Science in an age of globalisation : the geography of research collaboration and its effect on scientific publishing

SCIENCE IN AN AGE OF GLOBALISATION

The Geography of Research Collaboration and its Effect on Scientific Publishing

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Jarno Hoekman
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SUMMARY

Although scientific knowledge is considered by many a universal and context-free product, its producers are often embedded in geographically bounded networks of research collaboration. In an age of globalisation these local networks of knowledge production are challenged, in order to make science more efficient and to align its priorities with problems of global relevance such as climate change and worldwide epidemics. Against this background, the dissertation sets out to examine changes in the contemporary geography of research collaboration and explores how these changes affect the publication of research findings in scientific journals.

The dissertation starts with introducing a framework to understand how geographical space structures collaborations among researchers. The two structuring principles in this framework are a logic of proximity that provides solutions for coordination problems in research practice, and a logic of stratification that provides researchers with means to engage in collaborations. The logic of proximity follows from the importance of physical co-presence for carrying out the complex tasks associated with scientific research and for establishing trust in research results. The logic of stratification is an outcome of the reward system in science which provides differential credit to researchers on the base of their past productivity. Globalisation impacts upon these logics through technological advancements in ICTs and mobility, and through the harmonisation of research policies and practices across territories. It is hypothesised in this dissertation that this process changes the geography of research collaboration, as well as the way research findings are communicated in scientific publications.

The empirical validation of this framework centers around two main themes that very much bear the imprint of globalisation in science. The first theme concerns the research policies of the European Union that aim to harmonise regional and national institutions in Europe, in order to create an integrated and more competitive 'European Research Area' (ERA). The Framework Programmes are explicitly designed to facilitate this process and in doing so they fund thousands of transnational research projects making it the largest transnational funding scheme in the world. Against this background, *Chapter 2* evaluates the extent to which European research collaboration networks are already integrated based on publication and patent data with multiple addresses. The results indicate that collaborations in Europe are structured by geographical proximities as the choice

for collaboration partners is impeded by the kilometric distance between researchers and by national borders separating them. The chapter also presents evidence that research collaboration networks are stratified on the base of similarity in productivity and resources. This stratification logic operates irrespective of the location of researchers vis-à-vis one another. The main conclusion from these results holds that the efforts towards the creation of ERA are well justified.

The empirical study in *Chapter 3* develops a dynamic approach to the geography of research collaboration by studying whether the logic of proximity is changing over time. The main argument of this chapter holds that one should make a conceptual distinction between a possible changing effect of geographical distance and a possible changing effect of territorial borders when studying proximity dynamics in research collaboration networks. When making such a distinction in the context of the European research system, the chapter shows that it is primarily the importance of regional and national borders that is decreasing over time, while the importance of geographical proximity is remarkably stable. The findings indicate that globalisation in science is mainly realised through the harmonisation of territorial institutions, but that physical co-presence remains an important coordination device for exchanging complex forms of knowledge.

The objective of *Chapter 4* is to study to what extent the Framework Programmes (FPs), as the main funding instrument of the European Commission, are affecting the geography of European research collaboration. It is hypothesised that, in case the FPs indeed render territorial borders less important, they are likely to create (new) stratified networks of research collaboration which will disproportionally favour high-performance researchers located in Europe's core regions. Contrary to expectation no evidence for this hypothesis is found. The analysis indicates that the FPs indeed have a substantial effect on promoting international scientific collaboration networks that are still relatively uncommon in comparison to national collaboration networks. However, chapter 4 also shows that acquisition of FP funding is equally distributed over Europe and that the FPs are more effective in establishing ties between poorly connected researchers than in further strengthening existing ties. When stimulating already existing networks, the FPs run the risk of being a substitute for other funding sources. This implies that current EU research policies are in line with the cohesion objective of the EU.

The second theme of this dissertation concerns the global standardisation of experimental drug research in human beings. In recent years, proponents of an evidence-based medicine have pushed for standards concerning clinical trial conduct and subsequent publication of research findings in clinical trial registers

and scientific journals. This standardisation process is closely associated with a rise in the number, size and geographical distribution of clinical trials. The empirical chapters address whether standardisation in research practice and writing have an effect on several aspects of scientific publishing including the constitution of authorship on publications, the communication of evidence after study completion, and the presence of error in scientific publications. In order to analyse these questions, a database is created that matches information from registered clinical trial projects (www.clinicaltrials.gov) with scientific publications that report on the main findings of these projects.

