70s, however, with the development of mass academic education, the scientific revolutions linked mainly to microelectronics and molecular biology (developed mainly in the USA) and the crisis of the traditional industries mainly connected with the polytechnics, in many cases industry-university interaction has further weakened. To remedy this gap, a re-proposition of the “specialized model” has tended to spread in more recent years for the management of the interactions between research and industry and technology transfer. Differently from the US case, where universities have gradually extended their functions (an integrated model centered on universities), one observes in Continental Europe the development of various types of specialized institutions for technology transfer, who act as intermediaries between research and industry (an institutional specialization model).

The coupling between scientific, organizational and entrepreneurial capabilities thus constitutes an essential pre-condition for subsequent developments in industry-university relations. However, it is also important to notice that such developments are to some extent to be considered as part of a much more general tendency towards the diffusion of an increasingly favourable attitude towards the establishment and enforcement of strong intellectual property rights.

The establishment of clearly defined property rights played indeed an important role in making possible the explosion of new firm foundings in the US, since the new firms, by definition, had few complementary assets that would have enabled them to appropriate returns from the new science in the absence of strong patent rights (Teece, 1986). In the early years of "biotechnology" considerable confusion surrounded the conditions under which patents could be obtained. In the first place, research in genetic engineering was on the borderline between basic and applied science. Much of it was conducted in universities or otherwise publicly funded, and the degree to which it was appropriate to patent the results of such research became almost immediately the subject of bitter debate. Similarly a growing tension emerged between publishing research results versus patenting them. Whilst the norms of the scientific community and the search for professional recognition had long stressed rapid publication, patent laws prohibited the granting of a patent to an already published discovery (Merton, 1973; Kenney, 1986). In the second place the law surrounding the possibility of patenting life-formats and procedures relating to the modification of life-forms was not defined. This issue involved a variety of problems (see OTA, 1993), but it essentially boiled down first to the question of whether living things could be patented at all and second to the scope of the claims that could be granted to such a patent (Merges and Nelson, 1994; Mazzoleni and Nelson, 1995).

In fact, these trends were partly spurred by a growing concern about how to exploit more efficiently academic research and by the need to put some order in the system that governed the conditions at which universities could obtain patents – and therefore income - on the results of publicly funded research. The Bayh-Dole Act in 1980 sanctioned these attitudes, by greatly facilitating university patenting and licensing. Parallel to Bayh-Dole, a series of judicial and Congress decisions further strengthened the appropriability regime of the emerging sectoral system. In 1980, the US Supreme Court ruled in favor of granting patent protection to living things (Diamond v. Chakrabarty), and in the same year the second reformulation of the Cohen and Boyer patent for the rDNA process was approved. In the subsequent years, a number of patents were granted establishing the right for very broad claims (Merges and Nelson (1994). Finally, a one year grace period was introduced for filing a patent after the publication of the invention.

The third pillar of this emerging system was of course venture capital. Once again, venture capital was a long-standing institution in the American financial and innovative system. It was already active – in various forms – ever since the 1920s (or even before) and emerged as a vibrant industry with the electronic revolution in the 1960s. Most likely, the existence of a vibrant venture capital industry which developed with the ICT revolution was a factor that favoured in different ways the emergence of the Bay Area and Boston as leading biotechnology clusters (Prevezer (2001), Audretsch (2001), Niosi and Bas (2003)).

However, it has to be emphasised that these factors - industry-university relations, IPRs and venture capital – were not simply pre-existing at the onset of the biotechnology industry, but they co-evolved over time.

First, as Mowery et al (2001) have shown, the emergence of the “industry-university complex” (Kenney, 1986) and of the entrepreneurial university pre-dates Bayh-Dole. Similarly, other studies (e.g. Kortum and Lerner (1998)) concur in indicating that the growth of patenting activities in the USA over the past 10-20 years does not seem to have been spurred so much by a tighter appropriability regime, but rather on the the rise of the two main technological revolutions of the second half of the century, micro-electronics and, especially biotechnology. Thus, the relationship between patent protection, innovation and commercialisation of academic research appears to be much more complex than it would appear at first sight. New technological opportunities have provided new opportunities for invention and for its economic exploitation as well as improvements in the productivity of R&D. Stronger and wider IPRs have certainly incentivized and facilitated the commercialization of academic research, especially in the form of academic spinoffs, but the extent to which they have also directly spurred invention remains more doubtful. To the extent that the development of biotechnology rests primarily on the absolute excellence of scientific research, the influence of IPRs on innovative activities in biotechnology appears mediated by this latter factor.

