Cluster Genesis

Technology-Based Industrial Development

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Accounting for Emergence and Novelty in Boston and Bay Area Biotechnology*

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> All happy families resemble one another, each unhappy family is unhappy in its own way.
>
> Leo Tolstoy

Existing studies of innovation and clusters all too often begin with Tolstoy's insight that successful regions resemble one another, while those that falter do so idiosyncratically. This conjecture, however, is rarely an *a priori* proposition. Instead, we suggest it is a substantive artifact of reliance on methods that emphasize comparative statics over analyses that focus on emergence and dynamics.

The San Francisco Bay Area and Cambridge/Boston are the world's largest and most commercially successful biotechnology regions. The attributes and successes of these regions are widely studied and their efforts broadly emulated (Powell et al. 2007). Despite similarities in scale and outcomes, however, each region emerged through a distinctive process that continues to influence its outputs. These variations, in turn, suggest that there are multiple pathways to similar outcomes and offer a corrective to efforts to transpose a 'standard' model of regional innovative success that may never have existed.

Drawing upon a data-set that tracks strategic alliance networks in human therapeutic and diagnostic biotechnology over a twelve-year period (1988–99), we examine patterns in the development of two canonically successful biotechnology clusters in the Boston/Cambridge Massachusetts metropolitan region and the San Francisco Bay Area. We emphasize the extent to which interesting variations in the form and substance of

innovative activity are apparent when viewed with a dynamic lens. Broad similarities in ascendant clusters, we contend, can be outcomes of divergent patterns of development. Moreover, we suggest that these patterned variations can shape the nature of innovations produced by firms.

Regional Advantage and Industrial Development in Biotechnology[1]

We focus on the commercial field of biotechnology, which developed scientifically in university labs in the 1970s, saw the founding of hundreds of small science-based firms in the 1980s, and matured in the 1990s with the release of dozens of new therapeutics. The field is notable for both its scientific and commercial advances as well as for the diverse cast of organizational players—universities and other Public Research Organizations (PROs), government laboratories, Venture Capital (VC) firms, large multinational pharmaceutical corporations, and smaller dedicated biotechnology firms (DBFs)—involved in its development.

In this field, where the sources of scientific and technical leadership are widely dispersed and rapidly developing, and where the relevant skills and resources necessary to produce new medicines are scattered, collaboration among organizations became a necessary component of success. An elaborate system of private governance emerged to orchestrate the interorganizational networks such collaborations constituted (Powell 1990, 1996) and the internal structures and practices of DBFs changed accordingly as firms co-evolved with the networks that characterize the industry.

During the very early years of the industry, from the early 1970s to the late 1980s, most biotech firms were very small start-ups that relied, of necessity, on external support. Lacking the skills and resources needed to bring new innovations to market, they became involved in elaborate lattices of relationships with universities and large pharmaceutical firms (Kenney 1986; Powell and Brantley 1992). Lacking a knowledge base in the new scientific field of molecular biology, large companies were drawn to start-ups by the latter's capabilities in basic and translational science (Galambos and Sturchio 1996; Gambardella 1995). Asymmetries in technological, regulatory, and financial muscle drove early collaborative patterns in the industry (Hagedoorn and Roijakkers 2002; McKelvey 1996; Orsenigo 1989; Orsenigo, Pammolli, and Riccaboni 2001).

Despite arguments that the new field would undergo a shakeout as large pharmaceutical firms developed the technical competencies that would

allow them to assert dominance over weaker small firm partners (Sharpe 1991; Teece 1986), the founding of new firms accelerated. Established firms' efforts to cherry-pick promising new ventures faced significant obstacles imposed by deeply collaborative R&D efforts and a mobile scientific labor force. Instead of consolidation and shakeout, the industry's later years witnessed the give-and-take and mutual forbearance characteristic of relational contracting (Macneil 1978), which became the dominant practice in the field.

By the late 1980s, several biotech firms (e.g. Biogen, Genzyme, Chiron, Genentech, Amgen, and Immunex) had become large organizations and numerous pharmaceutical firms had created in-house molecular biology research programs. Even when mutual need declined as a spur to collaboration, the pattern of dense interconnection deepened, suggesting that the original motivation of exchanging complementary resources had shifted to a broader focus on mining innovation networks to explore new forms of collaboration and product development (Powell et al. 2005).

An analytic story that places networks alone at the heart of biotechnology's development misses an important component of the analysis, however. Despite the evolution of dense and expansive networks, geography played an essential role in the industry's evolution and remains an important feature even today. The networks that now characterize this complex commercial field emerged from distinct geographic roots. Beginning in the Bay Area and Boston, then spreading to other areas, such as San Diego, Seattle, and Bethesda, MD, clusters of biotech firms, VC firms, and PROs forged local networks that reached out as they developed, creating a national industry network from regional origins (Owen-Smith et al. 2002). Yet these regions remain important to understanding conditions in the industry. Evidence is mounting that the network effects that drive much of the action in biotechnology vary with the geographic location of partners (Owen-Smith and Powell 2004; Whittington, Owen-Smith, and Powell 2006). Networks played an essential role in the development of stable regional clusters, but those clusters seeded the geographically dispersed structures that have come to characterize the field. We thus turn to analyses of network connections in the two largest and most successful US biotechnology regions in order to demonstrate that collaborative arrangements help to underpin successful clusters. Those regional communities vary in their character, evolutionary path, and approach to innovation.

We draw upon a data-set of strategic alliance ties involving 482 DBFs and their more than 2,000 partner organizations over the period 1988–99 to

illuminate patterns in the structures connecting regionally colocated biotechnology firms. Data are drawn from *Bioscan*, an independent industry directory published quarterly. We focus on independently operated, profit-seeking entities involved in human therapeutic and diagnostic applications of biotechnology—but omit companies involved in agricultural and veterinary applications as those sectors draw on different scientific capabilities and operate in different regulatory environments.

