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I. Introduction

Universities in the United States and Europe are often compared with respect to their divergent levels of involvement in the private economy. The U.S. university system, with its mix of both public and private institutions, has long played a significant role in conducting research that contributes to technological development and industrial performance (Geiger, 1988; Rosenberg and Nelson, 1994). Historically, this “knowledge plus” orientation, in which high-quality public and academic research tends to be driven by “joint goals of understanding and use” (Stokes, 1997, p. 15) was contrasted to the European scene, where universities were believed to contribute more to knowledge for its own sake and to the preservation of distinctive national cultures (Ben David, 1977).

Over the past decade, the development of a number of key science and technology-based industries – most notably information and communication technologies, and biotechnology – has helped spark economic growth. The United States has broad commercial leadership in many of these new areas, and commentators suggest that U.S. universities and research institutes played a significant role in this process (Mowery and Nelson, 1999; Mowery, Nelson, Sampat and Ziedonis, 2001). The diverse interfaces between U.S. research universities and the private sector have been widely documented (Link, 1999; Mowery, 1999). Patenting by U.S. universities increased nearly seven fold over the period 1976-1998 (Owen-Smith, 2000) and licensing revenues from the sale of intellectual property have grown briskly as well. The science-based startup firm has been the cornerstone of the commercial field of biotechnology, with university researchers playing a significant role as founders, consultants, and members of scientific advisory boards.

In contrast, industry-university relations in Europe have lagged behind, in part due to legal prohibitions in some countries against faculty collaboration with commercial entities, and cultural predispositions against academic involvement with commerce. Since the late 1980s, however, European attention has shifted to technology policy and academic technology transfer (Howells and McKinlay, 1999). In a climate of strong anxiety about European Union competitiveness in science-based industries, programs developed following the Single European Act of 1987,¹ encourage

matches between universities and firms, placing particular emphasis on quick delivery of tangible commercial results (Peterson and Sharp, 1998).

Strong contrasts exist between European and U.S. research infrastructures, however. Consider, as an illustration, differences in university organization and governance between the U.S. and Germany. The U.S. system is highly decentralized. Even public universities rely on diverse funding sources, including state and national governments, foundations and corporate supporters, tuition revenues, and alumni gifts. Private universities, especially elite ones, are also supported by generous endowments. Financing is considerably more centralized within European nations, and this centralization entails more hierarchical control, especially in the absence of continental funding agencies (Clark, 1993). Faculty members in the U.S. have much more research independence at early career stages, and academic scientists frequently move between universities in an effort to better their labor market position. In Germany and elsewhere on the continent, there is much less autonomy and mobility for younger scientists. In addition, blurring boundaries between basic and goal-oriented research and increased competition for research support and funding enable greater mixing of disciplines in the U.S (Galambos and Sturchio, 1998; Morange, 1998). In Germany, a number of the highly prestigious Max Planck institutes are organized hierarchically around a single field, such as biochemistry, genetics, or immunology. Elite research institutes in the U.S., such as Cold Spring Harbor, Salk, or Scripps, routinely bring together faculty from multiple fields.

Against this background, we undertake a broad comparison of linkages between research universities, public research institutes and the private sector in the field of the life sciences and analyze how differences in the pattern of these relationships have shaped the development of biotechnology in the United States and Europe. Our expectation is that the competitive, highly decentralized, and more autonomous U.S. setting is likely to foster more free-flowing relations with industrial partners, more interest in technology transfer, and more involvement in the commercial development of research. We draw on a variety of databases to compare the U.S. and Europe with regards to the processes by which biomedical research moves from the academic laboratories into clinical development.

The explosion of knowledge in molecular biology and genetics has generated a wide range of new medical opportunities. Because the relevant scientific knowledge and organizational skills are broadly dispersed, no single organization has been able to internally master and control all the competencies required to develop a new medicine (Powell, Koput, and Smith-Doerr 1996; Pammolli, Riccaboni and Orsenigo, 2000; Orsenigo, Pammolli and Riccaboni, 2000). Biomedicine, then, is characterized by extensive reliance on collaboration among many parties, including universities, research institutes, new biotechnology firms, and mature pharmaceutical and chemical corporations (Arora and Gambardella, 1994; Lerner and Merges, 1998; Stuart, Hoang, and Hybels, 1999; Arora et. al., 2000). These varied combinations of organizations afford us the opportunity to analyze cross-national differences in the roles these diverse organizations play in knowledge commercialization.

In section II below, we sketch the institutional terrains in Europe and the U.S. that have shaped the division of labor in biomedical innovation. The research systems in the U.S. and Europe are organized in qualitatively different ways, hence any comparison must be sensitive to variation on multiple dimensions. We use the methods of correspondence analysis and large-scale network analysis to capture these systemic differences. Methods and data sources are discussed in section III. In section IV, we present the comparative analyses, beginning with relational data on collaborative R&D projects. We look at R&D projects that were originated by public research organizations (PRO),² and subsequently developed by an array of different types of organizations. The distribution shows U.S.-European variation, as well as strong cross-national linkages. To better understand these linkages, we examine the position of countries in an international network of collaborative R&D projects. We then view more closely these national patterns through an assessment of patent co-assignment relationships. We find, again, strong national-level patterns. We analyze these national-level characteristics by looking at the focus of R&D at leading research organizations in Europe and the U.S., matching patenting activity with therapeutic categories. These analyses point out the heterogeneity of the U.S. system, on both scientific and organizational dimensions. We examine this heterogeneity by mapping the evolution of interorganizational ties in the United States at the

regional level. We conclude our analyses with a fine-grained view of the Boston area, one of the leading centers for biotech in the United States.

We assess the implications of our analyses in section V, stressing the twin importance of integrative capacity (i.e.: the ability to move back and forth from basic research to clinical development) and relational capability (i.e., the ability to collaborate with diverse kinds of organizations). We conclude by noting that while many analyses of the biomedical systems in the U.S. and Europe highlight differences in financial and labor markets and note key policy differences, (for a review see Gambardella, Orsenigo, and Pammolli, 2000), we stress fundamental variation in the organization of the upstream R&D process.

II. Trajectories of development in the U.S. and Europe.

The canonical explanation for differences in the rate of development of U.S. and European biomedicine is straightforward, emphasizing first-mover advantage in the growth of small, research-intensive U.S. biotechnology firms. Along with the biotech boom, emphasis has been placed on the evolution of supporting institutions ranging from federal policy initiatives (e.g. the 1980 Bayh-Dole Act) to the availability of venture capital, intellectual property (IP) law firms, and university technology transfer. We think this story is accurate, but incomplete. Our focus is more on the division of innovative labor. We highlight the importance of the underlying science and the diversity of organizations involved in R&D activities. Using data on public-private R&D relationships, we demonstrate that there are very different constellations of players in R&D networks in Europe and the U.S., and that these participants are engaged in different kinds of research and clinical activities.

To foreshadow our argument, the United States is characterized by 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, 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. From these disparate starting points, European and U.S. innovative networks branch out in different ways.

The science underlying biotechnology was developed in university and government laboratories. The leading centers of research in the new molecular biology were dispersed widely throughout advanced industrial nations.³ Initial technological breakthroughs – most notably Herbert Boyer and Stanley Cohen’s discovery of recombinant DNA methods and George Köhler and Cesar Milstein’s cell fusion technology to create monoclonal antibodies – occurred in Californian and British universities. But from the outset, U.S. universities and academic scientists actively worked to help create the biotechnology industry and reap rewards from their involvement (Liebeskind, Oliver, Zucker and Brewer, 1996; Zucker, Darby, and Brewer, 1998; Mowery et. al. 2001). Consequently, small science-based firms were initially located in close proximity to key universities and research institutes. In time, established pharmaceutical companies (EPCs) were also attracted to the field, initially collaborating with biotech firms in research partnerships and providing a set of downstream skills that were lacking in the R&D-intensive startups. Eventually, the considerable promise of biotechnology led nearly every EPC to develop, with varying degrees of success, both in-house capacity in the new science and a wide portfolio of alliances with small biotech firms (Arora and Gambardella 1990; Gambardella, 1995).

The early development of dedicated biotech firms (DBFs) created an initial advantage for the United States in biotechnology, as close contact between DBFs and universities became commonplace by the mid-1980s. Important differences in the nature and level of support for academic life science research have also played a key role in shaping this comparative advantage of the U.S. system (Gambardella, et. al., 2000).⁴ The structure of the research system and the strategies pursued by funding agencies are crucially important. In the U.S., substantial R&D monies have been administered through the NIH, which has supported significant interaction between the producers of fundamental biological knowledge and those involved in clinical research and drug development at public research centers and universities. Moreover, the U.S. biomedical research system is characterized by numerous alternative sources of support, with selection mechanisms that

complement the NIH and act according to different principles (Stokes, 1997). These varied funding sources permit diversity to be explored.

