
Explaining spatial patterns of innovation: analytical and synthetic modes of knowledge creation in the Medicon Valley life-science cluster

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Abstract. The authors address the dichotomy around ‘proximate’ and ‘distant’ learning processes by looking specifically at the characteristics of the knowledge-creation process. By way of suggesting an alternative conceptualization to the well-known tacit–codified knowledge dichotomy, they propose a distinction between ‘analytical’ and ‘synthetic’ modes of knowledge creation. Analytical knowledge creation refers to the understanding and explaining of features of the (natural) world. Synthetic knowledge creation refers to the design or construction of something to attain functional goals. By applying this framework to qualitative empirics from the Medicon Valley life-science cluster, the authors demonstrate the complementarity of globally distributed analytical knowledge creation and locally oriented synthetic knowledge creation.

1 Introduction

The geography of innovation is one of the main topics addressed by economic geographers in recent decades (Scott, 2000). The subdiscipline builds on an extensive research tradition, ranging from Marshall’s early work on the innovative capacity found in industrial districts (Asheim, 2000) to the more recent work on the creative class (Florida, 2002). Many studies have dealt with the beneficial effects of proximity in enhancing processes of interactive learning and innovation between economic agents by virtue of trustful relations between various actors, easy observation, immediate comparison, intensified face-to-face interaction, and short cognitive distance (Malmberg, 2003). Eschewing universal explanations it is, however, important to note that these beneficial effects take various forms and produce dissimilar outcomes for different types of sectors (Asheim and Coenen, 2005; Oinas and Lagendijk, 2005; Weterings, 2006).

According to Cooke (2005), the life-science industry is characterized by ‘open innovation’. The concept of open innovation originated in the business literature and maintains that, in a world of increasingly complex and widely distributed knowledge, companies cannot afford to rely entirely on their own research but should, instead, source knowledge ideas from other companies or research organizations locally as well as nonlocally (Chesbrough, 2003). However, it does not specify that such knowledge is not equally available to all actors, as size and power of companies as well as the presence of regulatory intellectual property right regimes will determine accessibility. As a result, innovation is unevenly distributed across the global geographical landscape. It is a well-known assertion that the life-science sector exhibits a strong concentration in a handful ‘megacentres’ (Cooke, 2004), such as San Diego, Boston, Cambridge, and Munich. In such places, typical cluster advantages are available based on commonalities and complementarities, offering nearby local learning relationships

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between related actors. At the same time, global network connections are indispensable for novel knowledge creation and innovative activities. This has resulted in a local node–global network geography of innovation (Gertler and Levitte, 2005).

Even though it is broadly agreed that agreement can be found in the notion that localized and nonlocalized learning are complementary processes which enhance, rather than erode, each other, there is still considerable discussion concerning the underplayed or overplayed role of geographical proximity in facilitating learning processes (Amin and Cohendet, 2004; Morgan, 2004). Whereas the existing body of knowledge on clusters and regional innovation systems provides an established explanatory framework for concentration tendencies (Maskell and Malmberg, 1999), global learning processes which operate between and across different scales tend to be less closely researched and less clearly conceptualized (Bunnell and Coe, 2001). In this paper we seek to address the dichotomy concerning ‘proximate’ and ‘distant’ learning processes by looking specifically at the characteristics of the knowledge-creation process. How are spatial patterns of innovation in biotechnology related to the characteristics of the knowledge-creation process itself?

The remainder of the paper is as follows. Section 2 describes the spatial patterns of knowledge collaboration observed in the life-science industry of the Swedish–Danish cross-border cluster of ‘Medicon Valley’. We ‘map’ the spatial patterns of innovation of one of the main actors in life-science clusters—dedicated biotechnology firms (DBFs). However, the data provide no explanation for the patterns observed. Therefore, a shift towards a more intensive research design (that is, case analysis) is required, with particular focus on the actual content of the knowledge collaboration. Hence, explanations for the patterns are sought through intensive, qualitative studies of innovation projects carried out in Medicon Valley. Section 3 introduces the conceptual framework which we applied in the case studies. With inspiration found in previous work by Asheim and Gertler (2005) on industrial knowledge bases, we aim to develop further the notions of analytical and synthetic knowledge bases through a detailed discussion of different modes of knowledge creation and their spatial implications. The conceptual framework was developed through a combination of theoretical reasoning, readings of the innovation literature, and in-depth studies of innovation projects of ten biotechnology firms in Medicon Valley. Two representative but contrasting case studies of innovation projects in Medicon Valley are reported in section 4 to concretize and corroborate the claims made in section 3.

2 Medicon Valley—spatial patterns of innovation

Since the 1970s, when the fundamentals of modern biotechnology were explored,⁽¹⁾ the number of possible life-science applications—both in pharmaceuticals and in the agrofood sector—has increased dramatically. Fierce innovation-driven competition, mainly evolving around new product varieties, requires specific skills in very complex procedures which are hard for large pharmaceutical and food companies to manage completely in-house (Cooke, 2005). Hence, they have become increasingly dependent on specialized, research-intensive DBFs as well as universities and other (public)

⁽¹⁾ Even though biotechnology has a long history (for example, fermentation processes have been used in the food and pharmaceutical industries for several decades), the ‘new biotechnology’ applications (which is what is meant by ‘biotechnology’ in this paper) took off in a dramatic way during the 1990s. In particular, recombinant DNA, based on findings by Stanley Cohen and Herbert Boyer in 1973, and monoclonal antibodies, developed by Georges Kohler and César Milstein in 1975, offer key fields of applications. In the second half of the 1990s the number of ‘new biotechnology’ applications in life science has exploded, which can be seen not only in growth in total activity, but also in the numbers of actors.

research organizations (PROs) to acquire and absorb knowledge (Nilsson, 2001). As a consequence, life-science innovations are often organized in cross-functional project teams, involving several (company as well as university) partners. The spatial organization of these teams often includes local as well as nonlocal collaborators. By organizing activities in projects, (potential) spatial and hierarchical barriers can be transcended, making knowledge exchange and innovation more effective (Söderlund, 2005; Zeller, 2002).