Our data-set, like the industry it represents, is dominated by US firms, although recent years have seen considerable expansion in Europe. The sample of firms includes both public and privately held firms, and the former include companies with minority or majority investments by other firms as long as their stock is independently traded. Large pharmaceutical companies, investors, government agencies, and PROs enter the data-set as partners that collaborate with biotech firms. We link these relational data to patent grant and citation information for the period 1976–99 drawn from the National Bureau of Economic Research patent citation database (Jaffe and Trajtenberg 2002). In total, there are 10,067 US utility patents issued to the 482 firms in our sample over this time period. Organizations are identified by type and location, which enables us to isolate ties among colocated organizations in two established biotechnology regions.

The San Francisco Bay Area and Boston are well-studied examples of densely connected and intensely innovative regional economies. In our data-set, Boston is home to more than 14 percent of US firms in our sample. Bay Area biotechnology firms account for almost 21 percent of US firms. Together, these regions were issued 51.5 percent of the patents assigned to US biotechnology firms through 1999 and developed 32 percent of all biological therapeutics approved by the US Food and Drug (FDA) administration between 1988 and May 2004.[2] Five of the ten best-selling biotechnology drugs in 2001 were developed by firms in these two regions. Boston and the Bay Area thus represent notable success cases for biotechnology regions.

The Bay Area and Boston Networks

In order to examine the evolution of the Bay Area and Boston networks, we identify all organizations located in the two regions that have contracted with a local biotechnology firm. Our data-set includes four types of formal interorganizational connections and five types of organizations. In addition to biotech firms, we include VC firms, government agencies, large

multinational pharmaceutical corporations, and PROs in the partner sample. These diverse organizational forms are connected by four varieties of contractual ties. R&D connections represent agreements for shared research and development efforts. Finance ties reflect investments in one organization by another. Licensing ties are agreements that transfer the rights to intellectual property across organizations. Commercialization ties include downstream product development activities, ranging from clinical trials to manufacturing, sales, and marketing.

During the period 1988–99, the Bay Area network is the larger of the two, involving 159 organizations (82 biotech firms, 12 PROs—most notably Stanford University and the Universities of California at Berkeley and San Francisco, one government laboratory—Lawrence Livermore Labs, and some 64 VC firms), connected by 243 local contractual ties. The Boston network is home to 113 organizations (57 biotechs, 19 PROS—including MIT, Harvard University, Massachusetts General Hospital, and the Dana Farber Cancer Center, and 37 VC firms), connected by 201 local contractual ties. Neither region was home to a multinational pharmaceutical corporation during this time period.[3] While the regions differ in scale, in the demography of organizational types that occupy them, and in the availability of local VC funds (Powell et al. 2002), both are characterized by organizationally diverse and structurally cohesive networks.

How, then, do the regions differ? Figures 4.1 and 4.2 track yearly changes in Boston and the Bay Area in terms of the distribution of dyads that comprise each region's main network component. The main component of a network is its largest connected subset. In practical terms, the main component represents the largest group of organizations in a structure that can reach one another through network paths of finite length and thus captures the minimal level of connectivity necessary to enable broad information diffusion (Owen-Smith and Powell 2004). Put colloquially, imagine drawing linkages among nodes without ever lifting your pen. These figures paint a very different evolutionary trajectory for the two regions.

The most basic unit of a network is the dyad. In this case, a dyad is a pair of organizations connected by a formal R&D, finance, licensing, or commercialization tie. Figures 4.1 and 4.2 characterize dyads in terms of the types of organizations that comprise them, without regard to the class of activity connecting a given pair. Three types of dyads are possible in these main components: Biotech firms can connect with each other (a DBF–DBF dyad), with PROs such as universities or hospitals (a DBF–PRO dyad), or