In Europe, funding has tended to be administered at the national level, with strongly differentiated approaches apparent across countries. This process may have hindered the development of a critical mass, especially in smaller countries. In many cases, resources have either been spread among a large number of “small” laboratories, or they have been excessively concentrated in the one or two centers of excellence. Support coming from the various European-wide programs has only partially changed the situation. In addition, research funds are less likely to support integration between basic science and clinical development.

European biomedical research has also been less integrated with teaching. The relevance of the research-teaching nexus in fostering high quality scientific research and integrating academic and industrial science should not be understated. In particular, the diffusion of molecular biology into general training in many European countries is a relatively recent phenomenon. As compared to the U.S., research in molecular biology has tended to be confined to highly specialized university and research institute laboratories (Morange, 1998). Particularly in Continental Europe, policies have been targeted mainly to creating specific organizational devices to manage technology transfer, such as science and technology parks. These intermediary institutions may even increase the distance between universities and industry by introducing an additional layer to the relationship. We argue that these institutional differences in funding, and the relationships among research, clinical work, and teaching, shape the structure of university-industry R&D networks in the U.S. and Europe.

Partly as a consequence of the institutional differences sketched above the founding of new biotechnology companies in Europe was more difficult. Rates of formation of start-ups are strongly correlated with the strength of university and public research institutes in the underlying science (Zucker et al, 1998). In the absence of small local firms, the large European companies turned to small American partners to tap new competencies as they struggled to catch up. Given the head start and faster rates of technological development in the U.S., European start-ups may have been preempted by American firms. Finally, we expect that the more dominant and geographically dispersed large European firms have had a pronounced effect on the development of European R&D networks,

as these organizations serve a ‘clearing-house’ function for the development of more specialized innovations from national research clusters.

III. Data and Methods

Analyzing cross-national differences in research funding, organization, and practice, as well as differential integration across R&D, clinical activity, and teaching is most effectively accomplished with methods that visually represent patterns of relationships. We are less interested in the attributes of individual research organizations and much more concerned with the linkages that structure innovation systems. Hence we utilize methods that capture these relational features graphically. We use correspondence analysis and Pajek to examine key characteristics of life science knowledge networks. Correspondence analysis is an analytical technique for studying the canonical correlations between two (or more) sets of categorical variables.⁵ We perform correspondence analyses to visually represent correlations among therapeutic patent classifications and public research organization assignees in a common two-dimensional space. We use Pajek⁶ to graphically display collaborative networks at the national, cross-national, and organizational level. Unlike more traditional visualization methods, which arbitrarily locate network nodes in two-dimensional representations, Pajek draws upon a meaningful scaling algorithm based on the idea that points may push and pull at each other in different ways and an optimal representation is one where there is a minimum amount of stress placed on the ‘springs’ connecting the entire graph. Pajek uses the Fruchterman-Rheingold (1991) algorithm that attempts to simulate a system of mass particles. The vertices simulate mass points repelling each other, while the edges simulate springs with attracting forces. The algorithm minimizes the overall “energy” of this system to represent distance among actors in the collaborative networks. The representations we present to illustrate our argument capture not only the pattern and density of collaborative activity, but also are a meaningful indicator of the extent to which such collaborations create actual clusters of tightly connected partners.

We draw on several complementary data sets to analyze European and U.S. research organization-industry innovation networks for the period spanning 1988-1999. Two patent data sets and two research collaboration data sets form the core of our analyses. The databases developed by Powell and Kenneth Koput, and by Owen-Smith focus primarily on the United States. In their examination of the role research universities play in the commercial field of the life sciences, they find 1,026 linkages between public research organizations and dedicated biotech firms over the twelve-year period. For each relationship, data are available on the purpose of the affiliation, its duration, and the identities of the participants. These relationships represent formal contractual ties established between firms or through the auspices of the United States Patent and Trademark Office. The larger database from which these relationships are extracted focuses on dedicated biotechnology firms (Powell and Koput) and Research One Universities as designated by the Carnegie Foundation classification system (Owen-Smith). Both databases have been used extensively in previous research (Powell et. al. 1996; Powell et al. 1999; Owen-Smith 2000, 2001).⁷

The biotech database covers independently operated, profit-seeking entities involved in human therapeutic and diagnostic applications of biotechnology.⁸ The sample includes 482 firms, 180 of which exist in all years over the period 1988-99. There were 229 entrants during the period, and 91 exits overall. The database, like the industry, is largely centered in the U.S., although in recent years there has been significant expansion in Europe. In 1999, 80% of the companies were located in the United States, while 10% made their homes in Europe. The U.S. university database focuses on the role that research-intensive campuses have played in biotechnology through the specific lens of patent co-assignment. Drawing on a data set coded from bibliographic information drawn from patents assigned to 89 Research One Universities from 1976-1998, we identify 181 co-assigned pharmaceutical patents were jointly owned by R1 universities and dedicated biotech firms or non-university research institutes and hospitals.⁹

Pammolli and Riccaboni have developed two comprehensive data sets with extensive coverage of Europe and the U.S.. The Pharmaceutical Industry Database (PHID) developed at the University of Siena covers 4,358 collaborative R&D projects among industrial and nonindustrial sources.¹⁰ For each R&D project, the PHID database distinguishes the organization that originated a

new pharmacologically active compound from the organization(s) that licensed that patent for further development. In addition to originator-developer information, each project is classified according to the Anatomic Therapeutic Classification (ATC), which identifies pharmacological actions and biological targets.¹¹

The second database draws upon 8,031 patents for therapeutically useful compounds or processes issued by major world patent offices (U.S., U.K, Germany, France, Japan, European, and the Patent Cooperation Treaty legal office) and assigned to the 98 most prolific non-industrial research organizations worldwide.¹² These 98 institutions represent more than 70% of all non-industrial patents in this sample. These patents were also coded according to the same pharmacological classification used for R&D projects.

Taken together, these four data sources enable us to develop a comprehensive and novel view of patent co-assignment and collaborative networks involving European and U.S. biotechnology firms, pharmaceutical corporations, and public research organizations. Our data are broad in scope and involve thousands of relationships among multiple types of organizations, enabling us to map qualitative differences in public-private R&D networks in the life sciences.

IV. Analyses: Cross-National Networks and Organizational Competencies in R&D.

We begin by presenting data on R&D projects generated by PROs and developed collaboratively with other organizations.¹³ We distinguish the roles of originators and developers, with the former responsible for the underlying basic science, focusing on the early stages of target identification/validation and drug discovery, and the latter handling downstream stages of R&D and subsequent manufacture and/or marketing. We identify originators as the institution that started the R&D project and, typically, held the relevant patent. Note that a variety of organizations – PROs, DBFs, and EPCs perform the roles of developing, producing, and commercializing new biomedical products.

[Insert Table 1 here]

The bulk of the collaborative projects occur within the U.S., while a much smaller number are carried out in Europe. But we are somewhat less interested in the scale of activity than in what kind of organizations are involved. In the U.S., dedicated biotech firms do the lion's share of the development work (nearly 55%) on PRO-originated innovations. When a U.S. PRO turns to a European partner, the large multinational corporation is the dominant option. In Europe, there are real differences in collaboration within and across nations. In local collaborations, European PROs turn to DBFs and other PROs much more readily than to large EPCs. But when collaboration occurs across countries, the EPCs become the dominant partner. When European PROs reach across the Atlantic, however, dedicated biotech firms become the primary developers. The picture that emerges is one of very different roles for small firms and large multinationals in Europe and the U.S., with the EPC responsible for the bulk of cross-national collaboration in Europe and the small firm the key participant as a developer in the U.S. We turn now to an in-depth examination of these organizational differences.

Organizational Underpinnings. Figure 1 represents the R&D projects data graphically, locating the position of nations in a global network. In this figure the spatial position of the nodes represents individual nations' relative centrality in the international R&D project network. The size of the nodes corresponds to the number of biomedical patents held by PROs in each nation. Thus, node size reflects relative differences in the stock of patented biomedical knowledge held by PROs in each nation, and indicates the volume of innovations generated by each national research system. The numbers associated with the lines are counts of the number of cross-national R&D agreements. For example, the close connection between the U.S. and the U.K. represents 441 individual R&D project ties between PROs and commercial entities. Figure 1 portrays several key characteristics of the international biomedical R&D projects network, reflecting relative national positions in terms of both stocks and international flows of knowledge.

[Insert Figure 1 here]

Note the centrality and size of the American node. The large and diverse public research system in the U.S. dominates global patenting and is central in the cross-national project network. This centrality is reflected in the spatial location of the node (a result of Pajek's clustering

algorithm), in multiple connections to otherwise isolated European nations (e.g. the Netherlands, Spain, Belgium, and Denmark), and in high volume cross-national ties. Note that each international link involving the U.S. represents a higher volume of individual R&D agreements than any of the cross-national ties between other nations. Figure 1 clearly implies that the public research organizations in the United States are structurally central and quantitatively dominant in cross-national R&D project networks.