These stylized arrangements can be found in Medicon Valley. Historically, various big pharma corporations have had important parts of their corporate networks located in and around Copenhagen (for example, Novo Nordisk, Lundbeck, and Ferring) and in Southern Sweden (for example, Pharmacia and AstraZeneca in Lund). Moreover, there is a strong and dedicated research and development (R&D) infrastructure employing approximately 6000 life scientists (Cooke, 2005). The first biotechnology activities emerged in Scania through spin-off companies from Lund University during the 1980s (for example, BioInvent). Denmark shortly followed suit with the creation of Neurosearch by researchers working at Novo Nordisk and Ferrosan. Ever since, there has been an impressive growth in the number of DBFs: fifty-five new firms have been established since 1998 and now, in 2006, there are approximately 130 DBFs in Medicon Valley. The majority of these DBFs focus on pharmaceutical applications. Recently, applications in functional foods have also started to emerge. The spatial patterns of knowledge collaboration among DBFs in Medicon Valley is presented in table 1.

The patterns observed through this extensive research design display strong similarities with other global life-science nodes in Europe as well as in North America (Gertler and Levitte, 2005; McKelvey et al, 2003; Zeller, 2004). The indicators clearly show the importance of local as well as nonlocal collaboration. Local partners seem to be most frequent in knowledge collaboration that results in patents (78%), whereas half of all collaborations in scientific publications were built on a nonlocal partnership (52%). The spread of formalized partnerships shows that both localization and globalization effects are operating. In addition to this secondary data-based mapping, personal interviews were conducted with research managers of ten DBFs in Medicon Valley. The purpose of these interviews was to discuss the findings of the surveys and to obtain access to information about informal collaboration which the DBFs may be involved in. From the interviews it was found that: (1) firm–firm collaboration in basic research is rare—most research collaboration is with PROs; and (2) informal collaboration

Table 1. Relative share (%) of partners (by location) involved in knowledge collaboration with 109 dedicated biotechnology firms in Medicon Valley. The material has been used as proxies for previous and ongoing knowledge collaboration between the actors listed (sources: company webpages, annual reports, Science Citation index, and United States Patent and Trademark Office).

Type of collaboration	Location of partners in collaboration ^a								Total	Absolute numbers
	MV	North America	Rest of EU	UK	Other SE	Other DK	Asia	Other		
Formal partnerships	28	33	21	10	4	1	1	3	100	218
Scientific publications	48	10	18	6	8	7	1	3	100	1397
Granted patents	78	3	10	1	3	1	1	3	100	977

^a MV—Medicon Valley; Other SE—other parts of Sweden; Other DK—other parts of Denmark.

exists, but to a very limited extent. Nearly all collaboration is formalized by contracts at a very early phase. The findings presented in table 1 roughly map the pattern of knowledge collaboration for Medicon Valley DBFs. But on a substantial level they give no *explanation* of the spatial patterns of innovation. To address this question, in-depth studies of specific innovation projects, which allow for an unpacking and analysis of the knowledge interplay between actors, the role of their competence profile, and the spatial implications of this, are applied. The following section presents a conceptual framework for such an analysis.

3 Modes of knowledge creation—a conceptual model to explain spatial patterns of collaboration

The most common way to analyze the relation between knowledge characteristics and the effects of location on innovation has evolved around the question of whether knowledge is codified or tacit. The more articulable knowledge is, the easier it is to standardize, codify, and transmit via journal articles, project reports, and other tangible media (Feldman, 2000). The dominant argument regarding the spatial aspects of this has been that the more codified the knowledge, the less space sensitive these processes tend to be. If the knowledge is tacit, such interaction and exchange is, it is argued, dependent on spatial proximity between the actors. However, even if codified knowledge can be transferred almost frictionlessly over time and distance, it relies on tacit knowledge embedded in people and organizations in order to be understood and applied (Nightingale, 1998). This also pertains to the importance of absorptive capacity as an important determinant for spatial patterns of innovation (Giuliani, 2005). The binary argument (tacit–local versus codified–global) can therefore be criticized as a restrictively narrow understanding of knowledge and learning (Håkansson, 2005; Johnson et al, 2002) and of the spatial implications (Bathelt et al, 2004; Gertler, 2004). Hence, there is clearly a need to go beyond this simple dichotomy. One way of doing this is to take more explicit account of the content of the actual interactions that take place in networks of innovators (Archibugi et al, 1999).