Chapter 5 focuses on the standardisation of good clinical practice (ICH-GCP) which has made the exchange of clinical data between geographically dispersed research sites less complicated. This has resulted in a process of global outsourcing with increasing enrolment of patients from emerging economies, especially in Central and Eastern Europe, Latin America and Asia. The chapter describes this globalisation tendency and studies whether worldwide patient involvement in clinical trials is reflected in the geographical composition of scientific management teams that design those trials and interpret their findings. An empirical strategy is developed to determine the geographical distribution of management teams by using authorship data from primary outcomes publications of clinical trials. Using this data it is shown that authorships are disproportionally granted to researchers in a few leading countries. The chapter discusses possible adverse consequences of this situation especially with respect to the monitoring of clinical trial quality and (the lack of) interactions between management teams and researchers that are in immediate contact with patients.

Chapter 6 concentrates on the publication behaviour of pharmaceutical companies who are well known for their strategy to withhold negative research findings from the scientific literature. To remedy this situation several authorities have recently mandated both registration of clinical trials before study onset and publication of major research findings after study completion. The chapter starts from this new institutional context and studies under what conditions pharmaceutical companies decide to publish their clinical trial findings in scientific journals and under what conditions they prefer publication in web-based repositories. It is hypothesized that despite institutional change, pharmaceutical companies will continue to highlight positive results in the scientific literature as it provides them with certification that their research findings are scientifically sound, methodologically rigorous and thus credible. In contrast, companies are expected to publish their negative findings on the web. The hypothesis is tested against a sample of clinical trials that assess the efficacy of glucose lowering agents in diabetes patients. The results indicate that firms

continue to highlight positive results in scientific journals. This implies that there is an ongoing and persistent bias in the scientific evidence on the safety and efficacy of experimental drugs.

Finally, *Chapter 7* studies the production and detection of error in scientific publications on the base of published errata and retractions. In line with previous chapters, the starting assumption holds that geographical proximity remains an important coordination device in research practice. This begs the question whether researchers that operate in geographically distributed projects are also more likely to produce error as effective peer-control may be lacking and the establishment of mutual understanding hindered. This question is adressed by conceptually distinguishing modes of coordination that are hypothsised to influence error production from the prestige of research findings which is likely to influence error detection. With respect to prestige it is shown that editorial policies of scientific journals may steer the process of error detection by organising impact around particular findings and by enforcing strict publication guidelines. After controlling for these factors, the study finds that geographically distributed research results in less accurate scientific publications. Globalisation tendencies thus put increasing responsibility on the publication system to detect these errors.

Based on the findings of the empirical chapters, the overall conclusion of the dissertation is three-fold. The first conclusion holds that changes in the contemporary geography of research collaboration are mainly visible in institutional harmonisation across territories, rather than in a tendency towards the 'death of distance' per se. This paradoxical process provides new prospects for worldwide research collaborations, but limits at the same time the possibilities to make these prospects work in actual research practice. Second, the presented analysis indicates that in an age of globalisation, science does not become a global level playing field where chances of success level off. Rather, stratified structures are reproduced at different spatial scales via the creation of new reward systems and global research collaboration network that exhibit high entry barriers. Third, globalised science reveals new publication practices with respect to authorship norms, the prevalence and correction of error in scientific publications and the conditions under which disclosure of research findings takes place. In this respect, new global contexts have often been cited as contributors to the quality, impact and practical application of research findings. The results presented here do not necessarily contradict this argument, but at least point to negative side-effects that are associated with geographically distributed research. These new insights require a rethinking of scientific institutions and research policies in light of globalisation.

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The geography of research collaboration: an introduction

1.1 Introduction

Science is a global communal endeavor. Not only is scientific research conducted in virtually every country, but the researchers from these countries "*are in fact co-operating as members of a closely knit organization*" (Polanyi 1962, p. 55). The global character of science is perhaps most clearly articulated when scientists formulate knowledge claims that are valid 'here, there and everywhere', and when recipients of these claims engage in critical debate, irrespective of their geographical location (Shapin 1995a). Likewise, science's global nature follows from functional achievements such as worldwide available technologies and recommendations on health, engineering and education that affect the daily life of individuals across the globe (Drori et al. 2003).