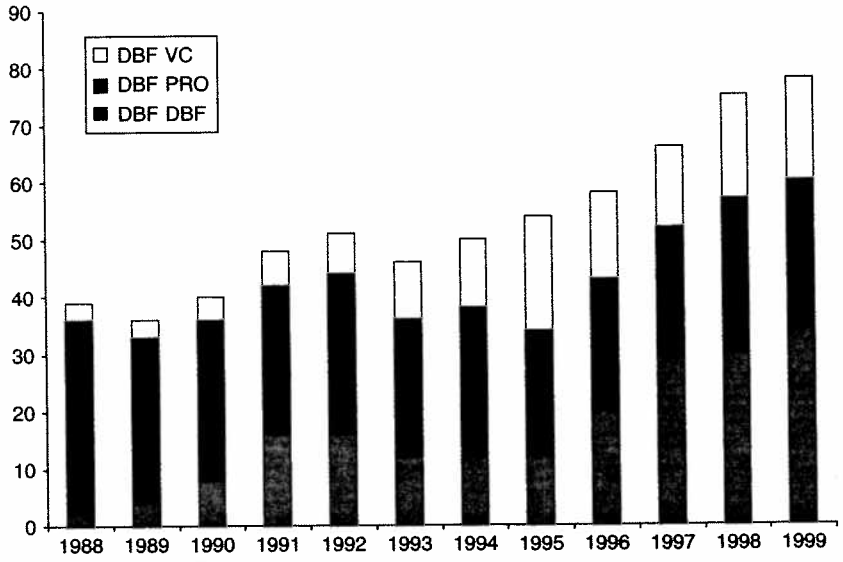

Figure 4.1. Boston main component ties by dyads and year, 1988–99

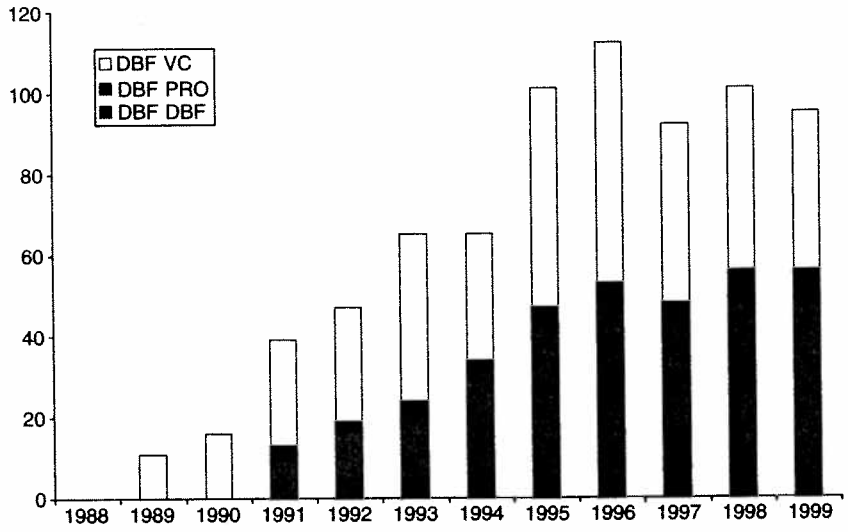

Figure 4.2. Bay Area main component ties by dyads and year, 1988–99

with VC firms (a DBF–VC dyad).[4] In addition to the distribution of dyads, regional networks grow at different paces and in different patterns.

Consider Figure 4.1, which tracks the growth of the Boston network. Note first the pattern of growth in ties (each dyad represents a single tie) implied by the height of the histogram bars. Our data-set begins in 1988, when we find a relatively large number of ties in Boston. The number grows slightly into the early nineties and then levels off for several years before climbing again through the latter years of the data-set. The bars are shaded to represent the relative prevalence of different dyads in the network. Note the bar that represents 1988, which shows a remarkable reliance on PROs. Only a very small number of ties link biotech firms to each other or to local VC firms in 1988 or 1989. These ties grow as the network expands and these commercial connections dominate the network by the end of our time frame.

The Boston network grew from origins in the public sector (Porter, Whittington, and Powell, 2005). Put differently, public science formed the foundation for commercial application (Nelson 1981, 1986). Industries where commercially viable technical advances emerge from the academic and public sector manifest more open technological trajectories than industries that rely more heavily on industrial R&D (Dosi 1982). The Boston biotechnology community is linked by shared connections to PROs early in its evolution. These connections remain an important part of the network, but increasing patterns of DBF to DBF and DBF to VC ties reflect the development of a commercial network that becomes structurally autonomous, while bearing the imprint of the public sector.

Contrast this trajectory with the different pattern illustrated by Figure 4.2. There is no dominant network component in the Bay Area in 1988, though a cohesive network forms in 1989. Unlike Boston's growth pattern, which saw a plateau in the early 1990s, the Bay Area grew markedly through 1996 before stabilizing in the late 1990s. These differences in volume and velocity are matched by very different dyad distributions. During the first two years when a main component existed, the Bay Area community was composed entirely of ties linking DBFs to local VC firms. Where the stability and technical diversity of Boston PROs anchored that network and fostered a more open technological trajectory (Owen-Smith and Powell 2004), the Bay Area relied heavily on the prospecting and matchmaking efforts of venture investors.[5] Later years witnessed the increasing importance of VCs, a smattering of ties involving PROs, and—most importantly—dramatic growth in DBF–DBF connections. By 1999, direct links among Bay Area DBFs outweigh the other two types of dyads.

Both Boston and the San Francisco Bay Area evolved from dependence on a non-DBF organizational form to a state where significant portions of the network were made coherent by direct connections among science-based biotechnology firms. In other words, similar endpoints in the evolution of the networks were reached through different routes. While both relied on the inclusion of organizations different from biotechnology firms, Boston was anchored in the public sector, whereas the Bay Area was dominated by venture capitalists. The endpoints of these trajectories are similar as both regions came to depend heavily on collaborations among ostensible competitors, but their different starting points and the lasting involvement of different partners may have produced distinctive patterns of innovation. Distributions of dyads, however, cannot tell the full story of a network's evolution; hence, we turn to an assessment of the overall topology of the networks.

Figure 4.3 fleshes out differences across the regions with images of the networks in three distinct time periods. These snapshots were generated using Pajek,[6] a freeware program designed for the visualization and analysis of large networks. The relative positions of nodes in these images are meaningful and result from two spring-embedded, graph-drawing algorithms. The first treats a network as a physical system where nodes repel each other and ties act as 'springs' that pull connected nodes closer together (Fruchterman and Reingold 1991). This algorithm moves unconnected nodes to the periphery of the image, and separates components (groups of two or more nodes) from one another. The second algorithm relocates connected nodes so that the Euclidean distances among them are proportional to their graph theoretic distance (Kamada and Kawai 1989).[7] These images, then, are replicable representations where the relative position of organizations is a function of the connectivity of the system and the degrees of separation among nodes.[8]

The shapes of the nodes in Figure 4.3 represent different types of organizations: circular nodes are DBFs, diamonds are PROs, and triangles are VC firms. Tie patterns likewise represent different types of collaborations. Solid black links are R&D ties, dotted black connections represent financial investments, dotted gray are licenses, and solid gray linkages indicate commercialization deals. The width of a given tie reflects the number of connections linking a pair of partners. When multiple ties are present in a dyad, the pattern of the linkage reflects the most recent type of activity. To gain purchase on the differences between the two networks at a given point in time, read across columns in Figure 4.3. To get a sense of the evolutionary pattern within each region, pick a column and read down.