In suggesting an alternative conceptualization, in this paper we make a distinction between ‘analytical’ and ‘synthetic’ types of knowledge creation. The distinction takes specific account of the interplay between actors and the knowledge that is created, transmitted, and absorbed in this process. Asheim and Gertler (2005) have recently introduced this distinction to explain different geographies of innovation for different industrial sectors, classified into different types of ‘knowledge base’. They argue that a synthetic knowledge base dominates in industries where innovation takes place through the usage or novel combination of existing knowledge whereby a common social and institutional context is considered a prerequisite for interactive learning processes. An analytical knowledge base, on the other hand, prevails in economic activities where scientific knowledge is highly important, and where knowledge creation is often based on formal models, codified science, and rational processes. Against this background, Asheim and Gertler argue that knowledge spillovers occur first, fastest, and most readily within established local social networks of scientists. In this paper we build further on this initial work by unpacking learning processes *within* one industry—in this case biotechnology—by referring to the different acts of ‘analysis’ and ‘synthesis’. ‘Analysis’ refers to the understanding and explanation of features of the (natural) world. ‘Synthesis’ refers to the designing or construction of something in order to attain functional goals (Simon, 1969). Analysis typically belongs to the realm of natural science, whereas synthesis typically belongs to engineering. Both these modes appear in most industries, with different intensities, in different phases of product/process development. In the following they are explained further.

3.1 Synthetic knowledge creation

Following received wisdom from the philosophy of science, an epistemological distinction can be identified between two more or less independent and parallel forms of knowledge production: ‘natural science’ and ‘engineering science’ (Laestadius, 2000). Johnson et al (2002, page 250) refer to the Aristotelian distinction between, on the one hand, “*epistèmè*: knowledge that is universal and theoretical” and “*technè*: knowledge that is instrumental, context specific and practice related”. The latter corresponds with the rationale for synthetic (or integrative) knowledge creation. Innovation, understood here as the design and construction of human-made, functional systems shaped as tangible and useful artifacts and technologies, stems mainly from applying or (re)combining existing knowledge in a novel way. Often these systems consist of numerous components, materials, performance constraints, and interactions, which make them analytically intractable (Pavitt, 1998). An example of this is modern automobile manufacturing. Broadly, this consists of three major systems: the body; components; and engines and transmissions (Dicken, 1998). For the overall performance of the car, it is important that these systems operate in a synchronized way. In turn, these systems can be disaggregated into smaller but related systems such as the braking system, the steering system, the engine system. It is important that engineers who are improving various aspects of the car’s performance know how the various subsystems influence each other, rather than knowing exactly how these systems function in detail. Also, the disciplinary base is typically heterogeneous rather than singular. To construct a car, for example, knowledge is needed which can be classified as aerodynamics, mechanical engineering, electronic engineering, etc. This collides with a too-strong reliance on theory-led deduction, the typical mode for knowledge creation in natural sciences. Instead, to deal with the messy reality of engineering practice, knowledge creation relies on trials and tests based on parameter variation (that is, induction), drawing on tools from various disciplinary fields. In the words of an engineering practitioner:

“We construct and operate ... systems based on prior experiences, and we innovate in them by open loop feedback. That is, we look at the system and ask ourselves ‘how can we do it better?’ We then make some change, and see if our expectation of ‘better’ is fulfilled” (Kline, 1995, page 63).

Given that the aim of synthetic knowledge creation is to develop complex, technical systems, the focus of the knowledge-creation process can often be boiled down to concrete, technical problem solving. Less glamorously, this can sometimes even be called ‘muddling through’ (Pavitt, 1998). In terms of R&D activities, synthetic knowledge can sometimes take the form of applied research when more fundamental questions need to be resolved in order to make the technical system perform better. A more common activity, however, is incremental product or process development related to the solution of specific problems presented by users and customers. It is in this context also that the user-centred innovation approach has found popular acclaim (von Hippel, 2005), drawing attention to the importance of user – producer interaction. The cognitive model of technical change suggested by Nightingale (1998) is useful to break down the aforementioned technical problem solving into a stylized set of steps. It starts with a set of beliefs based on previous design experience, which are then used by the engineer(s) to recognize similarity between problems, which is followed by testing the proposed solution; on the basis of which improved designs can be assessed. Such practical experimentation is a trial-and-error process involving success and failure. In practice, failure probably occurs more frequently than success, and, if not more, is at least equally valuable as a resource for knowledge creation and innovation (Thomke, 2003). Because of this strong experiential dimension, tacit knowledge is important for synthetic knowledge creation. Furthermore, although engineers and designers also use

mathematical theories and scientific laws, as do scientists, these differ substantially from the scientists' perspective as such theoretical tools are device specific and often have little universal explanatory power or scientific standing (Vincenti, 1990).

Translated into Lundvall's (1998) knowledge taxonomy, the primary type in synthetic knowledge creation is technical 'know-how'. This refers to concrete skills and capability to design and construct something that works: the artifact should fulfill the function for which it is designed. This corresponds in an inherent way with the operational principle in engineering practice: as long as the system or product works, the actual mechanisms and causal relations underpinning it ('know-why') are of secondary importance. Know-why, in the form of principles and laws of nature, can thus be helpful, but approximate rules of thumb can serve the purposes of functionality and performance equally well. An example of this can be found in beverage production. When brewing beer, the fermentation temperature required to convert yeast into alcohol depends on the type of beer desired (for example, ale or lager). A detailed explanation for the required temperature in terms of its chemical mechanisms is not really necessary: the temperature is often decided based on variation and testing in practice.

The outcome of synthetic knowledge creation is highly tangible and concrete. Ultimately, it is intended to result in artifacts with use value. These artifacts vary extensively in their technical complexity: generally, the larger the functional system is, the more interrelated are its respective elements. This imposes limitations on the degrees of freedom in the design of the system. One needs only to think of the immense complexity of a modern aeroplane to imagine the degree to which its individual parts are compounded and intricately connected. The initial result of synthetic knowledge creation is, therefore, often a technical blueprint which serves as a codification of the knowledge which describes (but does not necessarily explain) the functioning of the system and its components on paper. A crucial step in the engineering process is the translation of this blueprint into an actual artifact, a prototype. This process often reveals the practical shortcomings of the design which were not anticipated in the blueprint (and which originate from the fallible understanding of the technical system) and is thus considered a painstaking step in synthetic knowledge creation. Subsequently, the prototype is tested and adjusted (the aforementioned technical problem-solving process). When the prototype is able to stand the practical tests, it is taken into production which, in turn, creates new engineering challenges.