Famous social theorists like Karl Popper, Michael Polanyi, and Robert K. Merton have provided influential explanations for the capability of science to sustain this global endeavor by making reference to solid structural conditions as safeguards for the impartial production of scientific knowledge. Popper (2003, p. 243) notes for instance that "*what we call scientific objectivity is not the product of the individual scientist's impartiality, but a product of the social or public character of scientific method*". This public character is most clearly expressed in the universal norms of science that are supposedly internalised by every scientist. These norms prescribe scientific researchers to share all knowledge unconditionally with peers and evaluate their claims not on the base of social status or nationality but on the base of universal merit (Merton 1973).

The origin of these communal norms date back to the rise of early scientific societies in the seventeenth-century which linked researchers from Europe and beyond through travels, correspondence, and publications. At that time, the production and communication of scientific knowledge already thrived on crossing borders and a professional lingua franca. For instance, when Henry Oldenburg edited the world's first scientific publication in 1665 it enjoyed a wide international readership and drew on ideas from Italy, Hungary and the Bermudas, amongst other regions (Royal Society 2011). Since then, we have witnessed a hegemonic diffusion of Western Science and its specific form of collective rationality which is indicated by a worldwide rise in international science associations, international master programs and international research projects (Drori et al. 2003).

The increased geographical distribution of science can be best understood by making reference to time-space compression that renders the circulation of humans, goods and images an increasingly global affair (Harvey 1990). This process is made possible by "*innovations dedicated to the removal of spatial barriers - the railroad, and the telegraph, the automobile, radio and telephone, the jet aircraft and television*" (Harvey 1990, p. 232). The rise of an information technology paradigm is its latest expression and facilitates "*the application of…knowledge and information to knowledge generation and information processing…in a cumulative feedback loop*" (Castells 1996, p. 31).

The process of time-space compression "*forces reflection on the very meaning of basic spatial categories such as local, global, proximate, distant, location and territory'*" (Amin and Roberts 2008, p. 365). Contemporary research activities are increasingly organised in 'spaces of flows' that depend on time-sharing activities at a distance (Castells 1996). Physical proximity between researchers is only one form of proximity among many in such research activities and is neither a necessary nor a sufficient condition for successful knowledge production (Boschma 2005). In its most extreme manifestation this is articulated by the declaration of the 'death of distance' as already was done as far back as 1845 by Samuel F.B. Morse after he telegraphed the first electronic message, again by Herbert George Wells when he philosophised about a new world order in 1931 (Wells 1931) and most recently by Frances Cairncross when reflecting on the consequences of the information and communication revolution (Cairncross 1997).

The opportunities that follow from time-space compression are also incorporated in new modes of governance of science. In a globalised world characterised by intensified competition among (international) companies and a mass-educated workforce, it is frequently scientific knowledge itself that is being traded. It

follows that there is increased pressure to align scientific research with the goal of economic competitiveness and to steer its priorities in order to meet societal demands. These pressures have increasingly brought science in a 'context of application' where interactions between universities, governments and firms are intensifying (Gibbons et al. 1994; Etzkowitz and Leydesdorff 2000; Nowotny et al. 2001). The stakeholders that promote these new modes of knowledge production advocate a more distributed science system in institutional, organisational, disciplinary and spatial terms. Consequently, global research collaboration that serves the public interest, private utility or a combination of both is promoted for at least three reasons.

First, from an economic perspective the technological exploitation of scientific knowledge is considered as one of the prime sources for economic competitiveness and sustainable growth in the long run (Romer 1990; Foray 2004). It follows that there are economic benefits to the efficient organisation of scientific knowledge production that can be realised through the bundling of resources as a means to induce economies of scale and scope. Often, nation-states alone can no longer finance the costly research infrastructure for large-scale projects. International research collaboration is one way to gain in efficiency as it provides opportunities for savings in the costs of research infrastructures and training, helps to avoid duplication of research efforts and increases the pace of knowledge diffusion (Katz and Martin 1997). Current collaboration structures, however, still follow mainly from the uncoordinated efforts of nation-states which fragments research activities and research policies. The reduction of this fragmentation has therefore become a key policy concern with the transnational Framework Programmes of the European Commission being perhaps the best example.