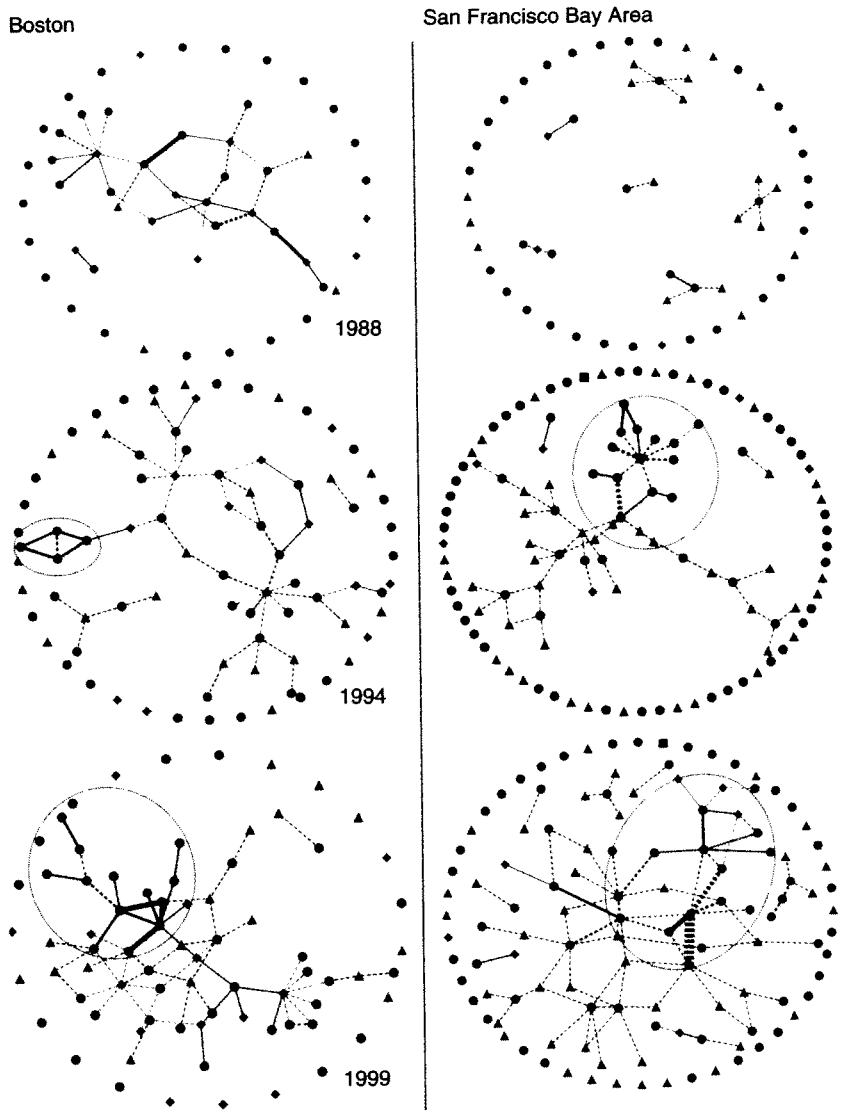

Figure 4.3. Boston and Bay Area networks: 1988, 1994, and 1999

Consider the first image of the Boston region, which bears out Figure 4.1's emphasis on ties between DBFs and PROs. Note the central role played by diamond nodes and the relatively few connections linking circles to each other. The main component of this network stretches across the center of the image; most of the ties are single connections between different types of organizations. Tie types are rather evenly dispersed, but gray (commercialization) and dotted gray (licensing) ties are in the majority. In the region's early years, DBF firms are stitched together into a coherent network by their shared connections to PROs. Harvard, the well-connected diamond in the lower right-hand corner of the image, and MIT, the center of the star in the upper left-hand quadrant, are the primary entry points to the network and their relative distance from each other suggests that the early years of the Boston biotechnology community may have been shaped by different kinds of academic involvement. In related work, we show that while both Harvard and MIT faculty have been active in founding Boston-based biotechnology firms, MIT scientists are much more active patentors, while Harvard faculty serve on more scientific advisory boards (Porter et al. 2005).

The 1988 Bay Area image paints a very different picture as ties in that year did not aggregate to create a dominant component. Instead, the early years of the region appear to be characterized by small clusters of firms connected either to multiple venture capitalists or, less commonly, to Stanford University (the diamond at the center of the three node 'chain' near the bottom of the image) or University of California, San Francisco (UCSF) (the diamond in the dyad—with Genentech, whose founder was a UCSF scientist—near the center of the figure).

The patterns suggested by the visualizations are echoed by careful archival research. In an analysis of the career histories of the founders of biotech firms in the Bay Area and Boston, Porter (2004) finds that Boston companies were often started by MIT and Harvard professors, many of whom maintained their university affiliations. In contrast, founders in the Bay Area were much more likely to come from VC or other biotech firms. Another key contrast was that Boston faculty founders were often senior professors with established reputations. When Bay Area faculty were involved in founding, they tended to be younger and much more likely to take a leave from their university positions. Almost all founders in Boston came from the region, while founders in the Bay Area came from diverse locales. Indeed, east coast faculty—from Yale, Columbia, and Duke—came to California to start companies.

Turn your attention now to the second row of Figure 4.3, which represents the regional networks near the middle of our time series in 1994. The

Boston network has grown, but maintains a reliance on PROs and both Harvard (now at the bottom of the image) and MIT (the well-connected diamond node at the top of the image) remain important players in the network. This image also suggests the growing importance of local venture capitalists (notably in the 'tree' structures that descend from Harvard's partners in the lower quadrant of the image) as well as the salience of DBF to DBF ties. Note the cohesive cluster (outlined by a dashed circle) formed by R&D connections among four Boston firms—Genzyme, Genzyme Transgenics (one of several spin-offs from Genzyme), Autoimmune (whose research tie to the Dana Farber Cancer keeps this nascent cluster attached to the larger network), and Creative Biomolecule. These firms, particularly Genzyme—a large and successful 'first generation' biotechnology company—seed the development of a dense DBF–DBF region in the Boston network.

Compare this view to the image of the Bay Area, whose large main component reflects the dramatic pattern of growth captured in Figure 4.2. This image is dominated by ties linking DBFs (circles) to venture capitalists (triangles). PROs play a minimal role in the network. The single diamond node at the top left is Stanford, which is linked to a young biotechnology firm by a license.[9] Note, however, the robust cluster of (often multiple) DBF to DBF ties outlined by a dashed circle at the top of the figure. This group, centered on Genentech—one of the first and most successful biotechnology firms—and Chiron—another large and established player in the industry—is characterized by diverse and repeated ties that directly link biotech firms to one another. Boston's Genzyme triangle and the Bay Area's Genentech cluster represent the beginnings of a network centered on collaborations among ostensible competitors. The size of these ties relative to those connecting younger DBFs to venture captital firms suggests a process by which newcomers are identified by investors and then linked into the DBF–DBF segment of the network by forging ties with incumbents or their partners. Where PROs are still the entry way and the gatekeepers of Boston in 1994, Bay Area VCs prospect for new talent, and established firms usher promising newcomers into an increasingly connected segment of the network.