3.2 Analytical knowledge creation

Analytical knowledge creation is geared towards understanding and explaining natural systems by the discovery and application of scientific laws. In contrast to synthetic knowledge creation, such application is not aimed at producing artifacts but, rather primarily at generating new knowledge about natural phenomena, possibly (but not necessarily) to acquire certain functions at a later stage. In other words, the knowledge itself is often the outcome of the knowledge-creation process. A very illustrative example of this is the development of antibody-based drug candidates. This is seen as one of the future fields of growth within modern pharmaceuticals (Nightingale and Martin, 2004). The basic idea behind antibody-based treatment is to use natural functions of the human body to affect other natural functions of the human body. By understanding the mechanisms by which cells or proteins (antigens) harm, causing, for example, cancer, inflammatory diseases, or HIV, researchers have been able to develop a method to block these by using the mechanisms of naturally evolved molecules (antibodies) which can recognize and eliminate the antigen (Brekke and Sandlie, 2003). The rationale behind this type of knowledge creation is not to arrive at new

combinations of existing knowledge, or the creation of a functional system but, rather, interpretation of an existing system by unraveling its structure and mechanisms. The system itself—the antibodies—are left unchanged. What has evolved is the knowledge about the system and the knowledge about how to use it for new purposes. After its causal mechanisms have been revealed, the system can be modified or, put differently, a new system can be created. Another example following the same rationale is nanotechnology. But here, instead of deducting from existing systems of living organisms (for example, cells, proteins, human molecules), nanotechnology focuses on an even smaller scale—atoms. By understanding the role and function of “the basic building blocks of matter” (Roco, 2003, page 181), nanotechnology can create ‘tiny machines’ by re-placing the atoms into new structures. In explorative experimentation conducted in the controlled conditions of laboratories, trials and tests are primarily used with the aim of validation/falsification of knowledge, as described by one of the founders of a Swedish biotech firm dealing with antibody-based drug candidates:

“You start with theory. You create theoretical models with a reasonable potential to succeed in practice ... or put differently, you *believe* it will succeed. You then take it to the lab to test if it works. If it doesn’t work, theory is useless. Then you have created a castle in the air, and those exist frequently but are seldom reported ... there are many ideas just disappearing that way.”

On the other hand, if it works, theory is confirmed and the aim is fulfilled—new knowledge has been created. Analytical knowledge creation hence often starts with well-known basic scientific principles and methods, and moves towards more or less unknown end results (Nightingale, 1998). In Lundvall’s (1998) knowledge typology, know-why is superior in importance to know-how. Systems cannot be decomposed and interpreted only on the basis of knowledge about how they work: detailed knowledge of why they work in that way, and what the causal mechanisms are, is needed to identify the structure of the systems and the parts constituting it. This was confirmed by several research managers at Swedish biotech firms who have experienced major breakthroughs in the lab. These breakthroughs are of limited use if the causal mechanisms, the know-why, remain unknown: in this case the main product, the new piece of knowledge, remains missing.

The importance of know-why makes basic scientific research crucial for the knowledge-creation process. In this light, science comprises the practice of active exploration and codifying of patterns in the behavior of nature (Nightingale, 1998). Mathematics and explorative experimentation are important tools in the codification of these patterns into a consistent order (scientific facts, laws, and mechanisms). This process is not a linear one but involves multiple feedback loops (for example, through laboratory experimentation or peer interaction). Science is a continuous interplay between these patterns and its scientific representations.

“When patterns are subjected to tests and found to pass they are reinforced and when they fail they are rearticulated, which itself may entail the further testing of underlying assumptions” (Nightingale, 1998, page 695).

Knowledge-creation activities here are much more formalized than in synthetic knowledge creation.

The high degree of formalization and rationality makes codified knowledge highly important. This is further accentuated by the fact that the products are often intangibles. When the product is the knowledge itself, documentation is necessary for coworking. This does not mean that tacit knowledge is of no importance: all knowledge always has a tacit dimension which distinguishes it from pure information (Johnson et al, 2002; Nonaka and Takeuchi, 1995). Whereas information consists simply of data, knowledge also involves cognitive structures which can assimilate the information and put it into

context and make it useful (Howells, 2000). Moreover, a set of conventions is needed to speak the same universal scientific ‘tongue’. Kuhn (1970) refers to this as the “disciplinary matrix” (page 182), consisting of formal components or representations (for example, $E = mc^2$), commitment to beliefs in particular models (for example, that molecules of a gas behave like tiny elastic billiard balls in random motion), subscription to certain values (for example, the accuracy of predictions), and, finally, the well-known Kuhnian paradigms (for example, quantum mechanics).

It should be emphasized that the above descriptions of analytical and synthetic modes of knowledge creation refer to conceptual ideal types: in reality, innovation processes will involve elements of both. Apart from being heavily industry specific, it can be suggested that the degree to which (elements of) one mode of knowledge creation dominates is related to the actual stage and activity in the innovation process. Moreover, the dominance of one mode of knowledge creation arguably has different spatial implications for the knowledge interplay between the actors involved. A summary of the conceptual framework is given in table 2.

Table 2. Summary of conceptual framework.