Moreover, the IPR regime cannot account for geographical differentials in performance within countries, both as it concerns the USA and Europe, being a nationwide, rather than a cluster-specific factor. Even in Europe, no simple and direct relationship can be found between the development of biotechnology – at the nation state level, let alone at the clusters level - and IPRs regimes. If anything, the explanation might might then turn on the observation of more aggressive attitudes and better organisational structures of specific universities towards IPRs and technology transfer in different clusters. The case-studies literature does indeed provide evidence of this (Audretsch (2001), Niosi and Bas (2003)). A somewhat different, but germane interpretation is provided by Feldman (2001) in her analysis of the case of the Capitol region, where entrepreneurship was unleashed by on the one hand exogenous events like the downsizing in federal employment and increasing reliance on outsourcing and – on the other hand – by a mix of government policies that created demand for ICT and biotechnology services, as incentives and pressures for the appropriation and commercialisation of public research, despite the feeble commitment of some important research institutions (e.g Johns Hopkins) towards academic entrepreneurship.

Perhaps more interestingly, it is important to stress again that changes in IPRs regimes and greater "entrepreneurial" attitudes on the part of academics have themselves been spurred by the initiative of individuals, firms, industry organisations etc., in knowledge-rich environments which offered the opportunities for innovation and new firms creation. Similarly, while there is ample evidence that local availability of venture capital facilitates the development of new biotechnology firms, much less evidence is available that this was a necessary precondition for the take-off of the industry. In many cases, in Europe new firms have been founded resorting to capital located outside the cluster and even outside the the country and clusters have developed attracting venture capital rather than finding it already present within the location (Orsenigo 2001; Allansdottir at al. (2001))

3.2.3. Local demand, institutions, infrastuctures and policies

Analogous remarks can be suggested as it concerns the other factors that are usually claimed to be important ingredients of a cluster. While there is little question that these factors are usually present in a successful cluster, there is much less evidence about their specific nature and that they are a necessary pre-condition for the development of a cluster.

Thus, for example, Niosi and Bas (2001) find that biotechnology clusters in Canada are located in in large metropolitan areas, comprising high level research is conducted in prestigious institutions, an ample pool of venture capital, large and research –oriented hospitals, etc.. Aharonson, Baum and Feldman (2004) also support the finding that urbanisation economies are an important factor in the Canadian biotechnology industry. Similar results are found for some European clusters (e.g. the Stockholm area), although in general clusters appear to form around centres of academic excellence, rather than cities a such (Allansdottir et al 2001; Pammolli and Riccaboni, (2001)).

Similarly, the local presence of large corporations does not systematically emerge as a fundamental ingredient of clusters. Large companies are frequently located outside the cluster, both in the USA and Europe, although linkages between local actors and big corporations is invariably a crucial component of the successful development of a biotechnology industry. Moreover, in some European cases, there are instances where new firms are created as spinoffs of large firms undergoing processes of restructuring, typically after episodes of M&As (Orsenigo (2001)).

As already mentioned, the existence of related industries and the relations between the various segments of the biotechnology industry appears in some studies as an important determinant of the (local) development of biotechnology (Prevezer (2003) and Swann and Prevezer (1996)). However, such relations are quite intricated and appear to vary significantly across different clusters and types of firms (Lemariè *et al*. (2001), Corolleur et al. (2003)).

Finally, the degree of variability is even higher in terms of policies. Reviewing the literature in this case is a tremendously difficult. Two main general (and generic) conclusions in this respect might simply be that:

i) especially but not exlusively in the American cases, early successful clusters developed almost spontaneously without any direct intervention, although even in these instances, the initiative of particular (and diverse) institutions plays an important role in the cluster;

ii) especially in Europe, one observes a bewildering variety of policies at the nation and regional level to foster the development of biotechnology. A fair assessment would seem to be that it is almost impossible to draw any kind of generalisation, both as it concerns experiences of success and failure. The development of successful clusters has been achieved through wildly different approaches: surely, there is no single way, let alone recipe, to success. On the other hand, failure is pervasive, irrespective of the policies that have been adopted.