These patterns became more robust in 1999, the final year of our data. In both networks the pattern of DBF–DBF linkages expands and deepens (relevant regions are outlined by dashed ellipses) and both sections of the network remain centered on the region's largest and most successful firms (Biogen and Genzyme in Boston and Genentech and Chiron in the Bay Area). Despite the clear emergence of purely commercial portions of

both networks, however, the regions still manifest significant differences. While VC firms are important players in the Bay Area network, they only rarely form multiple connections to the same partner and (as one would expect) their ties are overwhelmingly financial. The field of dotted gray lines in the lower left quadrant of the 1999 Bay Area image exemplifies this trend. VCs play an important connective and prospecting role in this network, but their one-dimensional network portfolios suggest that much of the innovative action may emerge from the dense and multiplex cluster of biotech to biotech ties.

The linkages formed by PROs shrink in importance in the Boston network in 1999 (recall Figure 4.1). This distributional decline, however, masks the continued importance of these research-oriented public sector organizations. Universities, nonprofit research institutes, and hospitals forge repeated (and multiplex) ties to biotechnology firms (evidenced by the thicker connections linking diamonds to circles), and thus play a very different role in the region than do VC firms (the triangles that dominate a small portion of the Boston graph in the lower left segment of the image). Boston PROs remain important structural components of the network, however. Note the diamond nodes at the center of the image (just to the right of the dotted ellipse) that represent MIT and Massachusetts General Hospital. Both regions developed tightly interconnected DBF–DBF commercial networks, but they did so from different starting points and with very divergent types and levels of involvement from non-DBF partners. Though similar on many dimensions, we suggest that these disparate evolutionary trajectories have enduring effects on the nature of innovation in these regions.

The Form and Substance of Regional Innovation

How do varied starting points and evolutionary trajectories leave lasting imprints on regional innovation patterns? We contend that the networks more clearly dominated by 'open' public sector organizations will result in innovations that rely less heavily on internal R&D and that draw more on research conducted in organizations other than biotechnology firms. In short, we expect patents assigned to Bay Area DBFs, a region whose network was always based more on commercial firms, to cite proportionally less non-DBF prior art and to rely more heavily on self-citations than do patents assigned to Boston firms.

We turn to data on citations made by patents assigned to Boston and Bay Area DBFs to examine how regional effects may shape the process of innovation. We begin by presenting information on the R&D outputs of regional firms in the aggregate from 1988–99. We then turn to consideration of shifting patterns in prior art citations by DBF patents. Next we consider the substance of regional innovation by assessing differences in rates of FDA approvals as well as variation on Orphan Drug Indications[10] by region. Finally, we compare the patented innovations underpinning two comparable treatments for multiple sclerosis: Cambridge-based Biogen's Avonex and Emeryville-based Chiron's Betaseron.

The differences in regional scale that we identify are matched by differences in the volume of innovation. Table 4.1 presents a comparison of R&D outputs by region for the period 1988–99. The 82 Bay Area DBFs in our sample generated some 3,800 US utility patents in this time period, which is an average of slightly more than 46 patents per firm. This contrasts dramatically with Boston DBFs' average of slightly more than twenty-four patents per firm. In contrast, biotechnology firms located outside these two regions produced only slightly more than fourteen patents on average, suggesting the relative fecundity of both Bay Area and Boston DBFs.

These output differences also mask a highly skewed distribution of patents within regions. Bay Area outputs are more stratified than those in Boston. The five most prolific Bay Area patentors account for 63 percent of regional patents, while the top five Boston patentors were issued 42 percent of the region's patents. Despite these patterns, patents assigned to regional firms had very similar citation impact. Two-tailed *t*-tests discerned no significant difference between the impact of Bay Area and

Table 4.1. R&D outputs by region, 1988–99

	Boston	Bay Area	Other locations
Number of DBFs	57	82	1,343
Number of patents	1,376	3,806	4,876
Mean citations received (standardized)	1.113	0.979	0.944
Variance in citations received	30.270	14.150	14.493
Number of citations made	12,659	41,389	43,610
Percentage non-DBF cites	71%	55%	68%
Percentage self-cites	12%	35%	11%
FDA approved therapeutics	18	40	89
Orphan indications and products	60	51	109

Boston DBF patents ($t = 0.774$, $p = 0.439$), but did suggest that firms in these regions develop higher impact intellectual property than those located elsewhere ($t = 3.837$, $p < 0.0001$).[11] The similar impact of Boston and Bay Area innovations masks broad differences in the distribution of highly cited patents within the regions. Patents assigned to Boston firms manifest a much higher variance in forward citations than do Bay Area patents, suggesting that Boston firms may more routinely engage in 'exploratory' innovative search, which typically yields a few very high impact patents at the expense of numerous innovations with lower than average future effects (Fleming and Sorenson 2001; Levitt and March 1988). On this view, the Bay Area's lower citation variance is indicative of a more directed and incremental, exploitative strategy, which is what one might expect of firms that are supported by investor networks that are interested in demonstrable progress. Firms that pursue exploitative strategies generally develop numerous related improvements on established components of their research trajectories. Such incremental innovations are less valuable on average than the riskier outcomes of more broad-ranging innovation efforts, but convey important benefits in terms of overlapping ownership rights. Exploitative patents, then, will have lesser variance in their impacts than will patents that result from more exploratory efforts to develop blockbuster technologies.

While impact variations suggest different patterns of search in innovation, prior art citations provide more direct insight into the precursors that firms rely on in developing new intellectual property. Such 'backward' citation data allow us to expand upon the relationship between regional networks and innovation in biotechnology.