	Synthetic knowledge creation	Analytic knowledge creation
Most commonly found in	Engineering (knowledge that is instrumental, context specific, and practice related)	natural science (knowledge that is universal and theoretical)
Refer to	designing or constructing technological (functional) systems	understanding and explaining features of the (natural) world
Important knowledge type	know-how	know-why
Characteristic activities	systems design, problem solving, fine tuning, testing in practice	laboratory-based experimentation, scientific discourse

4 Two modes of knowledge creation in life science

In this section we aim to concretize and substantiate the theoretical arguments presented above by reporting from two case studies, representing two different types of life-science applications, on which the conceptual framework was employed. While the first case, drug development, represents a typical illustration of biotechnology in a pharmaceutical context, the second case, functional food, belongs to the application of biotechnology in the food sector. Various aspects of the projects were taken into consideration in order to arrive at a more fine-grained analysis of the innovation trajectory against the framework of analytical and synthetic modes of knowledge creation. Explicitly taking a longitudinal perspective, the following dimensions are discussed: scope and purpose of the project; the range of actors involved and their competencies; communication patterns in the project; and achieved outcomes. Based on these analyses, conclusions vis-à-vis the spatial implications are discussed in the final section.

4.1 Drug development

This case is constructed around the development of antibody-based drugs targeting the Tat molecule. The Tat molecule plays a central role in HIV infection as it facilitates transcription of the viral genome, influences neighboring cells, and suppresses the immune system. This malign function could be diminished through a functional blockade of the Tat molecule by the use of antibodies. This would have great value in treatment of HIV, and could produce a potential ‘blockbuster’ on the pharmaceutical market.

The project, owned by BioInvent International AB, is currently in clinical trials phase I/II. During the course of the project, different partners in Sweden as well as abroad have collaborated with BioInvent.

It would be wrong to regard the project as a direct quest for a cure for HIV. Unpacking its complex history and following the steps leading to this application clearly show the iterative nature of the development trajectory of this project. The initial scientific work underpinning the commercial project has been in progress since the early 1990s, and encompassed a much broader focus than HIV treatment. It started as a typical academic project, with no specific commercial application. The work was initiated by a research group at the Department of Immunotechnology at Lund University. The department has established a good reputation in the area of immunotechnology and, particularly, in the subfield of monoclonal antibodies. In line with analytical knowledge creation, the initial driver for these researchers was clearly scientific curiosity—rather than thoughts on commercial applications. As described by one of the researchers involved in the early phases of the project:

“There was much pleasure and joy, like children drawing projects ... we wanted to create something new, something beautiful.”

Nonetheless, at the same time, they realized that there might be a useful (and commercial) application of their work in the future, and this gradually became clearer as the scientific work progressed:

“I don’t want to sound highfalutin’ and say that we wanted to save the world, but we definitely wanted to create something that mattered to someone in some diffuse future. Actually we started this in 1992 as an academic project, and we worked on it for 3–4 years until we realized that what we had created was damn good, probably the best there is at the moment. So we started to discuss how to pass it into some kind of commercial organization.”

What they had explored was a technique for the identification, selection, and reproduction of human antibodies. In 1995 they took these findings to BioInvent for further development and commercial exploitation. The technique was embodied in an application referred to as an ‘antibody library’, named n-CoDeR, which today constitutes the technological platform upon which most of BioInvent’s activity rests. This development clearly shows how the main rationale for knowledge creation had evolved from an initial ambition to understand natural mechanisms within the human body (typical for analytical knowledge creation) towards the creation of a functional system in the shape of a medical treatment (typical for synthetic knowledge creation).

In the early phase of scientific exploration most of the work was conducted by a group of three key researchers. Much of the initial progress and creative groundwork was established through face-to-face brainstorming among these three. Someone presented an idea, it was scrutinized by the collective scientific experience, and subsequently given more solid form allowing further exploration. The idea was often based on previous experiences from scientific work (theoretical knowledge, laboratory experiences, conference visits). As the ideas took more solid form a project was formally set up, engaging PhD students and postdoctoral workers who worked intensively on validation and further development of the findings. Several publications in *Nature Biotechnology* and other top-ranked scientific journals came out of the project. After some years, these findings were taken outside the controlled conditions of the academic laboratory and brought into the company with the aim of making them applicable in an industrial context.

As long as the project remained in academia, and was characterized by analytical knowledge creation, the process was functionally integrated among the project partners. Each researcher could more or less grasp the whole picture. When the project was

taken over by BioInvent, it evolved more towards development (synthetic knowledge creation), which meant that the different areas became more separated and divided between various specialist competencies. Even though the project followed a master plan to develop new drugs, progress sometimes occurred through unforeseen contingent circumstances. The development of the project specifically towards an HIV (and not, for example, cancer) application was in fact a result of such an unexpected opportunity. The Director of Technology Application at BioInvent was looking for targets and presented the n-CoDeR technology at a scientific conference. In the audience was a researcher from New Jersey who, at that time, was looking for antibodies to his recently discovered target Tat. After the conference, the New Jersey researcher contacted BioInvent and presented his idea to the company and they found that Tat would be a perfect application for n-CoDeR. However, it is important to note that it was not by pure coincidence that they met, as they were both members of the same scientific community, and both had a specific purpose in attending that particular conference. The collaboration was mutually beneficial. The New Jersey researcher was a crucial resource for BioInvent, partly because he owned the rights to exploit the Tat molecule, and partly because he had specialized knowledge in HIV biology which BioInvent needed. Similarly, BioInvent was a crucial resource for his further striving towards a solution of the HIV puzzle, because they had tool that could actually carry out the selection of candidate antibodies, a process which would otherwise, by means of established techniques, have been impossible to undertake. Furthermore, they had the commercial skills and capital necessary to bring the application to the market.