The nationally aggregated picture presented in Figure 1 does not tell the full story, however. R&D projects and patented biomedical innovations are generally the result of organization-level processes. Figure 2 examines the upstream collaborative network among individual PROs to analyze relationships among organizations whose patenting activity drives the size of the nodes in Figure 1. Figure 2 is based on patent co-assignment networks among public research organizations. Each node is a university, research institute or hospital, and each tie represents two or more patent co-assignments between the organizations. As was the case with Figure 1, the relative spatial position of nodes is a reflection of the minimum-energy algorithm we employ using Pajek. Several features stand out in this image.

[Insert Figure 2 here]

Consider first the regional and national clustering of organizations that we highlight with dashed and dotted lines. The tightly clustered French, German and British research organizations on the left side of the figure and the densely connected U.S. regions in the image's upper right hand quadrant are the result of minimum-energy network drawing techniques and not of arbitrary placement. In addition to demonstrating the coherence of national and regional R&D systems, close inspection of the patterns of patent co-assignment help explain the causes of the U.S. dominance apparent in Figure 1. Note the organizational homogeneity of the French and German national clusters, which include neither hospitals nor universities. Contrast these relatively isolated and homogeneous national clusters with the large and densely interconnected Boston region in the upper quadrant of the figure, which is composed of dense and repeated interconnections among a diverse set of PROs. Elite universities (Harvard, MIT), research institutes (the Dana-Farber Cancer Center),

and hospitals (Brigham and Women's and Massachusetts General) play central roles in innovative collaborations both within Boston and across U.S. regions.

Closely knit regional networks such as those found in Boston help account for the global centrality of American PROs. But connections across U.S. regions (note for instance the ties between Harvard, Stanford, and the UC system, connections from Dana Farber to the University of Chicago, and from Brigham and Women's hospital to Duke University) and co-assignment ties linking geographically dispersed universities to the National Institutes of Health illustrate a public research system that also reaches across regions and organizational forms. Recall that these relationships represent patent-co-assignments, a particularly close form of R&D collaboration. We argue that these systemic cross-national differences in the organization of early-stage research collaborations explain national differences in biomedical commercialization above and beyond variations in policies or later-stage technology transfer infrastructures. Consequently, we expect the structural clustering of European nations and U.S. regions, and the consolidating effect of inter-regional ties in the U.S., to result from characteristics of the science underlying these patent co-assignment networks. To consider this assertion, we turn to correspondence analyses of the specific therapeutic areas covered by public research institute patents in the U.S. and Europe. As we use the term here, a therapeutic class is one of 102 specific disease areas on which a patented innovation focuses. Thus we can distinguish both the scientific content and the specific target of patented research in the U.S. and Europe.

The Organizational Division of Scientific Labor. Figures 3 and 4 display the outputs from correspondence analyses relating U.S. and European public research organizations and the therapeutic classes in which they patent. Correspondence analysis is applied here to capture substantial differences between leading U.S. and European research institutions in terms of scientific specialization.¹⁴ As an output, correspondence analysis provides a graphical representation in a chi-squared metric such that institutions with profiles close to the average are plotted near the origin while more specialized profiles are plotted on the periphery. In Figures 3 and 4, the bold-faced labels represent the most prolific PROs in terms of number of patents, while the lighter labels denote therapeutic macro-classes. Institutions and therapeutic categories play dual roles, weighting

organizational profiles and rescaling the dimensions of the figures. Here again, the spatial relationships among PROs and therapeutic classes are meaningful representations of quantitative relationships. Inter-point distances are reflective of differences in institutional therapeutic profiles. For example, if a given institution holds the same number of patents for each therapeutic category, then it will be centrally located. In contrast, an institution specialized in one class will appear on the periphery of the correspondence map.¹⁵

[Figures 3 and 4 Here]

Figures three and four demonstrate that while research is proceeding on substantively similar topics across the continents, the division of organizational labor that produces it varies widely. Note the differences in the core actors. In the European case (Figure 3) universities are underrepresented. Instead, research institutes such as France's Institute Pasteur and Germany's Max Planck and Max Delbruck centers play important roles. This centrality is not surprising, given the preeminent role of these institutes in the history of molecular biology (Morange, 1998). In contrast, Figure 4 reprises Figure 2, showing that the core actors in the U.S. innovation system are much more organizationally diverse. Note the centrality of the U.S. government (the National Institutes of Health complex), and Johns Hopkins University and the University of California System. But also observe the key presence of elite research institutes such as Scripps and Salk, major research hospitals and medical schools (Brigham and Women's, Massachusetts General, and Baylor College of Medicine), and elite research universities (MIT, Stanford, Pennsylvania, Duke and Rockefeller). The clear implication is that the universe of central public research organizations is much more heterogeneous in the U.S. than in Europe.

Observe the relative dispersion of therapeutic classes that appear in both Figures 3 and 4. For Europe, Figure 3 indicates a relatively dispersed set of therapeutic classes, indicating that the organizations associated with them are specialized innovators whose patents focus on specific sets of therapies and biological targets. In contrast, therapeutic classes are not clearly separable in figure 4, since leading U.S. PROs tend to hold patents which span multiple substantive areas.

Finally, consider the co-location of therapeutic classes and public research organizations in the two figures. Figure 3 highlights not only specialization by organizational form, but also national

specialization in areas of innovation. There are two apparent clusters of research institutes and therapeutic classes. The French institutes on the left hand side of Figure 3 are located close to each other and co-located on a distinctive set of therapeutic classes relating primarily to infectious disease research. German research institutes, at the right hand side of the figure, are more involved with hereditary cardiovascular diseases. The more dispersed and diverse British institutions, e.g. Cancer Research Campaign (CRC), Medical Research Council (MRC), and the British Technology Group (BT) are somewhat broader in focus but still cluster in therapeutic classes largely related to cancer research. The greater breadth of the British research system, and its higher degree of diversity compared to France and Germany, may explain its more central role in international R&D networks (recall Figure 1). Figure 4, on the other hand, tells a quite different story. In the U.S. national innovation system, diverse public research institutions play the role of generalist innovators regardless of geographic location, though the prevalence of Boston and California-based research organizations in the core suggests the importance of regional agglomeration.

This is a critical finding, which implies that increases in scale alone will not alter the focus of R&D efforts because organizations typically engage in local search, and would continue to patent in those areas in which they are most skilled. In essence, then, we argue that one reason for greater integration across and within U.S. regions can be found in the scientific overlap among generalist patentors. Likewise, alterations in the scale of patenting activity without corresponding shifts in this division of labor will not make the European system resemble its American counterpart. Instead, we contend that mere increases in scale would deepen specialization and heighten fragmentation among European national research systems.

One key message of the correspondence analyses is that national specialization in Europe falls along scientific lines. In the U.S., there is abundant regional clustering, but, unlike the European case, agglomeration is not driven by scientific specialization. Points of excellence develop in both the U.S. and European systems, but in the Europe those clusters are limited to narrower medical specialties and specific nations. The U.S. represents a very different profile, characterized by diverse, substantively generalist research organizations connected both within and across key

regional clusters. To further our understanding of the organization of the U.S. national system, we turn to an analysis of its growth out of a few key regional clusters.

A National System From Regional Origins. We have stressed the dual role of universities and startup firms in biotechnology's origins. Here, we present data that confirm the co-location of universities, research institutes, and dedicated biotech firms in a small number of geographic regions in the United States. In 1988, 73% of all collaborations between DBFs and PROs occurred in just six areas: Boston, the New York metropolitan area, Seattle, San Diego County, the Bay Area, and Texas (principally Houston).¹⁶ This phenomenon has been attributed to a range of intellectual, economic, and social factors. Knowledge spillovers are clearly important, especially when novel discoveries are involved. The availability of skilled labor and access to venture capital are critical as well. Extensive social ties and reputational credibility catalyze further relationships, sustaining a process of increasing returns. But how do initial locational advantages and rapid technological development interact? In addition to institutional and labor market differences, we argue that the structure of scientific knowledge in biomedicine plays a key role.

The field of the life sciences has witnessed a rapid expansion of knowledge that has taken the form of a branching process, in which general hypotheses have given rise to sub-hypotheses, and in turn further inquiries (Orsenigo et. al., 2001). The structure of knowledge is hierarchical, highly cumulative, and, in the industry's early years, difficult to appropriate without close contact with cutting edge academic researchers. But discoveries that were considered revolutionary at the outset were soon incorporated into the standard toolkit of laboratory practice. As the skills became widely accessible and new transversal technologies (e.g. genomics, combinatorial chemistry, and high throughput screening) allowed for sophisticated production and screening of new molecular structures absent contact with established research centers, DBF dependence upon prestigious university researchers declined, and the central importance of network connections to local partners waned.