Second, as scientific knowledge is increasingly stimulated for the sake of wealth creation, more and more aspects of our daily life and its material environment come under the scientific spotlight. The consequences of these advancement are not merely positive, because the very progression of science also produces new risks that can no longer be considered as side-effects. Ironically, as history unfolds itself in irreversible trajectories, managing these risks can only be done with the aid of science itself. Theories, experiments, and measurement instruments are needed to understand and monitor complex challenges such as climate change, cyber-crime and global epidemics. These challenges are neither bounded in space nor in time but have been metaphorically described as a driverless out-of-control 'juggernaut' (Giddens 1990). The political reaction to these 'grand challenges' is one of scaling-up research efforts in order to alleviate global problems with global approaches (Beck 1992). The increased funding of

international research projects is part of this endeavor and is increasingly seen as a panacea for global scientific risk management.

Third, global research collaboration is stimulated for its prospect to alleviate global problems, but it may also produce new divides or deepen existing ones as evidenced by ongoing disparities in the access to health services, food and education. One of the causes of this continuous reproduction of inequalities lies in "*a growing disjuncture between the globalization of knowledge and the knowledge of globalization"* (Appadurai 2000, p. 4). Within the science system this is articulated when those researchers that have the power to engage in global science take their "*hidden armature of…research ethic as given and unquestionable, and proceed to look around for those who wish to join*" (Appadurai 2000, p. 14). In this process less favoured researchers may be excluded from agenda-setting discourses or they may only gain access to resources when they establish relations with scientific powerhouses and conform to their norms. According to this view, internationalisation in science should not only be about establishing international collaborations but also about discussing the types of knowledge that are created and consolidated in these relations and the extent to which they serve the interests of scientific centers and peripheries (Paasi 2004).

It follows that the globalisation of research collaboration and its effect on knowledge production can take many forms and it would therefore be too simple to assume that globalisation simply creates a scientific level playing field among researchers. Rather, time-space compression may result in new forms of stratification of scientific knowledge production not least because of the possibilities that emerge as a consequence of globalisation itself. As spatial barriers to collaborate vanish, scientists are increasingly able to self-organise their collaborations keeping in mind their personal interests. Increased mobility can in this case for instance result in a concentration of reputable researchers in a few scientific centers rather than in a more equal distribution of scientific activity across the globe (Saxenian 2006). At the same time, globalisation may also augment differences between researchers in their access to resources especially when transnational funds are mainly allocated on the base of 'global excellence'. The nature and effects of globalisation are thus multifaceted, and its study therefore requires a proper theoretical framing of the specific research questions at hand.

The discipline of geography has a long tradition in dealing with questions of globalisation, yet it is only recently that they have been taken up in the context of scientific knowledge production as indicated by the declaration of a 'geographical turn' (Shapin 1998) or 'spatial turn' (Finnegan 2008) in science

studies. While most of this work has been of a qualitative and historical kind looking at specific case studies (Livingstone 2003; Meusburger et al. 2010), quantitative work based on bibliometric data has also been growing recently. In a recent review, Frenken et al. (2009) proposed to call such quantitative research in science studies 'spatial scientometrics' as to highlight the link to the field of scientometrics and its differences with the type of work done under the label of 'geography of science'. This dissertation is part of this programme. It studies the changing spatial patterns of research collaboration and points to some of the consequences of these changes for the practice of scientific publishing. The research questions at hand can be stated as follows:

RESEARCH QUESTION 1: *What are the spatial determinants of research collaboration?*

RESEARCH QUESTION 2: *How do the spatial determinants of research collaboration affect scientific publishing?*

The remainder of this chapter frames the theoretical background of this dissertation by introducing the geography of research collaboration and its relation with proximity and stratification as two organising principles of scientific knowledge production. We subsequently introduce the two empirical cases of this dissertation and provide an outline of the work that is presented in the six remaining chapters. The chapter ends with some concluding remarks.

1.2 GEOGRAPHY OF RESEARCH COLLABORATION

The geography of research collaboration is a framework to understand how space structures collaborations between researchers and how aggregates of such collaborations constitute spatial networks between locations. In this framework, research collaborations are structured according to a logic of proximity that provides solutions to the problem of coordination, and according to a logic of stratification that provides differential means to engage in collaboration. These structuring principles are not stable over time but change as a consequence of globalisation. More specifically, globalisation as a process of time-space compression changes actual research practices due to technological advancements in ICTs and mobility, whereas globalisation as a process of institutional harmonization leads to the emergence of transnational institutions and globally operating organisations in which research practices become embedded.

