Pioneering, variety and entrepreneurial science: the growth of biotech clusters (1978 - 2015)

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Intro

Over a few decades time, biotechnology has evolved from an area of fundamental scientific enquiry into various application areas - from pharmaceuticals/health care to agriculture, food, and materials - with a substantial economic footprint. Moreover, given potential convergence with information technologies, nanotechnologies and other areas of applied science, biotechnology provides a strong foundation for future innovation and growth[1 2 3 4].

As a technical and economic activity, biotechnology displays high levels of geographical concentration in a relatively small number of locations [5]. Successful clusters, characteristically have world-class scientific research, high levels of entrepreneurial activity (both academic spin-offs and industrial ventures), high labor mobility and dense social networks, access to venture capital, and a dedicated support infrastructure geared towards startups and spin-offs [6 7 8 9]. Not only do private firms and entrepreneurs play a prominent role in the development of biotech activities, universities and public research organizations also contribute significantly [10 7 11 12].

Whereas previous studies have provided valuable insights into, and detailed information on, the characteristics and dynamics of biotech clusters, they typically cover one or a small number of, geographical regions within a specific time frame, or phase of development. Large-scale, longitudinal, empirical studies addressing the features of biotech clusters are lacking. To address this void, we performed an in-depth longitudinal analysis of the technological performance of biotech regions on a global scale by creating a dataset that includes biotechnology patent applications filed over nearly 40 years (1978-2015) and scientific publications in the field of biotechnology published over the period of 1998-2015.

The use of patent and publication data has several advantages [13 14]. In the absence of globally comparable data on the number, nature and economic impact (e.g., employment, added value) of biotechnology-enabled processes and products, patent and publication indicators provide a reasonable proxy to R&D output (innovation) and reveal the scale of activity in specific emerging fields [15] [16] [17] [18]. Moreover, patent and publication data provide validated and reliable information on the time and location of technological and scientific inventions, as well as the organizations and institutions involved. Furthermore, patent and publication data have global coverage and allow a field-specific perspective.

For this study, we retrieved all the triadic patent families in the field of biotechnology filed between 1978 and 2015. Triadic patents are defined as patent families consisting simultaneously of American, European, and Japanese patent applications (or grants). Working with triadic families avoids the introduction of home biases of applicants and as such allows for a comparison of the technological performance of regions on a global scale [19]. Biotechnology patents were identified based on the classification of OECD [3] [20]. Together, the 25 countries with the largest number of biotech patent applications (Table 1) applied for 133,193 patents which represent 98.6% of the total triadic patent applications in the field of biotechnology during the period of our study.

Next, biotechnology publications were extracted from the Web of Science Citation Index Expanded database based on a set of journals assigned to subject categories related to biotechnology (biochemical research methods, biochemistry and molecular biology, biophysics, biotechnology and applied microbiology, microbiology, cell biology, genetics and heredity, and developmental biology).

All addresses of patent applicants and publication authors located in the top 25 countries have been geo-coded and allocated to their respective regions. Table 2 lists, for every country, the regional level of analysis selected in this study. We also identified which type of actor (private firms, universities, governmental agencies and non-profit organizations, hospitals, and medical centers, and/or persons) owns the patent or is involved in the publication [21] [1]. Within the biotech dataset, 78% of patents have been filed by companies while for biotech scientific publications, universities account for 83% of all publications.

The evolution of biotechnology (clusters)

The overall evolution of triadic patents in biotechnology from 1978 to 2015 is shown for North America, Europe and Asia-Pacific in Figure 1. In the early phase of the biotech industry (1978-1993), the number of patent rose steadily, followed by a substantial growth in the number of patents between 1993 and 2002. The rate of patents started to decrease in 2002, attributable to the completion of the Human Genome Project in 2003, as well as the public debate on genetic engineering generally and, more specifically, on the patentability of genes [22]. The subsequent tightening of national rules for granting patents on genetic material resulted in an overall drop in genetic and biotechnology patents [23]. Although, worldwide, North America[2]. accounts for the largest fraction of total patent applications (48%), more

[1] The identification of the type of actor is based on the name and address information on patents and publications, and follows the sector allocation method developed at ECOOM, Expert Centre for R&D Monitoring, KU Leuven.