We seek to explain how the evolution of the science has affected the network of collaborative relationships. Several possibilities can be sketched, with different roles for various types of institutions. For example, universities and firms that were first movers on the research frontier could

continue their close ties as the research moves into clinical development. But as initial successes are achieved and publicized, many other participants are attracted to the field, both in the U.S. and abroad. An alternative process could involve the initial entrants as the carriers of the field, moving from co-localized relationships to more distant linkages with other firms and universities. This process might be driven by a production logic, in which diffusion occurs with movement from upstream R&D to downstream commercialization. A different trajectory would emphasize the catalyzing role of geographic centers, stressing the capacity of initial entrants to identify new knowledge and relevant skills developed outside their regions. In this scenario, the most well-connected early entrants would be the most capable at accessing new ideas (Koput and Powell, 2001). Combined with the overwhelming initial importance of regional clusters, this latter pattern implies that we should observe a process of de-localization of PRO-DBF ties over time. This delocalization would be facilitated by the generalist research focus of core organizations highlighted in Figure 4.

We begin by mapping alterations in the level of geographic clustering of PRO-DBF relationships in the United States. The biotechnology industry's early development in the U.S. depended upon regional concentrations of co-located universities, firms, research organizations, and key resource providers such as law and venture capital. Thus the earliest linkages between biotech firms and public research organizations should be dominated by relationships in which both partners are co-located in the same geographic region. If this sector evolves as established 'local' players expand their set of potential partners and as new technologies become standard practice, then the proportion of ties with regionally co-located or 'local' partners should decline over time.

Figure 5 presents both graphical and quantitative evidence for the process of industry evolution. The figure on the left represents 1988, on the right, 1998. The triangles represent the six most active regions where biotechnology originated, and their location on the pyramid reflects the volume of the interorganizational linkages that connect them to other areas. The size of the triangle reflects the number of ties within the region. Thus, Boston is both the most connected region internally and the most extensively linked externally.

[Figure 5 here]

Note the aggregate decline in the percentage of local ties from a high of just over 40% in 1988 to a low of 8% in 1998. This decline occurs 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. The combination of an increasing number of collaborations and a decreasing proportion of local connections represents the declining importance of ties within the initial regional clusters. Figure five indicates that the rising volume of PRO-industry ties in U.S. biomedicine occurred in the context of a shift in the distribution of those ties, such that the importance of connections between organizations co-located in the same geographic region decreased, while the prevalence of network linkages between organizations in different areas increased.

As noted above, the sharp decline in local ties within established regions could, in the context of an aggregate increase in connections, result from three very different trajectories: (1) deepening ties across established regions (e.g. links between triangles in Figure 5); (2) connections from established regions to other areas of the nation (e.g. ties connecting nodes above the dashed lines to those below it); or (3) increasing linkages involving two partners located outside established regions. Figure 5 shows that the second of these options describes the bulk of changes in the regional distribution of ties as the U.S. national network expanded over a ten year period. While within cluster and cross-cluster ties declined, and ties that do not involve established clusters showed only a slight increase, the proportion of linkages involving a partner in an established cluster and one in another region of the country more than doubled, accounting for about 54% of all connections by 1998.

We contend that this important structural shift illuminates a dual process of network expansion that encompasses both increased scale and a shifting geographic distribution. In our view, this transformation is enabled by both the generalist scientific role played by elite PROs within established regional clusters (recall Figure 4) and by the integrative role of the National Institutes of Health (recall Figure 2). Moreover, the regional clusters that gave birth to the U.S. national network may have already contained the seeds of this distributional shift.

We turn to closer analysis of one U.S. regional ‘starting point’ to examine this possibility. Consider Figure 6, which presents two views of inter-organizational linkages involving the Boston

region, the most prominent regional cluster apparent in Figures 2 and 5. Figure 6a, represents only linkages internal to Boston in 1988. These specific inter-organizational ties are represented by the size of the Boston node in Figure 5. Figure 6b highlights all ties involving at least one partner in the Boston area in the same year. In both cases, the shape of nodes represents the type of organization. Triangles are universities, circles are DBFs and squares are research institutes or hospitals. Node size is a function of network degree such that the largest nodes are the most connected. As with other Pajek representations the location of nodes relative to each other is a function of the strength and pattern of ties among them. Figure 6b adds shading to image to capture the geographic location of partners. Black nodes (of any shape) are located in the Boston metro area. Gray nodes are located in one of the other established regional clusters (Figure five's triangles) and white nodes are located in other areas of the country.

In Figure 6a, the organizational diversity of the Boston area is clear. Firms (e.g., Seragen, Genzyme, Cambridge Bio), universities (Tufts, Harvard, MIT, BU) research institutes (Dana-Farber) and hospitals (Brigham and Women's, Massachusetts General) are connected to local partners. Nevertheless, that organizational diversity is apparent in a relatively sparse network of connections that makes the Boston region look less clustered than our earlier analyses suggest. Two key research institute and hospital players (Brigham & Women's and Dana Farber) are isolated from the central network corridor. Viewed through a Boston only lens, the region appears composed of loosely connected clusters surrounding MIT and Harvard. Organizational diversity was the rule in Boston in 1988, but the early density of the Boston network appears to be a function of organizations located in other areas of the nation.

At a glance, Figure 6b looks more like a coherent regional network than Figure 6a. Three important clusters (surrounding Dana-Farber, Harvard, and MIT) are brought into closer connection by diverse organizations located outside of Boston. Consider the structural roles played by the UC system, Stanford, Centocor (a Philadelphia-based DBF) and the Sloan-Kettering Cancer Institute (located in New York City). These four organizations add a coda to our story of organizational diversity. While Boston is internally diverse in 1988, the density of the region's innovation networks is greatly increased by the inclusion of diverse organizations from other geographic

locations. Figure 6b captures a single regional ‘starting point’ and demonstrates that the diversity and density of Boston’s networks is a function of both local depth and ties that connect multiple region. Note also the key role played by Boston DBFs in ‘reaching out’ to PROs located in other areas of the country. Recall from Figure 5 that it is exactly this type of tie (indicated by connections from black nodes to white nodes in Fig. 6b) that promotes the expansion of the U.S. national system. Unpacking the structure of the PRO-DBF network in Boston of 1988 provides two key insights into the development of the U.S. national system documented in Figure 5. First, the seeds of that expansion were already present in one focal region as early as 1988. The lesson of Figure 6b is that ties to key organizations in other parts of the country helped make Boston a major regional starting point. Second, Figure 6b emphasizes the central role that small science-based firms played in reaching out to other areas of the nation. A quick glance at the local Boston nodes (black) in the figure suggests that it is DBFs such as T Cell Sciences that connect to geographically distant PROs rather than the elite PROs linking to distant firms.

In essence, the dual process we highlight reveals that a truly national U.S. biomedical network grew from regionally clustered beginnings on the strength of overlapping scientific expertise, the critical integrative effect of the NIH, and the expansive role played by small firms. In the European case, the absence of strong scientific overlap (recall the national scientific specialization apparent in Figure 3), a single key upstream institution such as the NIH, or rapidly-developing small firms mitigate against this type of network expansion. These key differences, we argue, have several notable consequences. First the relative homogeneity of elite European PROs -- few European universities and no European hospitals appear in either Figure 2 or Figure 3 -- suggests that in addition to scientific specialization, European networks will be less integrated across the development process than their U.S. counterparts, which include universities, hospitals and research institutes. Second, the integrative role played by the U.S. National Institutes of Health occurs much further downstream in Europe, as large pharmaceutical companies undertake the bulk of cross-national European research collaborations (recall Table 1). Finally, our analyses point out a very different role for small science-based firms in the U.S. and European contexts. Where Figure 6 implies that as early as 1988 it was small firms in Boston that reached out to disparate and

geographically diffuse PROs, Table 1 indicates that in Europe, small firms play a primarily local role, deepening ties within scientifically specialized national clusters rather than reaching across them.

V. Conclusions

Our analyses of university-industry interfaces in the U.S. and Europe emphasize the importance of the division of innovative labor. We do not object to arguments that the United States' first-mover advantage was critical in establishing the trajectory of the field. But we supplement this explanation by stressing the diversity of actors involved and the varied roles played by specialists and generalists. Without recognizing these elements in the context of an evolutionary trajectory shaped by distinct cultural and institutional contexts, European efforts to “catch up” to the U.S. by mirroring established policies and arrangements will likely be misguided. Central to the U.S. system are two key factors: relational and integrative capability. A wide diversity of U.S. organizations have established protocols in place for fostering research collaboration. Moreover, these alliances span organizations with different missions and serve to link basic research with clinical development.

The institutional structure of biomedical research evolved quite differently in Europe and the United States. The diversity of the U.S. public research system, a highly mobile scientific labor force, and a host of regulatory and policy initiatives promoted widespread commercialization of academically originated research, largely through the founding of small biotechnology firms. In addition, the generalist technological role and integrative development profiles of U.S. public research organizations have capitalized on scientific developments in molecular biology that more closely link goal-oriented therapeutic research with fundamental biological investigation. European universities developed competencies in molecular biology less quickly than specialized research institutes. The disciplinary focus of these institutes, combined with the centralizing effects of national R&D funding infrastructures and regulatory contexts serve to limit universities' participation in commercially-oriented R&D and concentrate R&D networks in specialized national clusters.