Consider two ideal-typical possibilities: First, firms embedded in networks composed largely of competitors and investors are primarily concerned with speed and with commercial development, hence they pursue a more focused innovation process that relies heavily on internal R&D and attention to the efforts of direct competitors (e.g. other DBFs). As they are situated in structures that lack a significant PRO involvement, such firms may be less likely to rely heavily on innovations developed externally. In contrast, firms that are located in networks anchored by PROs and that lack strong investor involvement may feel somewhat less overt pressure to pursue immediate commercial returns.

To the extent that open, public sector research organizations alter the norms that govern information flow within a network, firms in such networks may reach more freely across organizational boundaries in efforts to develop new innovations and their patent citations may evince

less attention to the research efforts of competitors (Owen-Smith and Powell 2004). Again, we stress that these different patterns may reflect divergent time scales. Were we to have full data on Bay Area firms from the 1970s, we might well find patterns of relationships comparable to Boston in the 1980s and 1990s. We cannot rule out the possibility that these regional differences stem from the earlier start and success of Bay Area firms in bringing new medicines to market. Moreover, in their early years, several notable Boston-based firms opted to license their earliest lead products to large pharmaceutical companies in return for royalty payments (Robbins-Roth 2001).

If these two conjectures have validity, we would expect innovations by firms in more overtly commercial networks—such as those in the Bay Area—to rely less heavily on prior art developed by organizations other than DBFs and to rely more strongly on citations to their own prior patents. In contrast, innovations made by firms situated in more open networks dominated by academic and public sector organizations—such as those in Boston—will rely on a broader cross-section of prior art sources and less extensively on internal R&D. Table 4.1 provides descriptive support for these claims.

The 1,376 Boston inventions make 12,659 citations to prior US patents, while the 3,806 Bay Area patents acknowledge 41,389 links to prior art. (An average of 9.2 cites per patent in Boston and 10.9 cites per patent in the Bay Area. Firms outside these regions cite just under nine pieces of prior art per patent.) Similar levels of reliance on prior art, though, mask significant variation in terms of the sources from which precursors are drawn. Patents assigned to Boston firms rely more heavily on non-DBF prior art—a full 71 percent of citations—than do either Bay Area patents, which make 55 percent of their citations to non-DBF prior art, or non-regional patents. In contrast, slightly more than one-third (35 percent) of citations made by Bay Area patents are to their own prior art.[12] Boston firms do cite their own prior art, but at a much lower (12 percent) rate that more closely accords with the overall trend in the industry. In sum, the R&D portfolios of Bay Area and Boston firms rely on quite different sources of knowledge, and these patterns appear to map onto the structure of the collaborative networks in each region.

The form innovation takes, then, is related to the characteristics and trajectories of the networks that support it. While both regions have been quite successful in biotech, and are emulated across the globe, we have shown that their respective origins and paths of development are rather dissimilar. This pattern may continue at the level of market outcomes as

well as patents. To explore this possibility, we draw on FDA approval records to identify the fifty-eight new drugs developed by Boston and Bay Area DBFs. Fifty-three of those medicines were approved between 1988 and 2004. All five of the drugs that appeared on the market prior to that period were developed by two Bay Area Firms—Alza and Genentech. Again, these early approvals reflect the commercialization strategy pursued in a region with a strong VC community.

Eighteen of these products are the work of Boston firms and forty stem from work by Bay Area DBFs. Another 89 therapeutics were developed by the 343 firms located outside these regions, but well-established firms such as Los Angeles' Amgen, Philadelphia's Centocor, and Seattle's Immunex account for much of the action. In terms of market outcomes, the Bay Area appears to be both quicker and more prolific than Boston and both regions represent concentrations of success. This outcome is to be expected given a more commercially focused network and a development-oriented strategy that relies heavily on internal R&D. Indeed, seventeen of the first twenty of these drugs to come to market were produced by Bay Area firms.

These differences in market outcomes, though, are much more suggestive of variations in strategy and focus than competency. Consider another source of information about the development of therapeutics, Orphan drug designations. The 1983 Orphan Drug Act was designed to enable the FDA to speed the development of therapies for rare diseases, and orphan designations offer tax breaks and regulatory assistance to organizations that develop such medicines. One hundred and eleven (111) orphan designations have been approved for Bay Area and Boston firms since 1985 (when the first such approval went to Boston's Genzyme for the drug Ceredase for patients with Gaucher's disease). Both Bay Area and Boston firms make use of orphan designations, but Boston firms, as one might expect for companies enmeshed in networks dominated by universities and hospitals, rely more heavily on indications for relatively rare diseases.

The focus on orphan drugs reflects another difference as well. The Boston-based firms build their product portfolios with an initial focus on smaller markets and medicines that have the added security of orphan drug exclusivity. These medicines, while targeted at relatively small populations, are very much desired by their patient communities. In contrast, Bay Area firms favor medicines for larger markets in which the potential patient population runs in the tens of millions, and for which there is likely to be product competition from other DBFs and major pharmaceutical corporations. This high-risk, high-reward strategy

demands speed in product development, and shows the obvious imprint of the VC mindset.

Descriptive patterns in prior art citations, forward citation impact, and market outcomes are complementary with observed variations in the evolution of the two regional networks. Despite sharing an industry and scientific base, Boston and Bay Area DBFs appear to differ systematically in the substantive focus of their R&D efforts. To further explore these differences in the focus of innovative activity, we turn to a natural experiment and compare the citation patterns for patents underlying two fairly similar biotechnology drugs.

Betaseron and Avonex are competing therapies for remitting and relapsing multiple sclerosis and several clinical trials have directly compared their efficacy. Both drugs began life with orphan designations and both are variants of the biological compound interferon-beta, which differ only slightly in chemical makeup.[13] The processes by which these compounds are produced are also very similar, and rely on Chinese hamster ovaries, though their differences are manifest enough that an infringement lawsuit between Avonex's developer and Betaseron's manufacturer (Biogen vs. Berlex Laboratories) resulted in a judgment of no infringement. Both drugs were approved during the 1990s (Betaseron in 1993 and Avonex in 1996). In short, these two drugs share notable scientific, clinical, and regulatory similarities, but they differ in the physical and organizational location of their development.