The understanding of space needs to be explicated in this context as contemporary geographers have provided multiple conceptions of place and space which refer to material as well as to perceptual dimensions (Lefebvre 1991; Massey 2004). We start from the physical location of individuals on the Euclidean surface and their media of communication and movement. Given these general elements, space can be defined as a fundamental material dimension that provides settings of interaction as a time-sharing activity between individuals (Hägerstrand 1970; Giddens 1984; Harvey 1990). This materiality can be both conceived in terms of places where researchers are co-present, as well as in terms of flows which allow for time-sharing activities at a distance (Castells 1996).

One can argue that research collaborations always involve some form of time-sharing activity between individuals, although it has been notoriously difficult to provide more exact definitions. There is for instance little consensus on the exact duration and intensity of interaction before it can be called a collaboration (Katz and Martin 1997). This is because most collaborations start with less formal interaction which makes the boundaries with a possible transition to collaboration fuzzy (Price and Beaver 1966; Laudel 2001). Thus Katz and Martin (1997, pp. 3-4) note that "*sometimes a researcher may be seen as a collaborator and listed as a co-author simply by virtue of providing material or performing a routine assay. In other cases, researchers from different organizations may collaborate by sharing data or ideas through correspondence or discussions at conference, by visiting each other, or by performing parts of a project separately and then integrating the results*". They conclude that what constitutes a collaboration in science is often considered a matter of "*social convention*" (Katz and Martin 1997, p. 8) which itself may vary across space and time.

Difficulties in providing general definitions of research collaboration also stem from the observation that many collaborations are not based on formal agreements that define common goals. As the conduct of science is ridden with uncertainty such goals often only emerge during the research process and not before onset (Amin and Roberts 2008). This implies that the existence of common goals is in many cases merely observed when collaborators make them explicit by taking mutual responsibility for the claims in a scientific publication. However, even in these cases individual responsibility may still be absent as has been noted with regard to 'hyper-authorship' (Cronin 2001) or when multi-author publications turned out to contain fabricated results. In the latter case, co-authors have often claimed that they were not involved in the research after all, or were not sufficiently aware of the fabricated parts of the publication (Biagioli 1998).

Traditionally, the settings of interaction for research collaboration rely on physical co-presence of researchers in space and time where they meet at certain locations and interact with one another face-to-face and body-to-body. The complex nature of scientific activities makes this form of interaction essential as some aspects of knowledge are tacit, implying that they *"cannot be put into words"* (Polanyi 1958, p. 4) or "*cannot be or - have not been - set out or passed on in formulae, diagrams or verbal descriptions and instructions for actions"* (Collins 2001, p 72). Acquisition of this knowledge therefore often necessitates 'enculturation' between researchers ranging from short-time visits to more structural 'master-apprentice relations' (Collins 1985). Moreover, it is not that tacit knowledge cannot be codified per se but rather that the acquisition of tacit elements is necessary for a meaningful interpretation of codifications (Frenken 2010). Collective sense-making in scientific collaboration thus involves a recurrent process of explicating, discussing and interpreting 'interim' codifications as ways to converge around a common product of scientific knowledge (Amin and Roberts 2008).

In addition to the acquisition of tacit knowledge which creates cognitive alignment between researchers, moments of co-presence also facilitate the establishment of trust which is an essential component of the credibility of research findings (Shapin 1995b). The establishment of trust can be best understood by the sensory effect that individuals have on one another when they are co-present (Simmel 1997; Urry 2000). This effect is mainly expressed by looking each other in the eye as this is "*perhaps the most direct and purest form of interaction that exists*", and provides the "*most complete reciprocity*" (Simmel 1997, pp. 111-112) between individuals. Likewise, Urry (2002) shows how co-present bodies actively engage in communication forms that do not only involve language but the entire behavioral complex such as body posture, positioning and tone of voice.