We also observe qualitatively different paths in the development of local centers of excellence in the U.S. and Europe. In the former case, generalist regional clusters developed around public research organizations that integrated innovation and development work. These clusters planted the seeds of accumulative advantage as the regions attracted talented researchers, high quality students, and increasing shares of R&D funding, in addition to for-profit firms dedicated to the commercialization of new technologies. In Europe, national clusters of specialists may also have benefitted from accumulative advantage in research funding and talent, but the funding sources were largely national rather than European, and research priorities and a community of local specialist firms may have deepened already narrow competencies rather than enabling broad exploration. The role that European pharmaceutical corporations played as clearinghouses for innovations developed within these national clusters may have also mitigated against the broadening of regional scientific and organizational competencies.

Finally, notable differences in the constellation of organizations able to capture and develop innovations aided in pushing U.S. and European industries in different evolutionary directions. We observe divergent roles played by public research organization originators, dedicated biotechnology firms, and large pharmaceutical companies that contribute to disparate industry outcomes in Europe and the United States. Our emphasis on the diversity of types of organizations and their multiple roles stands as a corrective to policy attempts to develop high volume collaborations in Europe through copying American policies. Our focus on the division of innovative labor implies that European efforts to adopt U.S. policies should be directed more at generating integration between basic research and clinical development and fostering extensive linkages among universities, small firms, and the heretofore dominant public institutes and large pharmaceutical companies.

Table 1. Developers for Public Research Organization originated R&D projects				
	Type of Developer			
	EPC	DBF	PRO	N by pair type
Euro PRO ---> Euro Partner _{total}	23.9%	42.9%	33.2%	669
Euro PRO ---> Euro Partner _{w/in country}	13.9%	46.6%	39.5%	476
Euro PRO ---> Euro Partner _{across country}	48.7%	33.7%	17.6%	193
Euro PRO ---> U.S. Partner	22.6%	49.4%	28.0%	243
U.S PRO ---> Euro Partner	66.2%	25.9%	7.1%	719
U.S PRO ---> U.S. Partner	17.6%	54.4%	28.0%	2,727
N by developer	1,170	2,078	1,110	4,358

Figure 1. Cross-National Network of R&D Projects Involving PROs and Commercial Entities, 1990-99

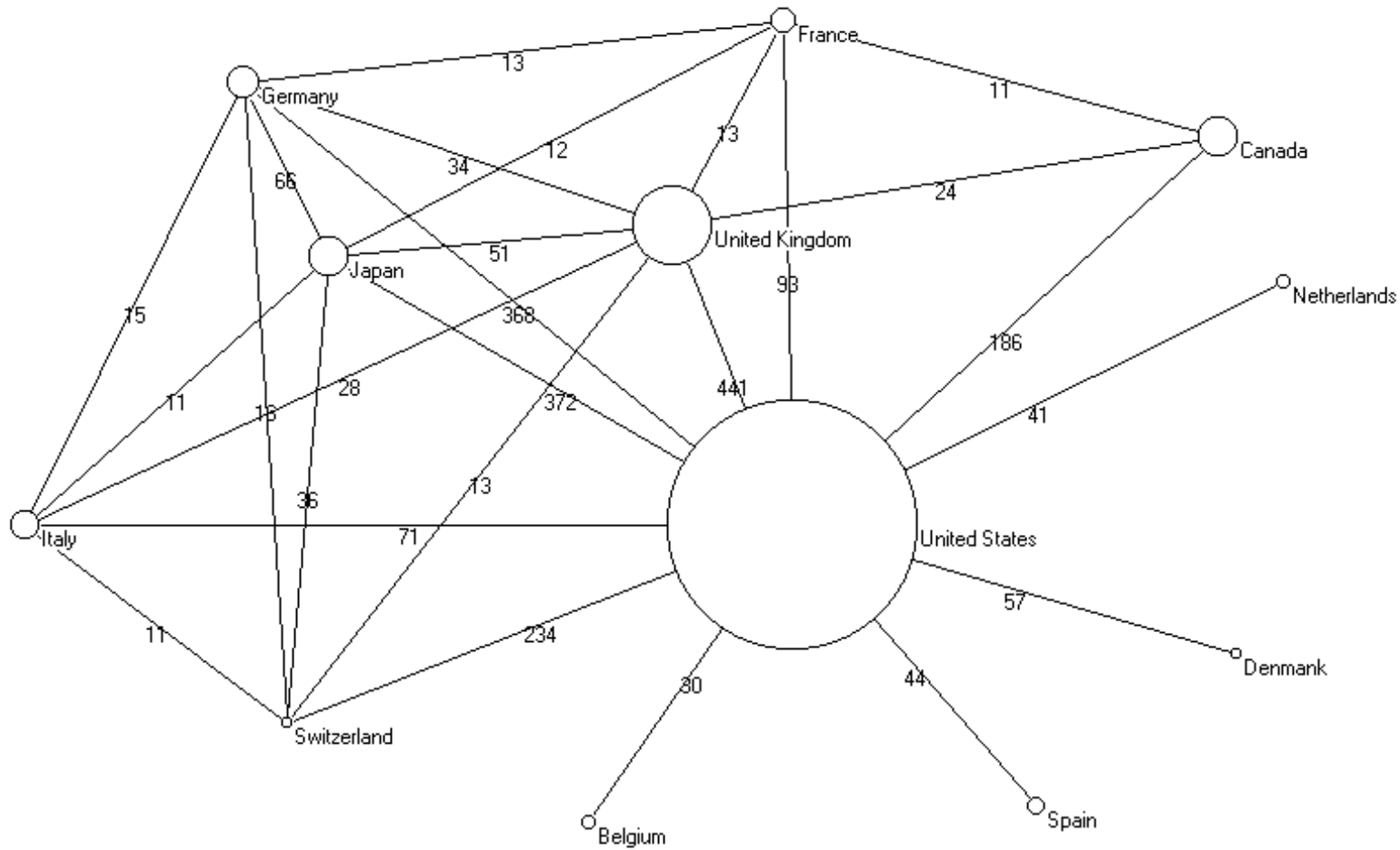
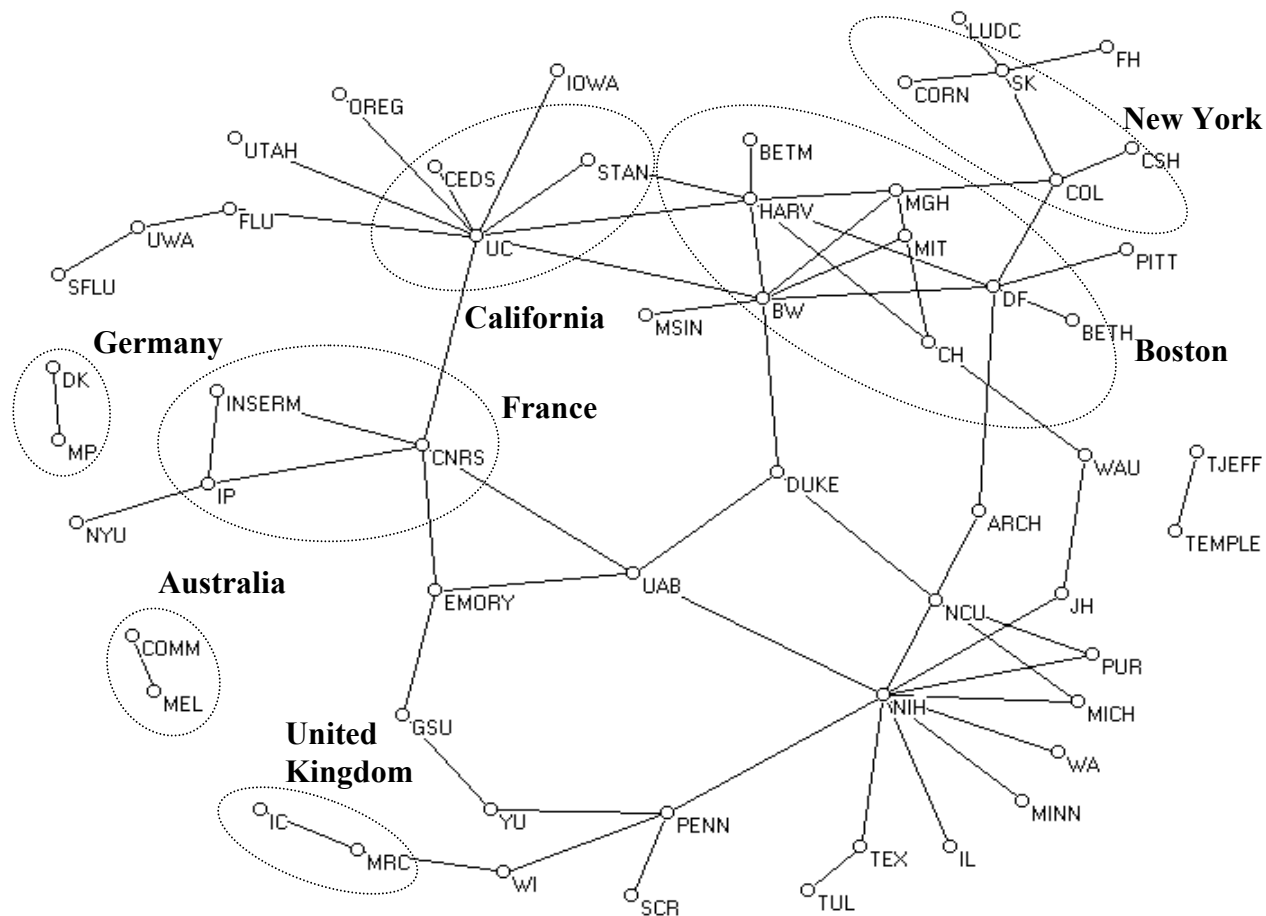
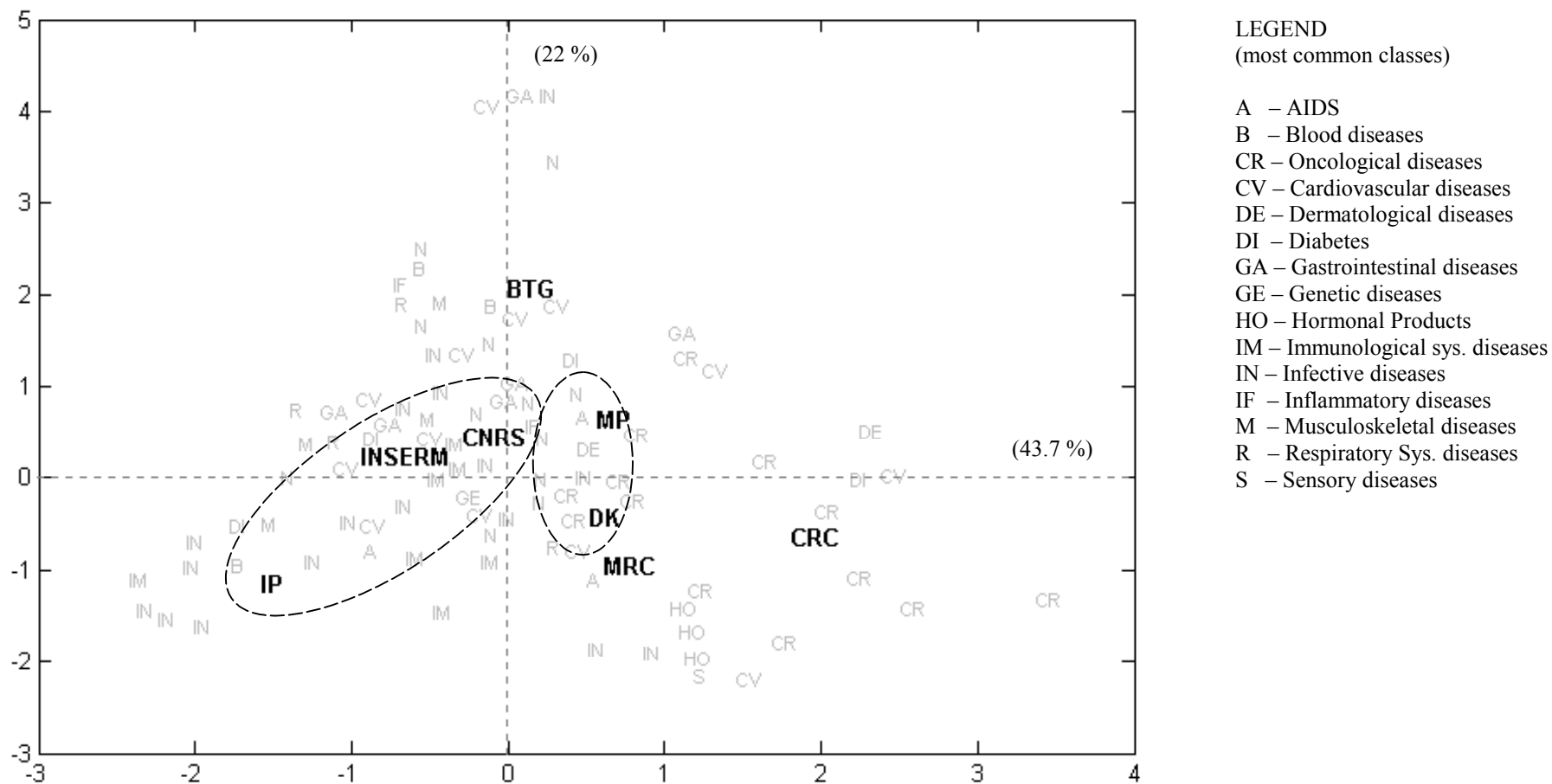