BioInvent in-licensed the Tat-molecule and applied it to n-CoDeR in search of suitable antibodies. Up to this phase, the development had been very much a matter of applying scientific principles and methods, both in the development of n-CoDeR (by BioInvent) and in the exploration of Tat (by the New Jersey researcher). However, now the process also became a matter of using the n-CoDeR and, through selection, finding an antibody that could bind to and block the Tat molecule. To illustrate the trial-and-error nature of this, the current project manager describes this process as a kind of fishing:

“You mix the protein [that is, the Tat molecule] with a collection of antibodies in a test-tube, and then you use a kind of magnet to extract the protein, and the antibodies that can bind to the protein are extracted with it. You then clean it from everything else a couple of cycles, refining the criterion and thereby minimizing the selection until you only keep the best antibodies. Finally you end up with some 10000 antibodies that you screen until you find the optimal.”

Of course, this screening process requires solid theoretical knowledge, but hands-on experience from the lab is as important. Know-why is needed to make the right choices with regard to selection criteria, and know-how is absolutely crucial to the conduct of the actual screening. This phase could, hence, be described as a combination of analytical and synthetic knowledge creation. The selection and screening process (that is, the synthetic part) was to a large extent an internal endeavor within Bioinvent. Global linkages were involved through the relation with the New Jersey researcher, particularly for the interpretation of results and choice of selection criteria (that is, the analytical part). Much of this last communication was handled by e-mail and other information and communication technology (ICT)-powered equipment, reducing the need for meetings between the company and external partners to a couple of times a year.

As regards the Tat application, an antibody was selected in 2003, and brought to preclinical tests in collaboration with the Swedish Institute for Infectious Disease Control at the Karolinska Institute in Stockholm. This collaboration is partly commercial

and partly academic. BioInvent was obliged to outsource the trials to an organization with laboratory facilities approved for HIV experimentation. Because the Karolinska Institute is regarded as a world leader in the field of HIV research, the choice was easily made; considerations of geographical proximity were not taken into account. For the Karolinska Institute the collaboration was primarily of academic interest, as it provided opportunities to publish for the researchers. As regards the content of the exchange, it was foremost a matter of codified knowledge. BioInvent delivered the materials that needed to be examined and the Karolinska Institute conducted the studies, wrote the reports, and delivered the data back to the company. These data were eventually analyzed by the company, though sometimes the Karolinska Institute, the New Jersey researcher, or researchers from the Department of Immunotechnology at Lund University were engaged as advisors in interpreting the results. Following highly formalized protocols, this phase of development is best described as analytical knowledge creation. The preclinical tests were successful, allowing the company to proceed with clinical trials. Currently, clinical trials phase I/II are being carried out in collaboration with the Chelsea and Westminster Hospital in London.

4.2 Functional food

This case concerns the development trajectory of Proviva, the first, and so far only, probiotic functional food in Sweden. In addition to our own research based on interviews, data from company webpages, and annual reports, we draw on the original work by Lagnevik et al (2003) which provides a detailed description of the innovation trajectory.

A 'functional food' is defined as food with added ingredients for which scientific evidence of positive health effects can be demonstrated. In other words, it is a hybrid form between nutrition and a pharmaceutical. The Proviva product line consists of dairy and fruit drinks to which the bacterial strain *Lactobacillus plantarum* 299v has been added, which improves the bacterial flora in the human bowel system. Among other effects, reduced flatulence has been documented. Proviva is formally owned by Sweden's second-largest dairy company, Skånemejerier, but it has been developed through the collaborative efforts of researchers at Lund University and the Swedish DBF Probi AB.

Even though Probi and Skånemejerier are the main actors which have brought Proviva to the market, its history started in the 1980s with academic research conducted at Lund University and Lund University Hospital. A group of researchers with a disciplinary spectrum that involved surgery, food technology, and applied microbiology were involved in a project to develop a fermented nutrient solution that could be administered by tube and which reduced the risk of leaking from the gut after surgery. The main questions that the researchers (and their staff) needed to deal with concerned to how to make the technique 'work': for example, which nutrient profile and bacteria would be best to keep the intestines functioning; how to arrive at a stable mixture; and what effects could be expected in the patients' intestines. Even though aim of the research was carried out completely in the academic domain, the aim of the research was heavily geared to medical application (typical for synthetic knowledge creation). Moreover, the various dimensions of the problem at hand necessitated combined competences from various scientific and technological areas. In addition to several doctoral theses at Lund University, the project resulted in a successful patent application concerning the bacteria in the product and the manufacturing process.

Building on the successful initial interdisciplinary collaboration, two key researchers in the medical project decided to also find and develop an application of the bacterial strain in commercial food products. But in order to bring such a probiotic functional

food successfully to market, the researchers realized that they needed a partner from within the food industry. Therefore, they approached a well-known serial entrepreneur of knowledge-based firms in Southern Sweden in order to approach and negotiate with larger food companies. Initially the idea was received with much scepticism by most food companies, but eventually a long-standing personal relationship between one of the researchers and the R&D manager at Skånemejerier ensured that a suitable industrial partner was found. Skånemejerier is a medium-sized dairy company with an annual turnover of approximately €270 million. It employs about 800 people (Skånemejerier, 2004).