Betaseron is based on research done by Cetus, an Emeryville, CA biotech firm that was acquired by Chiron, a Berkeley-based DBF. Chiron did the development work on Betaseron and shepherded the drug through the FDA approval process. Betaseron is manufactured and marketed under an arrangement with Berlex Laboratories, an American subsidiary of the pharmaceutical firm Schering-Plough. Avonex, in contrast is based on research done by Boston-based Biogen who also developed, manufactures and markets the drug. We use FDA-labeling information to identify the patents that underpin these drugs. We then turned to the NBER patent citation database to trace prior art citations by those patents and identify the sources of such prior art. In both instances we trace precursor inventions to three generations. Table 4.2 presents summary data for the innovations underlying these two drugs.

The patterns suggested by Table 4.2 are in line with the overall results in prior art citations by region, and with our expectations based on the evolution of each cluster's network. Betaseron relies on a set of four related patents initially assigned to Cetus (three were reassigned to Chiron

Table 4.2. Innovation data for Betaseron and Avonex, 1988–99

FDA approval date (initial indication)	1993-07-23	1996-05-17
Orphan status	Y	Y
Developer	Chiron	Biogen
Initial patent holder	Cetus Corporation	Biogen
Distributor	Berlex Laboratories (Schering Plough)	Biogen
Initial indication	Remitting and relapsing Multiple sclerosis	Remitting and relapsing Multiple sclerosis
Number core patents	4	1
Number first generation citations	4	14
Number second generation citations	31	32
Number third generation citations	16	108
Total patents (original + 3 generations)	55	155
Number of prior art patents owned by fiduciary firms	6	0
Number of prior art patents from same region	2	4
Number of non-US prior art patents	26	61
Number of shared prior art patents	39	39

Notes: Both intra-region cites for Betaseron are to other Silicon Valley DBFs (Genentech, ICN). The within-region cites for Avonex are to PROs (Mass Gen (1) MIT(2)) and a non-DBF firm (Ionics).

following the merger of the two firms; the fourth, a process patent for producing interferon, was reassigned to Berlex Labs). These four patents cite a small group of prior art patents (4). These four 'first-generation' precursors make another thirty-one second generation citations, which in turn cite a further sixteen pieces of prior art. All told, Betaseron rests on a history of some 55 interlocking patents. Avonex, which is based on a single compound patent, reaches more broadly into the prior art, relying on 155 separate pieces of intellectual property. None of the prior art on which Avonex depends is owned by Biogen. This last finding is particularly telling, as it suggests that Biogen developed its market leading therapeutic without the benefit of a thicket of intellectual property rights (IPRs), relying instead on a mix of partner's intellectual property and public domain science.

Differences in these two citation networks are instructive. Betaseron's underlying IP network includes six patents developed by Cetus. Avonex, in contrast, relies on a single Biogen-owned patent that makes no citations to other intellectual property owned by that firm. While internal R&D was

surely not sufficient to the development of Betaseron, that drug relied much more heavily on a single DBF's research effort than did its competitor. Both innovation networks reach well beyond the regions in which the two firms are situated. Betaseron cites only two patents held by other Bay Area organizations, but it is notable that both are biotechnology firms (Genentech and ICN). The Avonex citation network, in contrast, cites four patents held by Boston organizations, but none by DBFs. Three belong to PROs with whom Biogen has network ties (MIT holds two patents and the Massachusetts General Hospital a third). The fourth belongs to a non-DBF firm, a purification company called Ionics.

While the citation networks are fairly small, comparing these two very similar drugs offers a natural experiment that holds constant important technical, clinical, and regulatory features of biotechnology innovations. Even when such factors are very similar, the patent citation networks underlying these two drugs differ in a fashion that reflects aggregate differences in regional innovation patterns and expectations based on the interorganizational networks that characterize each region. The Bay Area–based drug relies more heavily on internal R&D and on the research efforts of other firms. In contrast, the Boston-based therapy draws on a broader cross-section of prior IP owned by a wider range of organizational types.

Conclusions and Implications

The Boston and Bay Area biotech communities became more similar over the twelve-year period under examination, shedding their respective reliance on PROS and VCs, and developing a strong firm-to-firm component. But these divergent roots have a notable impact on the innovation process. Boston-based companies that relied heavily on external sources of knowledge favored more exploratory efforts at discovery. This signature is captured by our measures of patent volume and impact, and by patterns of patent citations. Bay Area biotech firms were more self-reliant in terms of knowledge generation and more persistent in their efforts to further development of in-house intellectual property.

Similarly, Bay Area firms were faster and more prolific in terms of new product development, as well as more likely to pursue novel medicines for larger markets where they might face stiff competition. In contrast, Boston firms were more deliberative in their commercial strategies and more likely to focus on medicines for identifiable and active patient populations

in need of relief from specific illnesses. Most remarkably, these differences persisted even when we held constant market, scientific, and regulatory factors by examining Chiron and Biogen's approaches to the development of similar treatments for multiple sclerosis. Clearly, the continuing impact of VCs in the Bay Area and PROs in Boston is significant.

We lack data on the early scientific roots of technical advance in the life sciences in Boston and the Bay Area. Perhaps the patterns we have observed are the outcroppings of diverse academic approaches to scientific research in the life sciences. Boston is home to the remarkable institutional combination of MIT, a powerful basic science institution that lacks a medical school, Harvard, another powerhouse institution in basic science whose medical school is located across the Charles River at a considerable remove from the main campus, and a number of research-oriented hospitals and institutes. The upshot of this institutional mix appears to us to be a corporate focus on expansive science and patients. In contrast, the biotech community in the Bay Area has its earliest origins in the 'marriage' of Herbert Boyer, a UCSF scientist, and Robert Swanson, a prominent venture capitalist, who joined together to create Genentech, one of the very first biotech companies.