Figure 2. Organization Level Patent Co-Assignment Network for PROs, 1990-99



- | | | | |
|--------|--|--------|---------------------------------------|
| ARCH | Arch Dev. Corp., Univ. of Chicago (IL) | MINN | University of Minnesota (MN) |
| BETH | Beth Israel Hospital (MA) | MIT | Massachusetts Institute of Tech. (MA) |
| BETM | Beth Israel Medical Center (MA) | MP | Max Planck Institut (Germany) |
| BW | Brigham and Women's Hospital (MA) | MRC | Medical Research Council (UK) |
| CEDS | Cedars-Sinai Medical Center (CA) | MSIN | Mount Sinai Hospital (Canada) |
| CH | Children's Hospital Medical Center (MA) | NCU | University of North Carolina (NC) |
| CNRS | Centre Nat. de la Recherche Sc. (France) | NIH | National Institutes of Health (MD) |
| COL | Columbia University (NY) | NYU | New York University (NY) |
| COMM | Commonwealth Sc. and Ind. Res. Org. (Australia) | OREG | University of Oregon (OR) |
| CORN | Cornell Research Foundation (NY) | PENN | University of Pennsylvania (PA) |
| CSH | Cold Spring Harbor Lab. (NY) | PITT | University of Pittsburgh (PA) |
| DF | Dana-Farber Cancer Institute (MA) | PUR | Purdue University (IN) |
| DK | German Cancer Institute (Germany) | SCR | Scripps Research Institute (CA) |
| DUKE | Duke University (NC) | SFLU | University of South Florida (FL) |
| EMORY | Emory University (GA) | SK | Sloan Kettering (NY) |
| FH | Fred Hutchinson Cancer Res. Center (WA) | STAN | Stanford University (CA) |
| FLU | University of Florida (FL) | TEMPLE | Temple University (PA) |
| GSU | Georgia State University (GA) | TEX | University of Texas System (TX) |
| HARV | Harvard University (MA) | TJEFF | Thomas Jefferson University (PA) |
| IC | Imperial Cancer Research Fund. (UK) | TUL | Tulane University (LA) |
| IL | University of Illinois (IL) | UAB | University of Alabama (AL) |
| INSERM | Institut National de la Santé et de la Rech. Médicale (France) | UC | University of California System (CA) |
| IOWA | University of Iowa (IA) | UTAH | University of Utah (UT) |
| IP | Institut Pasteur (France) | UWA | University of Washington (WA) |
| JH | Johns Hopkins University (MD) | WA | Washington University (MO) |
| LUDC | Ludwig Inst. for Cancer Res. (Switzerland) | WAU | Wisconsin Alumni Research Found. (WI) |
| MEL | University of Melbourne (Australia) | WI | Wistar Institute (PA) |
| MGH | Massachusetts General Hospital (MA) | YU | Yale University (CT) |
| MICH | University of Michigan (MI) | | |

Figure 3. Correspondence analysis: Co-location of prolific European PRO patentors and therapeutic classes, 1990-99



LEGEND
(most common classes)

- A – AIDS
- B – Blood diseases
- CR – Oncological diseases
- CV – Cardiovascular diseases
- DE – Dermatological diseases
- DI – Diabetes
- GA – Gastrointestinal diseases
- GE – Genetic diseases
- HO – Hormonal Products
- IM – Immunological sys. diseases
- IN – Infective diseases
- IF – Inflammatory diseases
- M – Musculoskeletal diseases
- R – Respiratory Sys. diseases
- S – Sensory diseases

BTG – British Technology Group (UK)
CNRS – Centre Nationale de la Recherche Scientifique (FR)
CRC – Cancer Research Campaign (UK)
DK – German Cancer Institute (GER)
INSERM - Institut National de la Santé et de la Recherche Médicale (FR)

IP – Institut Pasteur (FR)
MP – Max Planck Institut (GER)
MRC – Medical Research Council (UK)