3.2.4. Some final remarks about ingredients

This discussion suggest few conclusions and many open questions.

The dominant and robust result is that excellency in scientific research spanning over a differentiated spectrum of areas and integration along the horizontal and vertical dimensions of the innovative process are the crucial ingredients for the development of biotechnology. The role of the other factors appears to be ancillary or irrelevant, absent these capabilities.

Conversely, the developed, successful clusters appear to profit from the concomitant presence of all the ingredients, although their role and specific nature varies significantly. Yet, in many cases, these ingredients were not simply in place simultaneously at the beginning, i.e. at the time of the genesis of the cluster. Certainly, those locations where most of these conditions are or were available enjoy(ed) significant advantages. But this neither a necessary nor a sufficient condition. Rather, in almost all cases, the process of construction of such ingredients would seem to be a crucial part of the story: in a sense the process is a fundamental ingredient itself.

Putting it in other words, clusters are born and develop on the basis of specific combinations of capabilities, incentives and opportunities. The three elements are inseparable and linked to each other in intricated ways. Competencies obviously contribute to create and define opportunities as well as the ability to take advantage of existing opportunities. The latter feed back on the processes of accumulation and development of new competencies. Competencies without incentives remain unused. But incentives without sufficient capabilities are sterile and might even be destructive. More interestingly, particular sets of capabilities identify sets of appropriate incentives, which in turn and once again influence the speed and directions of the processes of accumulation of competencies. Understanding how different types of opportunities, incentives and capabilities match with each other would require sophisticated taxonomical exercises and hard theorising. This appears to be a fundamental chapter in the agenda of future research. (see Hall and Soskice (2001), Casper and Kettler (2001) for an interesting and promising attempt in this direction).

3.3 Processes: mechanisms of agglomeration, networks and network dynamics

The evidence on ingredients tells a story whereby clusters are not simply born with all the necessary ingredients in place, but in many instances such ingredients are rather constructed and developed over time. In other cases, the empirical evidence reviewed so far hints and sometimes openly recognizes (Feldman 2001) some “historical accident” unleashing self-reinforcing processes on the basis of cutting edge scientific research and variegated and wide-ranging scientific and technological capabilities. The preceding discussion highlights also that a dynamic perspective is useful and probably necessary to understand the forces leading to clusterisation. Thus, in this section, attention is focused on the available evidence concerning how biotechnology clusters develop over time.

In particular, linking also to the broader theory and empirical analysis of the spatial concentration of production and innovation, the question can be reframed around the following issues:

a) Can concentration of innovative activities be "predicted" on the basis of some "static" pre-conditions (e.g. "endownments" and comparative advantages), much alike standard models of trade?
b) Given particular sets of initial conditions, what are the main processes leading to agglomeration?
c) In particular, how much does clustering result from processes of continuous reproduction of competencies (e.g.spin-offs from universities) and from processes of attraction of competencies generated elsewhere?
d) More specifically, what are, if any, the particular advantages of agglomeration itself?

3.3.1 Static preconditions and mechanisms of agglomeration

As now already mentioned in several occasions, the crucial role of strong scientific capabilities, particulary academic research, is the single better established "stylised fact" in the analysis of the evolution of the biotechnology industry. Consistently, in all econometric analyses and case studies, variables measuring the strength of the knowledge base turn out as the "best predictor" of performance. From this point of view, clustering of innovative activities is certainly not a purely random phenomenon which could have happened (or might happen in the future) anywhere.

However, this predictor is not an exceedingly good one. Thus, it becomes particularly important to examine the nature of the processes underlying the development of the biotechnology industry and its clusterisation.

However, little systematic evidence exists on the relative importance of alternative mechanisms of agglomeration in biotechnology. The previous discussion on the "ingredients" seems to suggest that classical Marshallian externalities related to the availability of skilled labour and economies of intra-industry specialisation (see in particular Prevezer (2003), Swann and Prevezer (1996), Aharonson, Baum and Feldman (2004)) play indeed an important role in generating agglomeration. However, almost all the case studies and the econometric findings by Aharonson, Baum and Feldman (2004)) emphasise consistently that proximity to universities and/or other sources of knowledge is important and the usual explanation is that it makes the circulation of tacit knowledge easier. Similar arguments are provided as it concerns venture capital: detailed knowledge of the opportunities offered by the knowledge-creating institutions, personal acquaintance with the scientists, continuous monitoring of companies are fundamental aspects of venture capital and this knowledge is much easier to be acquired at the local level.