Lacking the economies of scale of its major competitors, the company's competitive strategy is specifically aimed at healthy products and well-being. Against this background there was, arguably, sufficient support for the collaboration with the probiotic researchers. The researchers established Probi AB in spring 1991, and in 1992 Skånemejerier acquired 25% of the shares. Another important role in matching the two companies was played by the science park Ideon in Lund, as it provided the meeting place (literally) for the two companies. The collaboration between the two companies was organized by means of a product-development group whose task was to launch a commercially feasible dairy product containing *Lactobacillus plantarum* 299v. Probi's first managing director describes the strength of the collaboration as follows:

“It has been fun to create something completely new in the food industry. Skånemejerier and Probi could serve as a role model for the kind of collaboration researchers and industry should have. In Probi we know everything about biotech and medicine but not much about the market, production or taste quality. Skånemejerier is an expert in these areas and also has the advantage of offering direct distribution to the retail store (Wikström, 2000).

At this stage of Proviva's development trajectory, most focus was on the transformation of production in the laboratory to industrial-space production. There was a clear division of labor: Probi provided the mix of bacterial strains contained in an oat broth, and Skånemejerier carried the main responsibility for the final consumer product and the industrial production process. Important criteria in product development were issues concerning taste and function. The inherent oat flavor of the bacterial mixture was considered a real handicap to consumer acceptance. Drawing on typical engineering competences, product developers at Skånemejerier managed to hide the oat flavor by use of a rosehip and blueberry 'fruit soup'. Such fine tuning is a synthetic mode of knowledge creation. Despite the clear division of labor, it was considered essential that both partners have face-to-face meetings to discuss (and taste) outcomes of their combined industrial experiments. To quote the current R&D manager at Probi:

“[crucial for the collaboration with Skånemejerier has been to] bounce around ideas and possible solutions, to draw on the blackboard: what shall we do, which components should be included in the product, which ones do we think serve important functions.”

Employees from both companies collaborated intensively together at a local production plant in Southern Sweden which, according to the current Quality Assurance (QA) Manager (previously directly involved in research and product development), was a necessary precondition for success. Probi had the research experience and scientific knowledge, which food engineers from Skånemejerier could complement with practical reflections often unacknowledged by researchers. Despite their different educational and professional backgrounds, the communication between the researchers and engineers was relatively frictionless—even when dealing with complex issues. This was, according to the QA manager, largely thanks to good personal relations, where “both parts are open for new ideas and we can talk easily.”

Apart from making changes in the functional component of Proviva (that is, the oat broth containing the bacteria) in response to constraints posed by the industrial production process, Probi also took the lead in safeguarding health claims. These are highly important, not only for regulatory purposes but also to bolster consumer acceptance as scientific documentation constitutes a core characteristic of functional foods. During the 1990s positive health claims were corroborated through a number of doctoral theses and clinical studies conducted at Swedish research centers. These served as documentation aimed mainly at medical doctors, dieticians, and nutritionists. Helped by beneficial media attention, Proviva had a successful product launch in 1994 in Sweden. After that, international export markets in Finland and the United Kingdom were targeted. An important factor for the successful introduction of the product to foreign markets was the scientific certification and support by national researchers and physicians. Hence, Probi and Skånemejerier were forced to collaborate with foreign research and analysis centers. Moreover, an international scientific reference board was established to safeguard scientific quality. This phase displays strong similarities with the highly formalized preclinical and clinical trials of the drug-development project, and can hence be described as a typical example of analytical knowledge creation. Collaboration in this phase was easily handled at a distance, as the communication predominantly involved the exchange of laboratory test results and reviews of scientific papers. Another milestone for the product has been the formal certification to carry the brand 'functional food' in 2004. The certification was provided by the Swedish Nutrition Foundation, for which the product was tested by a team of experts from the Netherlands, Sweden, and Denmark.

The collaboration between Probi and Skånemejerier concerning Proviva was not a one-off event; it resulted in sustained cooperation around functional foods. The basics were, however, put in place through the success of Proviva and its success in creating synergy between two firms that operate in two quite 'distant' industries. Moreover, it served as a source of inspiration and as a role model for future activities for both companies. Probi has continued to offer specialized knowledge and competence in developing and producing bacterial cultures for partners in the food and nutrition supplement industry (for example, Danone and Institut Rosell), and Skånemejerier has recognized the need to access knowledge alliances with small knowledge-intensive, firms to facilitate product innovation related to positive health concepts.

5 Conclusions—spatial implications

In this paper we have addressed the question of how spatial patterns of biotechnology innovation are related to the characteristics of the knowledge-creation process to explain proximate and distance learning and innovation processes in regional clusters. A distinction has been made between analytical and synthetic modes of knowledge creation. In short, the difference boils down to knowledge creation necessary to understand and explain features of the natural world (analytical) as opposed to knowledge creation to design and construct something to attain functional goals (synthetic). An explanation of the importance of both local and global knowledge collaboration in a life-science cluster (as demonstrated for Medicon Valley in section 2) can be found by taking this distinction into account. Analytical knowledge creation tends to be less sensitive to distance decay facilitating global knowledge networks as well as dense local collaboration. Synthetic knowledge creation, on the other hand, has a tendency to be relatively more sensitive to proximity effects between the actors involved, thus favouring local collaboration. The case-based empirical illustrations show, however, that concrete innovation projects consist of a mix of analytical and synthetic modes of knowledge creation, resulting in a potentially more fine-grained picture.