Figure 4. Correspondence analysis: Co-location of prolific U.S. PRO patentors and therapeutic classes, 1990-99

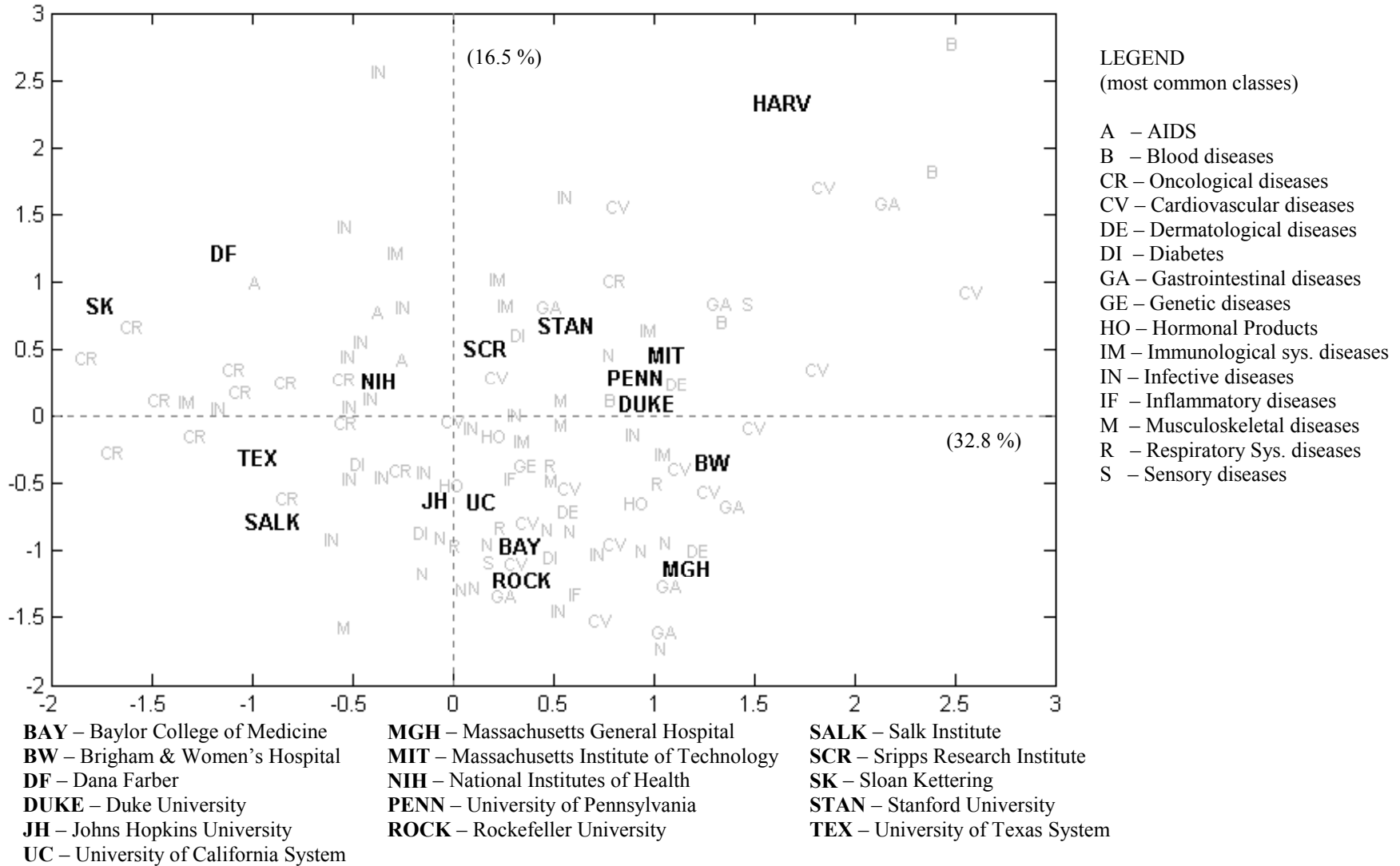


Figure 5. A. Interorganizational Linkages by Region in the U.S., 1988 B. Interorganizational Linkages by Region in the U.S., 1998

Coherent regional clusters

	1988	1998
w/in clusters	40.6%	8.3%
across clusters	12.5%	8.3%
to other regions	25.0%	54.2%
among other areas	21.9%	29.2%
N	210	515

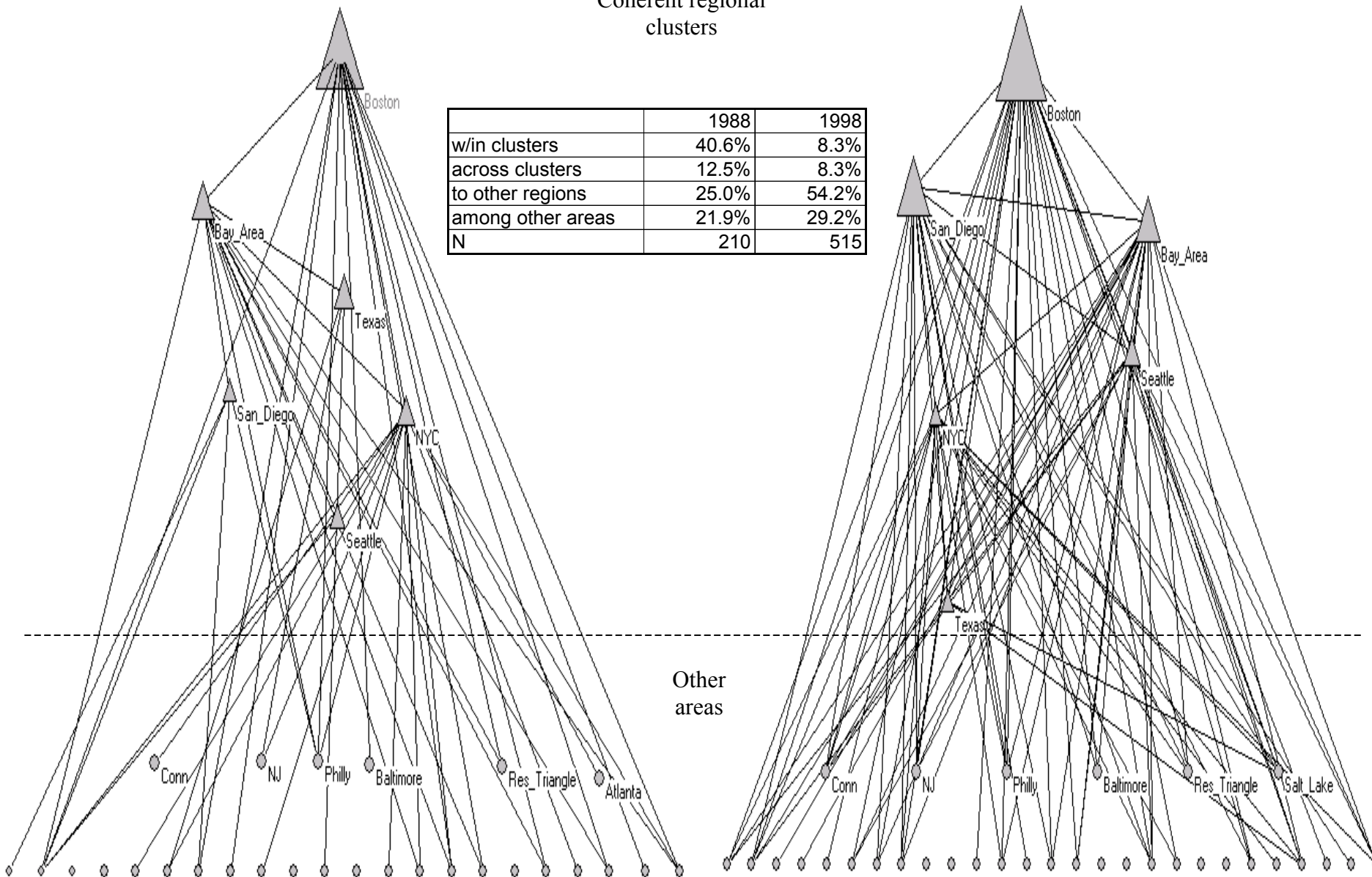
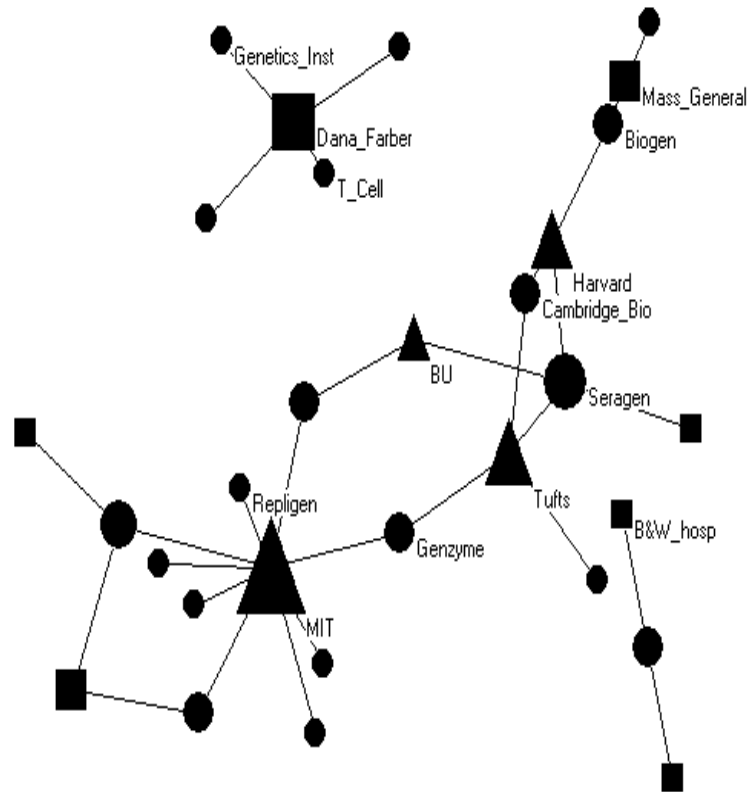