The materiality of space and the indivisibility of the body set limits on the presence of individuals in these settings of interaction. Individuals can only be at one location at the same time and movement in space involves movement in time (Hägerstrand 1970). Research collaborations that rely on moments of co-presence are thus structured by the location of scientists vis-à-vis each other and their means of movement in order to meet. It follows that the meeting places of collaborating scientists and their permanent locations overlap in space depending on the necessary frequency of co-presence and the advancement of media of mobility. More specifically, when either the necessary frequency of co-presence is

high or the means of mobility are low, it becomes a necessary condition that researchers work in close physical proximity on a permanent base.[1]

Technological advancements provide the possibility to relax this necessary overlap between co-presence and co-location (Torre and Rallet 2005). Transportation technology, the development of related material infrastructure and a relative decline in the costs of mobility have rendered a 'shrinking of distance' (Janelle 1969) in terms of the time and money needed to travel from one location to the other. As a result individuals can travel longer distances than in the past without necessarily travelling longer. In its most simple form this process renders an extension of the spatial range that can be covered given that a researcher wants to return to its permanent location within a particular time-frame. Indeed this spatial range is not a simple function of the kilometric distance between individuals because the material infrastructure that supports differential means of mobility (e.g. highways, airports) is unequally distributed in space. Moreover, the actual perception of distance is a subjective matter and differs between individuals according to their mental maps (Milgram and Jodelet 1976).

Physical proximity on a permanent base is also not necessary for collaboration when interacting through flows of communication that are supported by the material infrastructure of information technologies. Castells (1996) notes that these technologies create new spaces of their own which operate through flows rather than places. These spaces are not constituted by traditional settings of interactions based on co-presence, but are materialised in 'circuits of electronic exchange' that support time-sharing practice without physical proximity. As Callon and Law (2004) argue, ICTs allow for being absent and present at the same time. As such, space can no longer be conceptualised based on physical proximity alone but its materiality should also be conceived in terms of flows and their particular spatial forms.

As communication by means of ICTs is in principle not bounded in space, they substitute for moments of co-presence, albeit imperfectly. Olsen and Olsen (2000) question in this respect whether this substitution process can ever be perfect as modern media hinder the unique establishment of common reference frames and mutual understanding through amongst others rapid feedback, pointing and referring to objects in real space (i.e. acquiring ostensive knowledge), subtle

[1] In time-space geography this condition is visualised using time-space prisms that show the absolute boundaries of individual movement in space given that he/she needs to 'bundle' with other individuals at a particular moment in time (Hägerstrand 1970).

communication, informal interaction before and after 'meetings' and a shared local context. As long as those impediments do not disappear, we cannot yet abolish the friction of distance as a traditional gravitational force on the Euclidean surface.

Yet, the use of ICTs undoubtedly makes the necessity of co-presence more temporal. Both the nature of co-presence and the spaces in which they occur change accordingly, especially when the use of ICTs is combined with intermittent travels over long distances (enhanced by transportation technologies). Torre (2008, p. 880) notes for instance that individuals "*compensate for the intermittence of meetings and the costs of transport by spending a longer time together. The co-presence of individuals is maximized during times together and these times are normally filled with strong interactions. In other words, frequent yet short visits* [over short distances] *might turn into intermittent yet longer periods of face-to-face co-presence, of hosting and visiting*" [over longer distances]. Such interactions often take place at the location of one of the project partners, at temporary venues such as conferences or in close vicinity to mobility hubs (Urry 2002).

The spatial patterns of research collaboration that follow from these general observations depend on the actual coordination modes in research collaborations and the extent to which researchers in varying locations have the means to engage in such collaborations. The former logic is considered a function of proximities between researchers that provide solutions to the problem of coordination, whereas the latter logic is conditioned by the reward system in science and its fundamental stratified nature. We turn to these issues in the next two sections.

1.3 Logic of proximity

Proximities between researchers provide solutions to the problem of coordination in actual collaborative practices which is a main concern surrounding the uncertain activity of scientific knowledge production. Coordination involves the creation of alignments between researchers by integrating different pieces of a research project in order to accomplish collective tasks (Cummings and Kiesler 2005). As argued in the previous section, this alignment can be created through moments of co-presence that establish trust and facilitate the acquisition of tacit knowledge.