Both the drug-development and the functional-food projects were initiated in the local academic milieu. The drug-development project found its genesis in the ambition of a set of specialized researchers at Lund University to understand a natural phenomenon, namely, the behavior of antibodies. Subsequently, the researchers involved decided to take their findings into a more applied context by developing a platform technology for the identification, selection, and reproduction of human antibodies. For this purpose they in-licensed the invention to a local spin-off DBF. Complementary global knowledge relations were, however, also of major importance. The project evolved specifically towards the application of antibodies as a treatment for HIV through the collaboration with a firm based in New Jersey which possessed unique competences in this area. Nonetheless, it is important to specify the actual content of this global collaboration as being heavily based on analytical knowledge creation, whereas synthetic knowledge creation was coordinated and carried out within the boundaries of the firm. Nonlocal public research organizations were also involved to conduct preclinical tests and clinical trials, scientifically analyzing the behavior of the drug in nonhuman as well as human systems. In contrast, the functional-food project was aimed at the development of an application right from the start. But, similar to the drug-development project, the initial project partners were exclusively set in the academic environment of Lund University, although drawing on a broader disciplinary origin. By virtue of close personal connections, a local collaboration partner was found when the technology was taken from a medical application context into the context of food production. This product-development collaboration was heavily facilitated by allowing for face-to-face collaboration in hands-on experimentation. Distant partners were, however, needed to conduct clinical trials—especially when foreign export markets were targeted. Tables 3 and 4 provide a stylized overview of the main stages in the innovation trajectories. These figures clearly show that innovations consist of different phases and different dominant modes of knowledge creation. Moreover, it is clear that analytical knowledge creation can occur between close-by and distant partners whereby synthetic knowledge creation is more or less limited to local collaboration.

An important explanation for these different spatial patterns can be found in differences with regard to (1) the types of activities involved, (2) communication, and (3) outcomes of the knowledge-creating process. First, it appears that, irrespective of the activities being analytical or synthetic knowledge based, initial creative idea-spawning, brain-storming sessions are highly facilitated by face-to-face interaction between the actors involved. Collaborative product-development activities, belonging to a synthetic mode of knowledge creation, also seem to benefit strongly from proximity between actors as these activities involve a log of hands-on, trial-and-error experiments

Table 3. Innovation trajectory for drug development.

Project phase	Research to understand human antibodies	Development of antibody library (platform technology)	Research to discover antibody-based HIV drug	Clinical trials
Dominant mode of knowledge creation	analytical	synthetic	analytical/synthetic	analytical
Actors involved	Local: various researchers at university department	Local: university and DBF ^a	local: DBF global: DBF	local: DBF global: PRO ^b

^a DBF—dedicated biotechnology firm.

^b PRO—public research organization.

Table 4. Innovation trajectory for functional food.

Project phase	Development of probiotic in medical context	Development of probiotic in commercial food context	Clinical trials
Dominant mode of knowledge creation	synthetic	synthetic	analytical
Actors involved	local: various departments at university	local: DBF and food company ^a	local: DBF global: PRO ^b

^a DBF—dedicated biotechnology firm.
^b PRO—public research organization.

with concrete prototypes of the envisaged product. Short feedback loops can speed up these processes to a great extent. Research collaborations based on an analytical mode of knowledge creation, on the other hand, seem to be least affected when it comes to distance-decay effects. An explanation for this could be that laboratory-based activities are more standardized, following universally accepted protocols and building on universally accepted existing knowledge.

Secondly, these different types of activities involve different styles of communication between the partners. Both creative idea spawning and collaborative product development are characterized by dense communication lines, with a lot of information and knowledge being bounced to and fro. It could, in fact, be argued that valuable knowledge is created in the heat of the moment during such communication. For (product) development activities it can sometimes be very difficult to codify and transmit essential knowledge as it is inherently tied to the product or is very subjective (for example, taste). For research activities it is easier to transform important knowledge into easy-to-transmit codes and numbers that can be understood by other researchers who speak the same scientific language in other parts of the world. Geographical proximity is not much of an issue here. This is clearly illustrated by the ease with which clinical trials can be outsourced.

Thirdly, it can be argued that different forms of documentation of the outcomes of the knowledge-creation process have clear spatial implications. A lot of analytically produced scientific knowledge is condensed and codified in scientific publications. Even though this knowledge is universal, this does not mean that such knowledge has become ubiquitous (Malmberg and Maskell, 1999) as the extent to which these publications can be understood and interpreted is dependent on the absorptive capacity of the receiver (Giuliani, 2005). Even though a lot of knowledge is floating freely around through electronic databases and, as illustrated in our drug-development case, via the circuit of international scientific conferences, receptive actors need to be tuned into the cognitive framework of the transmitter to make sense and value of this knowledge. Cognitive distance (Nooteboom, 2001) seems to be more important in this context than geographical distance. The outcome of synthetically produced knowledge is much more embodied in a particular artefact or object. Even though the intellectual property rights can be encoded, protected, and traded through patents, the transformation from idea to product can be cumbersome—as the functional-food case clearly demonstrates. Small but essential changes in the design of the products are often required to make them work in different local circumstances. These adjustments involve much tacit, embrained knowledge that is released through user–producer interaction.

An important lesson that can be drawn from the above is that policy for constructing regional advantage needs to be sensitive to the specific activities that are involved in the innovation processes (Asheim et al, 2006). Exclusive focus on support for local learning and knowledge creation would hamper the innovativeness of firms, particularly in the long run. The choice of partners is heavily conditioned by the specific need for complementary competences in different knowledge-creation phases. Policy can contribute to this search for partners by setting up arenas and organizations that facilitate local as well as global networking. This points to the increased importance of triple-helix initiatives and collaboration at the regional level in the governance of the attempts to construct regional advantage of clusters.

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