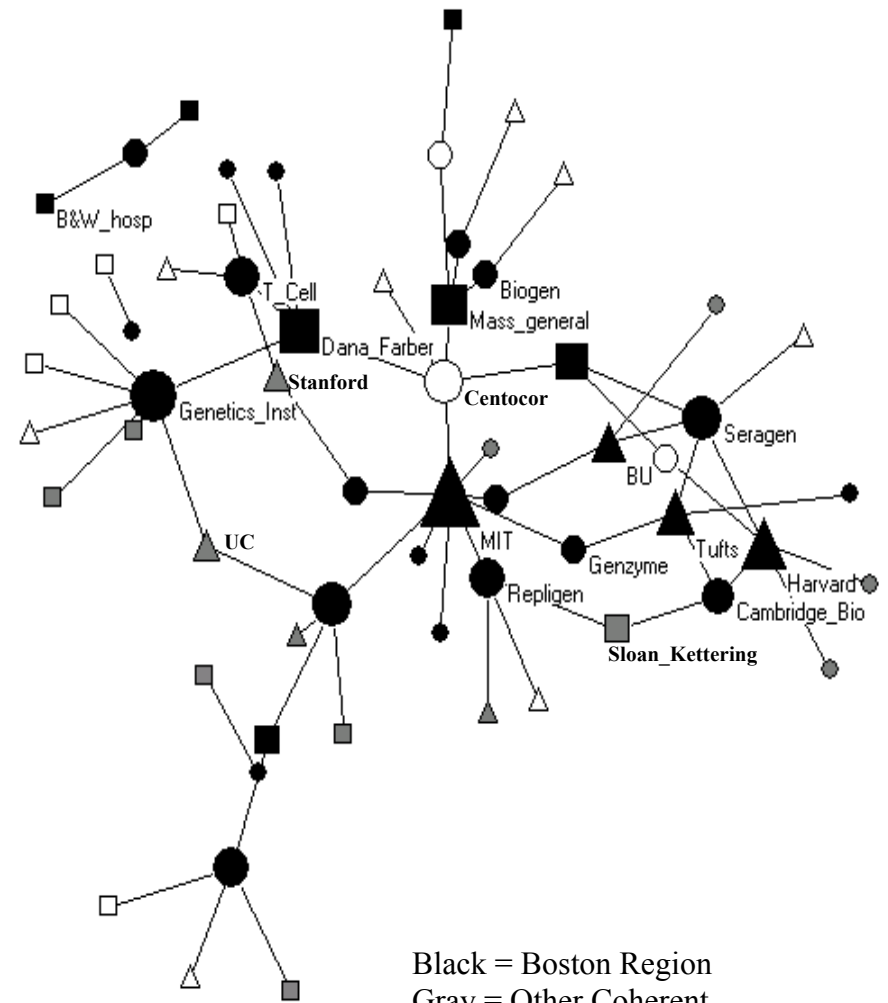
Figure 6.

A: PRO – DBF ties internal to the Boston region,
1988



Triangles = Universities
Circles = DBFs
Boxes = Research
Institutes/Hospitals

B: PRO-DBF ties internal and external to the
Boston Region, 1988



Black = Boston Region
Gray = Other Coherent
Region
(e.g. Bay Area, NYC)
White = Other Areas

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¹ The Single European Act provided, for the first time, a legal basis for European R&D programs (framework programs) developed by the European Commission to complement national programs and funds.

² We define PRO as any government research laboratory, public or private university, or nonprofit or public research hospital or institute.

³ A survey of high impact publications in molecular biology and genetics between 1988 and 1992 lists the Institute Chimie Biologique in Strasbourg, the MRC lab in Cambridge, UK, the Institute Pasteur in Paris, and the Karolinska Institute in Stockholm among the most prolific research centers. See Science Watch, July/August 1993, Vol. 4, No. 7, Institute for Scientific Information.

⁴ Pavitt (2000) estimates that the resources devoted to academic research in the life sciences in the U.S. are 50% larger than in Europe.

⁵ For illustration, see Greenacre, 1984, 1993.

⁶ A software package for large network analysis available online at <http://vlado.fmf.uni-lj.si/pub/networks/pajek>. Pajek has been used to analyze multiple types of large networks (Batagelj & Mrvar 2000; Albert, Jeong, & Barabasi, 2000).

⁷ For detail on the Powell-Koput database see Powell et. al. 1996 (pp 124-129) and Powell et. al. 1999 (pp 136-140). For detail on the Owen-Smith database see Owen-Smith 2000a (pp 59-66 and 76-81).

⁸ This data focuses on dedicated human biotechnology firms. Companies involved in veterinary and agricultural biotech, which draw on different scientific capabilities and operate in a much different regulatory climate, are omitted. We also exclude companies that are wholly owned subsidiaries of pharmaceutical and chemical corporations. We do, however, include biotech companies that have minority or majority investments in them by other firms, so long as the company is independently traded on the stock market. Our rationale for excluding both biotech subsidiaries and large diversified corporations is that the former do not make decisions autonomously and biotechnology may represent only a small portion of the latter's activities.

⁹ To accomplish this we use a recent Office of Technology Assessment and Forecasting crosswalk between United States Patent Office subject area classifications and 3 digit Standard Industrial Classification product codes. Patent co-assignment represents shared ownership of intellectual property and, as such, indicates a particularly close and potentially consequential form of inter-organizational collaboration. Co-assignment limits each partner's ability to unilaterally appropriate rents from intellectual property. Thus, it is not a relationship that organizations (especially for-profit organizations) enter into lightly. Co-assignment is common in cases where patents have multiple inventors who are employed by different organizations.

¹⁰ For further details about the PHID, see Riccaboni, 2000, (pp. 9-11 and 31-33).

¹¹ The ATC classification has been developed and maintained since 1971 by the *European Pharmaceutical Marketing Research Association*. The 3 digit ATC designation is a widely accepted standard for classifying pharmaceutical products and is used by anti-trust associations around the globe.

¹² Information on the patents is found in Patent Fast Alert, published by Current Drugs, Ltd., London, U.K..

¹³ In this paper we focus only on the PROs as originators, and do not examine cases where DBFs and EPCs are sources of new research opportunities, or cases where PROs were developers for PRO originators.

¹⁴ Correspondence analysis allows us to deal simultaneously with organizational and scientific profiles of the U.S. and European public research systems. For readers not familiar with dual scaling techniques, it may be worthwhile to notice that correspondence analysis is essentially a variant of principle component analysis tailored to categorical rather than continuous data (Hill, 1974; Greenacre & Hastie, 1987: 437). As with principle component analysis, correspondence analysis does not provide cut-and-dried conclusions, instead it is an explanatory technique which offers a framework for interpretation (Greenacre, 1993: 85).

¹⁵ In order to allow the same interpretation for therapeutic classes in the space defined by research organizations, we rescaled organization scores as suggested in Carroll, Green, Schaffer (1986). As a result, the plots in Figures 3 and 4 that report both institutions and therapeutic categories in rescaled *standard* coordinates are *symmetric* (Greenacre, 1993).

¹⁶ Those six regions contain 14.6% (13) of the universities, 14.3% (24) of the research institutes and hospitals, and 27.2% (131) of the DBFs in our sample. Clearly the aggregate concentration of ties in clusters is a function of their concentration in a handful of organizations. We do not attempt to separate the effects of organizational and geographic concentration of ties here. Instead, we content ourselves with noting their importance for a full understanding of regional and industry development. We treat each of the clusters as coherent units for the purposes of cross-national comparison, but we recognize that each area is itself a complex system of relationships with a core and periphery and a distinctive evolutionary trajectory. The same factors that we expect to effect industry development at the national level also play out within regions.