[2] In 2001, the USPTO started to release/publish also application documents, resulting in the presence of triadic patent families including USPTO applications only. We assessed whether this change in publication policy affects our indicator/dependent variable for certain regions in a systematic manner.

recently, the proportions of patents across world regions are starting to converge, as a consequence of processes of diffusion and catching up [24]

Looking at regional patenting activity, biotechnology is strongly concentrated within a few regions (Table 3). Over the period 1978-2015, the three largest biotechnology clusters are, Southern-Kanto (Tokyo, JP), Northern California (US) and Massachusetts (US), which together account for nearly one-fourth (24%) of all biotech patent activity. In Asia-Pacific, the region of Southern-Kanto accounts for 45% of the continent's triadic patents, whereas Northern California and Massachusetts account for 17% and 12 % of all North American triadic patents respectively. Europe counts several high-performing biotechnology clusters, notably in Switzerland (Nordwestschweiz (Basel), Région lémanique (Geneva)), in France (Ile de France (Paris)) and in Germany (Baden-Württemberg (Stuttgart)). On average, the United States have 20 of the top 50 regions per period. In Europe, Germany, Switzerland and the UK have the largest number of regions with high technological performance in biotech. Among the Asian-Pacific countries, Japan has the highest number of biotech top regions. As of 2000, the capital region of South-Korea enters the top 25 region rank, while Singapore substantially increased its number of biotech patents in the most recent period, entering the top 50 in 2010-2015.

Table 4 lists the top applicants of biotech patents, over the period 1978-2015. Overall, the top is dominated by incumbent firms active in pharmaceuticals (11), biotechnology (3), chemicals (2), food (1) and medical devices (1). However, also 7 universities and (public) research organizations rank in the top biotech applicants. Roche (Switzerland), an established pharmaceutical company, is leading the ranking with 2,486 biotechnology patents. The second-largest applicant is Harvard University located in Massachusetts, followed by the pioneering biotechnology firm Genentech (since 2009, also part of Roche) located in Northern California.

Looking over time, it is striking to observe that 17 out of the (current) top 20 regions had already obtained the status of top 20 biotech region during the early days of biotech (period 1978-1989). At the same time, several regions display a remarkable growth path (e.g., capital region (Seoul region), South Korea; Bayern, Germany; Région Lémanique (Geneva region), Switzerland, whereas others are in relative decline [e.g., Hessen, Germany, Indiana, US, London, UK). Hence, we conducted a multivariate analysis to reveal which regional characteristics coincide with (regional) technological performance.

Multivariate analysis

Within this analysis we include only regions that developed a substantial amount of biotech activity over the period 2000–2015[3]. The dependent variable is the total count of triadic biotech patent families per region per year[4], lagged with one year. The explaining variables are

ANOVA analysis whereby world region and/or country act as independent variable, do not reveal any indication of a systematic bias in this respect.

[3] Only regions with a minimum of 80 triadic patent families over the period 2000-2015, i.e., on average five patent families/year, are included in the analyses.

[4] We use full patent counts in the case of multiple assignees within different regions.

described in Table 5 and relate to the texture characteristics of regions. Descriptive statistics and correlations are presented in Appendix, as well as the results of the negative binomial regression with robust standard errors clustered at a regional level[5].

The multivariate analysis reveal a strong 'pioneering' effect for the performance of regional clusters: being a top biotech region in the emergent phase (1978-1990) still relates positively to the region's technological performance three decades later.