However, the already mentioned evidence provided by Zucker at al (1995, 1997, 1998 and 1998a) and by Audretsch and Stephan (1996) points to a radically different account. In essence, they suggest that the standard notion of geographically localised knowledge spillovers does not seem to apply to the case of biotechnology industry, at least in the phase of its emergence. Rather, they argue that discoveries in this technological area are characterised by high degrees of natural excludability, i. e. that the techniques for their replication are not widely known and anyone wishing to build on new knowledge must gain access to the research team or laboratory setting having that know-how. In these circumstances, the discovering scientists ('superstars') tend to enter into contractual arrangements with existing firms (contract or ownership) or start their own firm in order to extract the supra-normal returns from the fruits of their intellectual human capital. Moreover, the scientist work with or create a new firm within commuting distance of home or university (where they tend to retain affiliation) thus creating localised effects of university research.

These authors show that the innovative performance of biotechnology firms is positively associated to the total number of articles by local university 'star' scientists. However, when the number of articles written by university stars is broken down into those written in collaboration with firm scientists ('linked') and the remaining ('untied'), the coefficient on articles written by local university stars not in collaboration with the firm loses its significance and nearly vanishes in magnitude. Previous evidence on the existence of indiscriminate localised knowledge spillovers seems therefore to have resulted from a specification error, i. e. the inability to control for the actual relationships linking individual scientists to individual firms.

Similarly, Audretsch and Stephan (1996) confirm that geographic proximity is important only or mainly for scientists who are founders of companies, whereas members of the Scientific Advisory Board are much less co-localised. Corelleur at al. (2003) also show in ther econometric analysis of the French case that geographical localisation effects impact significantly on the localisation of new firms, but as firms grow these effects become much less important, confirming the earlier results obtained by Prevezer (2003) and Swann and Prevezer (1996).

These results suggest interesting insights.

First, the role of knowledge spillovers might have been overestimated in the case of biotechnology. On the contrary, knowledge tends to remain sticky within the cluster for rather different reasons linked to attempts at privately appropriating knowledge and restricting its circulation. Naturally excludable and rivalrous knowledge does not spill over, but people (teams) embodying knowledge move (locally) across organisations in order to exploit the value of their knowledge. In other terms, localised effects of university and industry research are most likely to result primarily from a combination of appropriability of tacit non-replicable knowledge and low geographical as well as organisational mobility of researchers (Breschi and Lissoni (2001).

Second, the relevance of "soft" institutions might also have been overestimated. Knowledge flows in the biotechnology industry appear to be channelled significantly through market transactions and inter-organisational rules. In this perspective, biotechnology would look much more similar to a market for technology (Arora *et al.*, 2004) than to the classical notion of the industrial district. In between these two extremes, knowledge flows appear to be structured in a fundamental way by the social and technical rules of interaction that govern scientific and technological research, as it will be discussed at some more length in the next paragraph.

Third, this interpretation is consonant with – albeit not identical to - the model proposed by Klepper (2002) for the automobile industry. According to this view, as discussed in Section 2, clustering results from processes of spin-off – as distinct from spillovers – from knowledge-rich organisations: companies in the case of automobiles, universities in the case of biotechnology. These organisations perform as incubators of capabilities which are then exploited in the form of new firms and more generally of the formation of a pool of highly skilled labour force. Going back to the discussion in Section 2, it would appear that increasing returns, in addition to externalities, are fundamental movers of the processes of agglomeration. The study by Romanelli and Feldman (2004) in this volume constitutes in this perspective a first and important attempt to disentangle empirically the mechanisms through which this type of increasing returns work, at least in the case of biotechnology. In particular, they show that around 75% of the biotherapeutics firms founded in the USA over the period 1976-2002 identified in their analysis have a local origin, i.e. they spun off from institutions, especially universities, but also other companies, located in the same geographical area. Moreover, successful clusters continue to exhibit high rates of internal firms formation, whereas weaker clusters are characterized by both lower domestic **prolificness** and higher propensity to migrate. Attraction of entrepreneurship from outside the clusters appears also to be a significant phenomenon. In other words, two interlinked and self-reinforcing processes seem to drive the evolution of clusters. First, a process of spinoff from local institutions and organizations – similar to Klepper's account – originates and sustains the cluster. Second, on these bases, immigration of new entrepreneurs and firms having an origin from outside the cluster is set in motion which strengthens and overlap with the former.