UCSF is an unusual institution, lacking disciplinary departments and a full panoply of research program and students. The organizational model at UCSF was an interdisciplinary, cross-functional approach to medicine, with an emphasis on translating basic science into clinical application (Varmus and Weinberg 1992). Genentech adopted and refined this interdisciplinary 'team' model, adding the impatience and restlessness of VC financiers and the attendant focus on 'swinging for the fences' by developing products for such major illnesses as heart disease, cancer, and diabetes. Here, an approach to translational R&D pioneered at an elite PRO is transferred by founding scientists to a region's leading firm, eventually becoming a dominant arrangement for the region.

One of the fundamental features distinguishing between the Boston and Bay Area networks is Boston's early and continuing reliance on the region's public sector research organizations. MIT, Harvard, Massachusetts General Hospital, the Whitehead Institute, Dana Farber Cancer Center, and other institutions anchored this network, catalyzed its development, and shaped firm innovation and product development. The imprints of evolutionary patterns, then, are a joint function of institutional roles and particular features that characterize such public sector organizations. In addition to providing stable anchors for networks, universities and hospitals contribute to more open information flows, more expansive

innovative trajectories, and, possibly, more patient-driven product development strategies. In short, PRO involvement is effective precisely because they operate in different environments and under different rules and constraints than their proprietary partners.

In Boston, universities, research institutes, and hospitals—organizations institutionally committed to open information flow, science, and public-health-based business strategies—altered the efforts of Boston firms by maintaining a formal and deliberate role in their region's networks. In short, Boston area PROs altered their local networks using formal contractual arrangements that structure collaboration and the transfer of intellectual property rights. In contrast, Stanford and UCSF's preference for informal, noncontractual ties in their regional network enabled financiers to shape innovative and organizational strategies. The implications are paradoxical: deliberate efforts by hospital and universities to control and shape information and resource flows in networks result in more open and expansive structures, while more informal, 'hands-off' approaches help create networks that are more tightly controlled and commercially directed.

The role that universities play in regional development, then, appears more complicated than a simple model of technology transfer and technical training would suggest. This coevolutionary dynamic suggests important sources of regional variation and also highlights the potential consequences of organizational action in evolving networks. Firm strategies in Boston and the Bay Area bear the characteristic footprints of their most important partners. At the same time, partners are constrained by the activities of local firms.

Consider a brief example. If success in the competitive arena of Bay Area biotechnology depends on early access to venture capital and that access smoothes entry into collaborations with the established firms that are key to innovative and commercial success, then savvy venture capitalists will seek to invest in newcomers whose strategies and arrangements match dominant patterns in the region: the very patterns that VCs' early efforts helped generate and sustain. Not surprisingly, then, Stuart and Sorenson (2003) find that while VC support became abundant in the Bay Area in the 1990s, the odds for success declined. One possible reason is lock in around a dominant model.

The contrast of Boston and the Bay Area, the most prolific biotechnology clusters in the world, should give pause to policymakers who look to successful clusters for models to emulate. Without awareness of underlying institutional variations and distinctive approaches to the development of new medicines, one could easily draw the incorrect inference that

combining PROs, VC, and small firms provides the ultimate recipe for successful economic development. We emphasize that similar approaches may be very deceiving and mask sharp differences in underlying causes of institutional and technical development.

Notes

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1. This section draws upon our earlier work on biotechnology (cf. Powell et al. 2005; Bunker-Whittington, Owen-Smith, and Powell 2005).
2. We base our calculations on approvals for initial indications by the US Food and Drug Administration's Center for Biological Evaluation and Research.
3. More recently, Pfizer and Novartis have moved R&D activities to Kendall Square in Cambridge, MA. The largest biotech firm, Amgen, has acquired a smaller Bay Area firm, Tularik, and created a beachhead in that region.
4. Our data are structured as a two-mode network (Wasserman and Faust 1994) that tracks connections among DBFs and between DBFs and partner organizations. Linkages between non-DBF partners (e.g. PRO–VC collaborations) are exceptionally sparse and thus are not included.
5. This different trajectory may reflect left censoring in the data. If we had comparable data for the Bay Area for the late 1970s and early 1980s, we might well observe important DBF–PRO ties. In particular, we would expect more linkages connecting UCSF and Stanford to local DBFs. We do know that the Bay Area biotech community developed earlier than Boston (Robbins-Roth 2001), hence the direct comparison for the later 1980s and early 1990s may capture a slower take-off in Boston.
6. A freeware program developed by Vlado Batagelj and Andre Mrvar and available for download online at http://vlado.fmf.uni-lj.si/pub/networks/pajek/
7. This distance is a function of the number of 'steps' it takes to traverse a network path connecting a given pair of nodes. Organizations that are connected by a tie are a distance one.
8. For more detail on network visualization using Pajek, see the appendix of Powell et al. (2005).
9. To be sure, this isolation does not imply that Stanford is not active in technology transfer, but at this point in time the bulk of its formal licensing activities are to firms outside the region.
10. An Orphan Indication is conveyed by the US Food and Drug Administration for products that treat rare diseases and thus have little potential to become huge commercial successes. Orphan indications are valuable to firms in that they convey tax breaks and reduced regulatory fees as well as short-term market exclusivity.
11. Forward citations—citations from future patents to current innovations—are a commonly used measure of impact. We standardize citation counts by year and technical class to avoid heterogeneity across time and technical areas (Jaffe and Trajtenberg 2002; Trajtenberg 1990).
12. Despite a greater reliance on self-citations, 65 percent of Bay Area prior art citations are to patents developed outside the firm. The majority of innovative work goes on through networks.
13. Interferon-beta-1a (Avonex) is a recombinant compound whose amino acid sequence is identical to natural interferon-beta. Interferon-beta-1b (Betaseron) in contrast is a recombinant compound that differs from natural Interferon-beta by one amino acid.