With respect to the involvement of firms, two important insights emerge. First, the contribution (share) of firms in regional technological development is statistically significantly associated with technological performance of regions (see Figure 2) whereby for a vast majority of (top) regions significant contributions from other types of actors (notably universities and (public) research organizations become visible as well.

Second, this positive contribution of firms cannot be confined to the presence (share) of a dominant anchor tenant firm. As figure 3 reveals, top regions display an average share of the dominant firm in regional biotech patenting around 20% (and below 30%). Together these findings do not support the 'anchor tenant' hypothesis (i.e., regions will benefit distinctively from the presence of one strong player in the region) for *biotech* regions: top regions benefit from technological activities shouldered by a variety of market oriented, actors.

Variety can also be observed regarding the contribution of science. Whereas both scientific quantity and quality relate positively with the technological performance of regions, also the contribution of firms to science is associated positively with growth. In addition, we find that regional technological performance is positively associated with the *technological* orientation of local universities. In terms of the scientific orientation of patents, the overall science intensity of local technology is shown to have a significant and positive relation to technological performance while we do not find any additional effect in terms of relying more on local science (the share of local non-patent references (NPR's)).

Finally, in terms of collaboration, we highlight some findings related to university-industry collaborations that are positively and significantly associated with technological performance. To this purpose, we created variables indicating whether local firms (universities) collaborate with universities (firms) situated within the region, country or abroad, based on patents (collaboration in technology) and publications (collaborations in science) with multiple applicants / publishing organizations. We find that local university-industry collaborations in technology development are not associated with higher levels of technological performance of the regions; rather, our findings provide evidence that collaborations that connect organizations beyond the region/cluster – both in technology as well as in science - have a positive impact on the region's technological performance.

Conclusions

In this study, we analyze the growth of biotech regions (clusters) on a global scale over a timespan of nearly four decades. The following implications emerge.

[5] Robustness of our findings have been tested and confirmed via various alternative model specifications, including variants where the number of triadic patents in biotechnology (independent variable) is weighted by the forward patent citations received on a fixed 5-year time window (Hall, Jaffe, and Trajtenberg 2005[5]).

First, while the literature on first mover advantages informs us that first mover advantages should not be taken for granted at the level of specific products (based on novel technologies) and even firms [25] [26], we show that at the *regional* level pioneering has a long and lasting impact: our analysis reveals that the impact of early investments in an emerging field like biotechnology spans across more than three decades.

Second, both the quantity and quality of the science do matter, even during the more mature stages of the industry. As such our findings complement the observations advanced by Zucker [27] on the importance of start scientists for biotech firm formation . While these scientific activities are mainly shouldered by universities and research institutes, our findings underscore the positive and additional effect of firms actively contributing to the scientific frontier. Furthermore, the results highlight the relevance of exploiting scientific findings in technology development as well as the entrepreneurial orientation of the scientific actors themselves. The results of our study emphasize the varied and multifaceted contribution of science to the technological growth of regions in science-intensive industries such as biotechnology.

Third, our findings point to the relevance of networks with partners situated *outside* the region/cluster. While studies on clustering of (high tech) economic activities focus mainly on local interaction patterns and innovation texture characteristics, our analysis underscores the importance of complementing this localness with a tangible connectivity to more comprehensive national, and especially international, actor networks [2812, 29]. Hence, the notion of (international) gatekeepers advanced by Allen [30] presents itself as highly relevant for cluster performance, in line with Burt's [31] work on the importance of structural holes for firm growth and survival. Our research adds to the insights on the role of international gatekeepers by extending the individual level networks that have been documented in the gatekeeper literature to institutional level networks spanning sectoral and regional/national boundaries in the market translation of scientific endeavors.