Fourth, the relevance of the local knowledge base is likely to change over time, as clusters evolve and mature; and across different typologies of firms. Moreover, local knowledge has a different impact on the entry and on the growth of firms. As already mentioned, local sources of knowledge appear to be fundamental in the early stages of the devevlopment of a cluster and for new, higly specialized firms. Access and ability to use (and integrate) external " knowledge becomes increasingly important for growth and diversification (Lemariè et al. (2001), Corelleur at al. (2003) Prevezer (2003) and Swann and Prevezer (1996)).

Fifth, these (partial and not entirely congruent) results might also begin to shed some light on the dynamic mechanisms that determine the advantages of agglomeration. Once again, rather than relying on spillovers as such, clusterization might be interpreted as the outcome of the intrinsic difficulties involved in the reproduction of knowledge outside their specific original contexts. Thus, spinoffs and startups tend to locate close to their "parents" and relatives also because what they know derives from region-specific practices, ways of doing things, etc.. , and their replication occcurs with higher probability and ease within the same context. Clealry, much more research is needed here (for example, looking at differential patterns of growth and peformances of local vs. immigrated firms).

3.3.2 Externalities, increasing returns and networks

The literature on networks in biotechnology provides further insights into this discussion, particularly as it concerns the role of the local knowledge base, the mechanisms that regulate the flows of knowledge and their dynamics over time.

There is no need to elaborate on the idea that networks of collaborative relationships among firms and other institutions are a fundamental form of organization of innovative activities in biotechnology. In fact, one finds 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.

According to an influential interpretation, 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, 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, coupled with the establishment of property rights on such knowledge, makes it possible, in principle, to separate the innovative process in different vertical stages. 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 actors can provide the necessary coordination of the innovative process in a division of innovative labor. Collaborations are likely to be a permanent feature of the industry, with a large (and possibly continuously expanding) number of entities interacting with each other, generating an intricate network within which each subject specializes in particular stages of the innovative process getting benefits from an increasing division of innovative labor.

According to another interpretation, collaborative relations are instead 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).

Finally, according to interpretations focusing on network advantages, 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 complementary resources and competencies (Sharp, 1985; Orsenigo, 1989; Pisano, 1991; Pammolli, 1997). 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 the network itself (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 Walker *et al*., 1997).

Without entering directly into this discussion, for the purposes of the present paper it suffices to highlight some broad results that have emerged from network-based studies which bear direct relevance to geographical clusters.

The first basic result is that participation in networks is indeed fundamental to firms. In other words, innovative activities in biotechnology are strongly embedded in networks of relationships and the position within the network is a powerful explanatory variable of firms' performance (Powell *et al* (1996); Barley, Freeman and Hybels (1992), Walker, Kogut and Shan (1997)).

Second, the performance of specific geographical networks is strongly associated to high degrees of internal differentiation in roles and behaviour, diversity of actors and linkages but also by the presence of actors who act as integrators of such diverse agents and relationships. Thus, Owen-Smith et *al.* (2002) compare the structure of the American and European networks in biomedical research. They show that the US network is characterised by extensive relationships between U.S. public research organizations and firms located in dense regional clusters that span therapeutic areas, cross multiple stages of the development process, and involve diverse collaborators. In contrast, European innovative networks are characterized by sparser, more specialized and upstream relationships among a more limited set of organizational participants located in national clusters. Both U.S. and European networks are geographically clustered, then, but in quite different manners. Similarly, Pammolli and Riccaboni (2001) and Allansdottir et al (2001) conclude, in their analysis of the European biotechnology clusters, that clustering derives to a large extent by the availability of a strong, heterogeneous but integrated research base that facilitates the transfer and the integration of knowledge, as well as the development of skilled labour, the mobility of such labour and – presumably – also the development of other supporting institutions like venture capital.

However, networks have a strong geographical dimension and overlap but do not coincide with geographical clusters. Not only networks of relationships usually span well beyond the boundaries of the geographical location, but the performance of the individual nodes within the network and of specific geographical networks is strongly associated to high degrees of openness to geographical distant nodes (see Owen-Smith *at al*. (2001), Pammolli and Riccaboni (2001), Allansdottir at al. (2001) among others). Moreover, in a dynamic perspective, the growth of geographical networks and the tendency towards towards clustering is accompanied by a parallel process of increasing openness of the original clusters. In Europe, recent trends suggest a combination of an increasing number of collaborations and a decreasing proportion of local connections (Pammolli and Riccaboni (2001), Allansdottir at al (2001). In the USA too, local ties moved from a high of 40% in 1988 to a low of 8% in 1998 (Owen-Smith, Riccaboni, Pammolli, Powell, 2001), in the context of a rising volume of collaborations (the number of ties active in 1998 is more than double the number a decade before). In general, the recent evolution of the biotechnology industry appears to have resulted from a combination of an increasing number of collaborations and a decreasing proportion of local connections, confirming other findings provided by econometric analyses and case studies, which consistently show that better performing and growing firms rely increasingly less on local sources of knowledge (Corolleur *et al*., 2003).

Third, network studies vividly show that the flows of knowledge occurring in a network are structured and mediated by a host of different mechanisms, among which geographical proximity is only one and it neither necessarily important. Thus, for instance, the rules presiding over the participation to scientific communities and communities of practice (Breschi and Lissoni 2003) or organisational proximity (Rallet and Torre (1998) define the principles of inclusion and exclusion as well as the channels through which knowledge is transmitted within the network. In many instances, such diverse rules and principles interact with each other, giving rise to novel patterns of interaction (see Murray, (2004) for an analysis of the differentiated rules governing the interactions between scientists, technologists and entrepreneurs in science-based start-ups). Other studies show that the access to the network of collaborations in biotechnology is not unrestricted. On the contrary, the network of collaborative relationships itself tends to consolidate and to become increasingly hierarchical, while also exhibiting expansion. Despite this growth, however, the network tends to consolidate around a rather stable core of companies, composed by large incumbents and early entrants in the network. This suggests the existence of first-mover advantages even in the network of collaborations, whose core becomes increasingly difficult to enter as time goes by and can be perturbed only and temporarily by new major technological discontinuities (see Orsenigo, Pammolli, Riccaboni, 2001).What is important to emphasise here is not only that these patterns of interaction are distinct from geographical proximity but also that what might appear as knowledge spillovers are actually the outcome of extremely complex structures. In other words, knowledge is not simply in the air, but can be accessed and transmitted only by compliance with a variety of interacting rules, which only in some cases happen to have a geographical dimension. If anything, the question might then be turned over: why and under what circumstances do those rules acquire a geographical embeddedness?

Fourth, once again network studies show that networks, patterns of agglomeration and more importantly the mechanisms determining the structure of the networks and of geographical clusters are different and change over time. For example, the above mentioned tendency towards the delocalisation of relationships in the European and American networks might derive from different factors. One most likely resides in the need to get access to state-of-the art knowledge, wherever it might be located. Sustained performances are based on leading edge research, which cannot be exclusively local. Second, the tendency towards clustering and subsequent delocalisation might also derive from the very properties of the evolution of knowledge in biotechnology. As discussed in Pammolli (1997) and in Orsenigo, Pammolli, Riccaboni (2001), scientific progress in biotechnology led to an explosion of the search space, with a continuous proliferation and branching of hypotheses and techniques at increasing levels of specificity. No single institution is able to develop internally in the short run all the necessary ingredients for bringing new products on the marketplace. These properties of the knowledge base and of the related learning processes induced particular patterns of division of labour between different types of firms and institutions. In general, two different logics of exploration and technological advance co-existed and were strongly complementary in the evolution of the network. The first trajectory generated patterns of division of labour in which older generations of firms worked at higher levels of generality and linked with successive generations of new entrants, who typically embodied increasingly specific hypotheses and techniques. The second trajectory, linked esentially to the development of platform technologies, induced instead collaboration between all types of firms, modifying the inter-generational structure of the agreements typical of the first trajectory.