Finally, our findings convey a comforting message for regions which are not heavily populated by large, incumbent (multinational) firms. While firms are essential to grow the field, becoming a world-leading region (in biotechnology) does not critically depend on the presence of one anchor tenant (firm). This finding resonates with previous studies that have shown that a variety of (bio)entrepreneurial firms are at the origin of cluster formation [32] [33] and hence are important drivers of sustainable regional innovation systems in a global (life science) economy [34]. Policies aimed at supporting firms when investing in (uncertain) research and development efforts thus should target a variety (and multitude) of beneficiaries, entrepreneurial initiatives, and medium/larger sized companies alike, without neglecting the existential contribution of a vibrant, excellent, internationally connected, and entrepreneurial science base.

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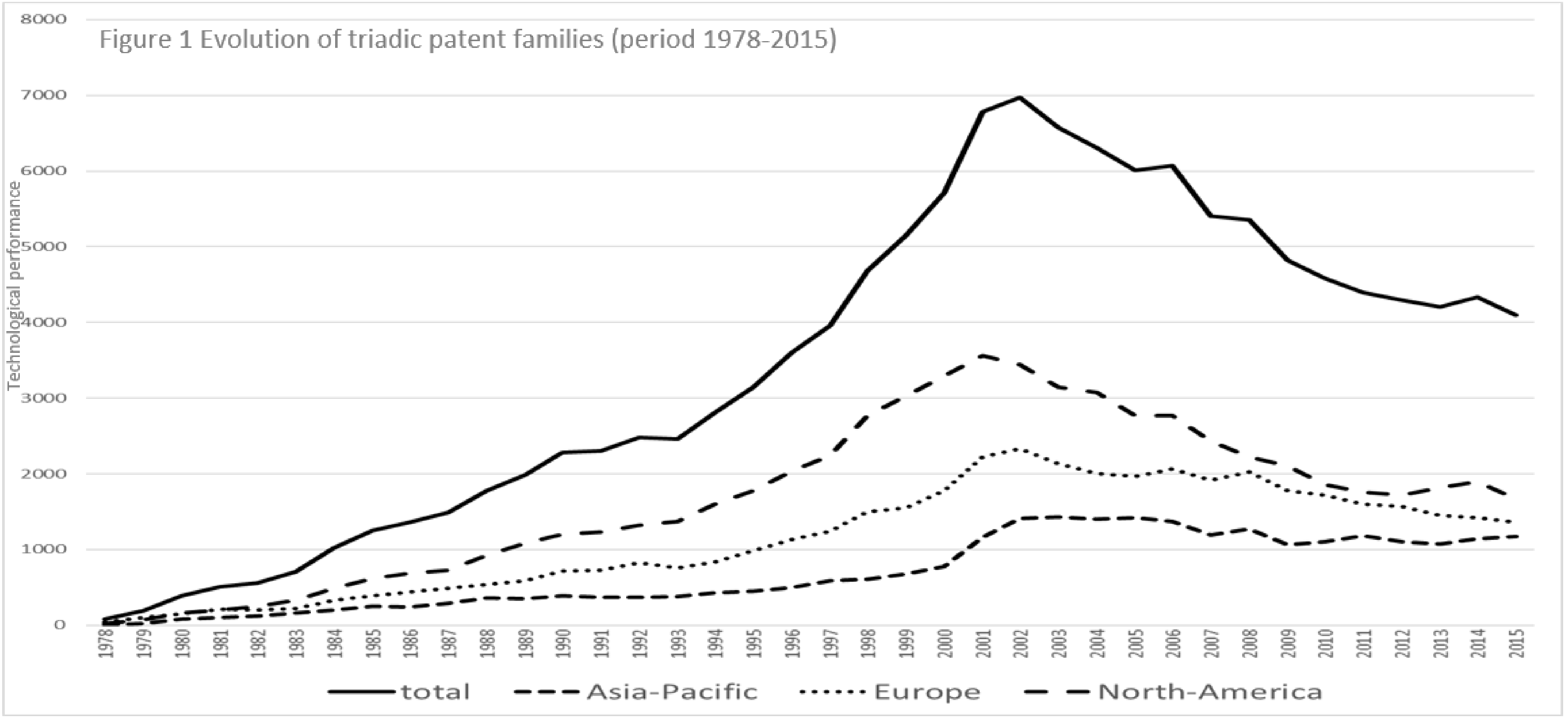
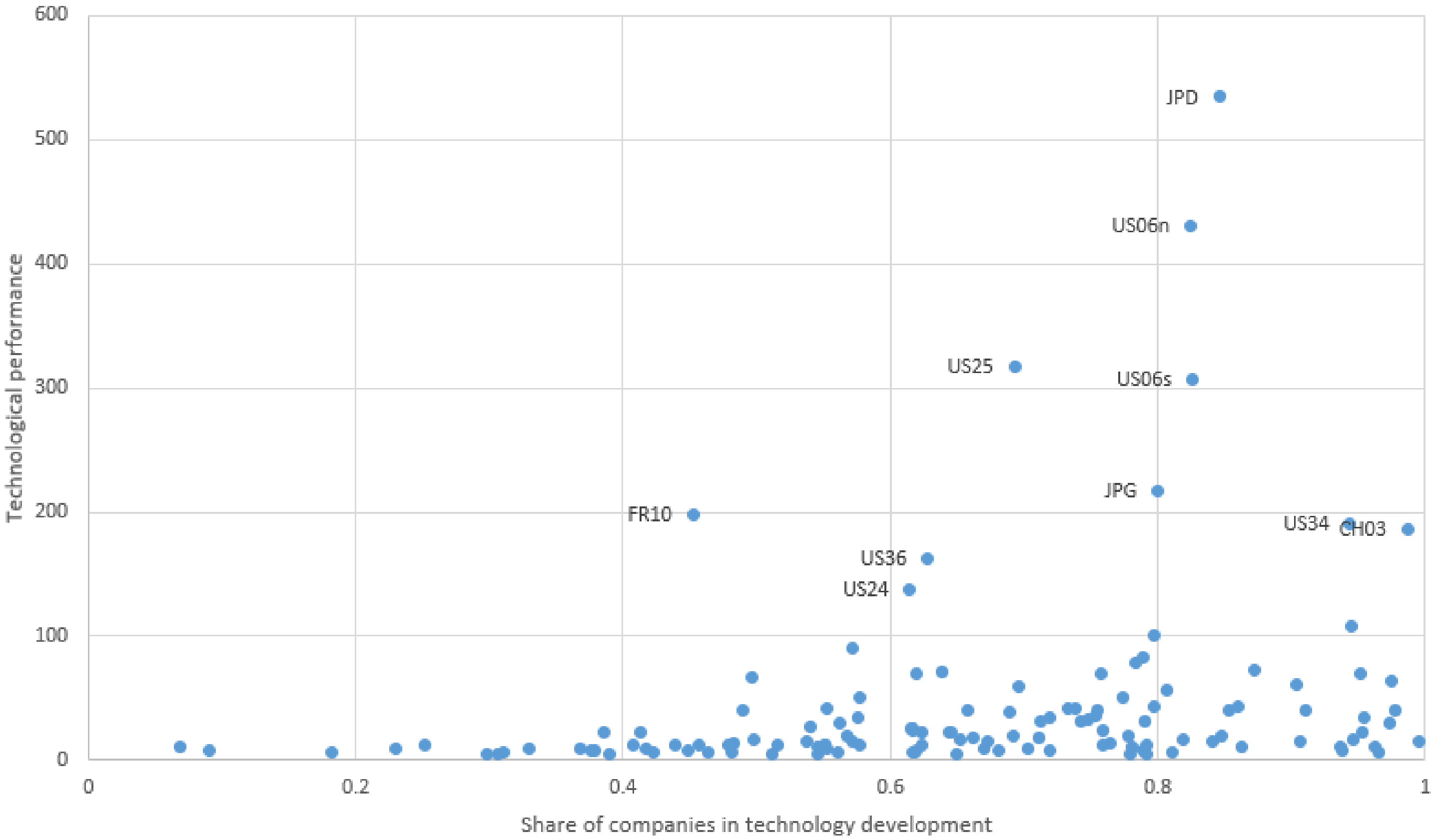


Figure 1 Evolution of triadic patent families (period 1978-2015)
Technological performance
8000
7000
6000
5000
4000
3000
2000
1000
0
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
total
Asia-Pacific
Europe
North-America

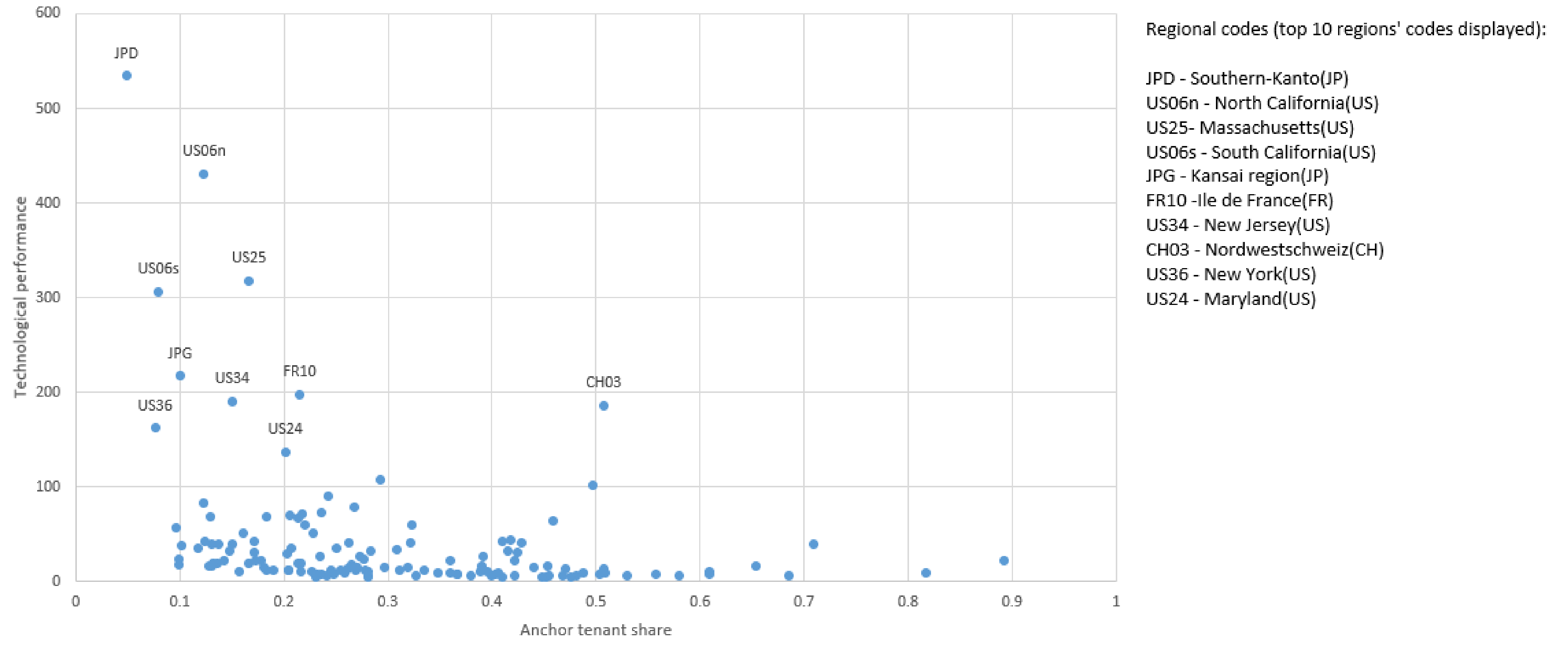
Figure 2: share of company-owned patents by region, (average value for the period 2000-2015)