In a different, but complementary perspective, Powell et al (2005) show that four alternative logics of attachment - accumulative advantage, homophily, follow-the-trend, and multiconnectivity - account for both the structure and dynamics of interorganizational collaboration in the field of biotechnology. Commercialization strategies pursued by early corporate entrants are supplanted by collaborative activities influenced more by universities, research institutes, venture capital, and small firms. As organizations increase both the number of activities on which they collaborate and the diversity of organizations with whom they are linked, cohesive sub-networks form that are characterized by multiple, independent pathways. These structural components, in turn, condition the choices and opportunities available to members of a field, thereby reinforcing an attachment logic based on connections to diverse partners that are differently linked.

4. Conclusion

This brief review of the literature on biotechnology clusters suggests – as mentioned in the intorduction – more questions than firm conclusions.

The evidence strongly supports the view that there are indeed advantages to agglomeration and powerful forces leading to the development of clusters in biotechnology. Yet, the strength of these clustering tendencies differ according to the indicators that are used and there are suggestions that biotechnology might actually be less localised than other industries and technologies. Moreover, what exactly those advantages and processes might be remains much less clear. They appear to be mainly related mainly to the stock of accumulated scientific and R&D capabilities within a geographical area, e.g. to the presence of a variety of world class research institutions, which provide competencies and opportunities for innovation. Adequate incentives for the use of such knowledge for commercial purposes are also obviously important, although their nature and their effects may differ substantially across space and time.

Thus, in the case of biotechnology, the emergence of clusters is certainly not a random phenomenon: initial conditions and "endownments" play certainly a crucial role in defining the geography of innovation in this field. However, these initial conditions are hardly interpretable as "given endownments" and do not suffice to account either for the genesis of clusters or for the failure of developing one.

Moreover, it is hard and probably misleading to distinguish between the ingredients and the processes that underlie cluster formation and development.

First, the processes do depend on and are shaped by initial conditions. Thus, different agglomeration forces may play a role under alternative initial circumstances. Indeed, the empirical evidence does not provide clear and homogeneous indications in this respect. If anything, the evidence seems to support a picture whereby the spatial concentration of innovative activities derives mainly from processes of spin-off from highly capable universities and research centres. However, classical Marshallian externalities and urbanisation economies play a significant role, but coupled with (and perhaps triggered by) processes driven by the increasing returns intrinsic in the generation of knowledge. In any case, both case studies and econometric evidence tell different stories, from which is hard to draw strong generalisations. Similarly, little evidence is available on the relative role of the processes of firms formation originating within the cluster and processes of attraction of entrepreneurs initially located outside the cluster.

In the same vein, the evidence concerning localised knowledge spillovers is mixed. On the one hand, a considerable body of results – both econometric studies and network studies – strongly suggest that knowledge is not simply in the air within a cluster, but knowledge flows are heavily structured by a variety of economic and social factors which in many instances do not have any clear geographical connotation. Yet, on the other hand, there are also overwhelming suggestions that indeed knowledge is spatially sticky and intense knowledge flows are an intrinsical characterstic of clusters. Most of this evidence is provided by case studies. Thus, the question might be asked if such knowledge flows are and can be captured by quantitative, econometric studies. But rather than simply dismiss the qualitative evidence, more efforts should be devoted to devise better measures and indicators.

Second, the evidence forcefully points to the observation that – as much as agglomeration forces are influenced by "structural" initial conditions – processes are the essence of what clusters are made of. The factors that lead to the genesis of a cluster are different from those that later sustain the cluster itself. The factors that influence firms' entry in a cluster are at least partly different than those which promote firms' growth. Again, it is hard to identify invariant processes across clusters. Yet, most of the case studies and of the dynamic network studies (but also some econometric results) suggest that clustering is the outcome of processes of construction and co-evolution of the conditions that allow clusters to exist, rather than the automatic effect of specific pre-conditions and agglomeration factors. In this sense, innovation generates clusters at least as clusters create innovation.

As disappointing as these thin results might be, they at least clearly indicate that an explicit dynamic approach is necessary for further progress in this field, both in terms of empirical research and formal modelling.

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