Regional codes (top 10 regions' codes displayed):

JPD - Southern-Kanto(JP)
US06n - North California(US)
US25- Massachusetts(US)
US06s - South California(US)
JPG - Kansai region(JP)
FR10 -Ile de France(FR)
US34 - New Jersey(US)
CH03 - Nordwestschweiz(CH)
US36 - New York(US)
US24 - Maryland(US)

Figure 3: share of anchor tenant (dominant company) by region, (average value for the period 2000-2015)



	Variable names	mean	s.d.	min	max	1	2	3
1	Regional technological performance	45,62	81,47	1	702			
2	Top 20 biotech region in 1978-1990	0,25	0,43	0	1	0,48		
3	Share of dominant firm (anchor tenant)	0,31	0,22	0,006	1	-0,23	-0,22	
4	Share of companies in regional technology development	0,66	0,25	0	1	0,2	0,24	-0,17
5	Technological orientation of local universities (university patenting)	0,01	0,02	0	0,28	0,12	0	0,04
6	Contributions of local firms to science (firms' publications)	0,05	0,05	0	0,37	0,33	0,25	-0,05
7	Share of local non-patent references	0,12	0,15	0	1	0,03	0	-0,06
8	Science intensity of local technology (building on scientific references)	0,39	0,21	0	1	0,04	-0,01	0,06
9	Science quantity/science intensity of the region (publication count)	0,34	0,29	0,002	1,56	0,03	0,17	-0,01
10	Scientific quality (citations to publications)	9,75	2,46	2,13	1,9	0,23	0,21	-0,1
11	Share of all collaborations in tech	0,18	0,19	0	1	-0,12	-0,17	0,07
12	Share of all collaborations in science	0,66	0,11	0,19	0,9	-0,1	-0,06	0,04
13	Share of local university-industry collaboration in technology	0,08	0,19	0	1	0,08	-0,05	0
14	Share of national university-industry collaboration in technology	0,16	0,26	0	1	0,18	0,04	-0,07
15	Share of international university-industry collaboration in technology	0,07	0,2	0	1	0,07	0,07	0,04
16	Share of local university-industry collaboration in science	0,01	0,01	0	0,07	0,34	0,26	-0,22
17	Share of national university-industry collaboration in science	0,04	0,03	0	0,2	0,23	0,16	-0,11
18	Share of international university-industry collaboration in science	0,03	0,02	0	0,22	0,14	0,2	0,04
19	Population	15,28	0,93	12,67	17,94	0,37	0,17	-0,31

4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
-0,23														
0,24	0,16													
-0,08	-0,06	-0,1												
-0,12	0,04	-0,01	0,18											
0,11	-0,2	-0,06	0,12	-0,02										
0,11	0,01	0,18	-0,1	-0,06	0,29									
-0,5	0,08	-0,15	0,13	0,13	-0,07	-0,13								
0,04	-0,14	0,03	0,01	0,05	0,26	0,1	0,14							
0,05	0,11	-0,01	0,05	0,07	-0,04	-0,02	0,12	0,06						
0,15	0,08	0,09	0,04	0,05	-0,11	0	0,12	0,01	0,4					
0,28	-0,09	0,2	-0,01	-0,03	0,17	0,07	-0,09	0,03	-0,07	-0,09				
0,29	-0,13	0,26	0,17	0,07	0,2	0,02	-0,14	0,16	0,05	0,06	0,12			
0	0,21	0,55	-0,08	0,04	-0,36	0,08	0,03	-0,14	0,02	0,16	-0,08	0,02		
0,36	-0,07	0,58	-0,09	-0,13	0,31	0,32	-0,25	0,16	-0,06	-0,04	0,33	0,28	-0,04	
-0,04	-0,02	-0,05	0,02	0,02	-0,48	-0,03	0,03	-0,22	0,11	0,18	-0,13	0,08	0,23	-0,31