In this framework, the exact intensity and duration of co-presence that is necessary for successful coordination is mediated by proximities that already

exist between collaborating researchers (Boschma 2005).[2] In similar vein, one can also argue that already established proximities mediate the success of coordination given a fixed amount of co-presence. Particular socialisation trajectories and previous moments of co-presence render in this respect socio-cognitive proximities between researchers which are expressed in trust and in tacit knowledge to understand each other. Proximities that create alignment between researchers may also follow from common hierarchical structures under which researchers operate which are expressed in institutional or organisational proximities.[3]

Due to the presence of these forms of proximity the necessary intensity and duration of co-presence can be reduced. In other words, researchers can substitute their need for co-presence with already established proximities both in space and in time. With respect to substitution in space, it has been shown that there is less need for co-presence in research collaborations between universities than in university-industry research collaborations as in the former institutional proximity is already established at different locations, whereas in the latter it is not (Ponds et al. 2007). Concerning substitution in time, researchers that previously functioned in a master-apprentice relation will be more effective in communicating by means of ICTs because trust and common references frames are already established in this case (Amin and Roberts 2008).

The location of researchers vis-à-vis each other is in this respect neither a necessary nor a sufficient condition for the coordination of research (Boschma 2005). As argued, it should merely be seen as a facilitator of moments of co-presence as transport costs increase when the physical distance between researchers decreases. As such, the location of researchers vis-à-vis each other

[2] Indeed, the necessary intensity and duration of co-presence also depends on the nature of knowledge that is being produced. The nature of knowledge can in this case potentially be understood from the 'search regime' of a particular field. This regime can be characterized by differences between fields in the rate of growth, the degree of internal diversity, and the nature of complementarities (Bonaccorsi 2008).

[3] We will mainly refer in this chapter to rules of the games that are enforced within particular territories. Note however that institutional differences can also be defined as the extent to which researchers operate under the same incentive structure which aligns the objectives of researchers. For instance, Open Science encourages the rapid disclose of research findings in scientific journals. In contrast, firms often rely on secrecy and protective mechanisms when producing knowledge in order to limit the risks of unwanted spillovers and to ensure returns to their investments (Dasgupta and David 1994; CHAPTER 6)

puts constraints on the spatial range of research collaboration inasmuch co-presence is important, although physical proximity does not fulfill a function of coordination in itself.[4]

This does not mean, however, that there is no relation between the physical proximity of researchers and the extent to which they share other forms of proximities. This is an important observation, because a decrease in the importance of co-presence does in this case not necessarily result in random spatial patterns of research collaboration. More specifically, even without a functional need for long periods of co-presence (making physical proximity on a permanent base unnecessary) research collaboration may still take place between researchers in close physical proximity for a number of alternative reasons.

First, the spatial patterns of research collaboration are structured by institutions that enforce 'rules of the game' (North 1990) within particular territories. In this respect, national scientific activities have always been a crucial instrument to sustain the authority of nation-states by means of education and to stimulate economic growth through the creation of national technological capabilities (Lundvall 1988; Crawford et al. 1993). As a result there are many idiosyncratic institutions at national level that govern scientific knowledge production, including those that govern research assessments, intellectual property rights, research ethics, scientific integrity and university-industry relations. Moreover, scientific institutions are also enforced at other spatial scales such as at the level of sub-national regions which may support the valorisation of scientific knowledge around localised sites with large scale supportive infrastructure (Cooke et al. 1997), or the transnational level where groups of countries or cross-border regions harmonise their institutions in order to promote scientific interaction.

Second, collaborations often take place within organisations with more than one location and incentives are as such aligned by common hierarchies. The spatial range of nearly all universities and major public research organisations is national in this context (e.g. National Institutes of Health, Max-Planck Gessellschaft, Centre National de Recherche Scientifique etc.), with the exception of some foreign affiliates (Stichweh 1996). In contrast, companies engaging in scientific activities often have a more international orientation with many

[4] The potential benefits of physical proximity are in this respect confined to random encounters in space and to the possibility of screening the actions of others and the material settings in which these actions occur (Malmberg and Maskell 2002).

multinational corporations having R&D laboratories in major world-cities across the globe (Friedmann 1986; Taylor 2004).

Third, socio-cognitive proximities established in similar socialisation trajectories or on the base of previous moments of co-presence are often sustained in local networks. It can be argued that the pioneers of laboratory studies implicitly took such local networks as a starting point by studying the laboratory as a bounded microcosm that provides the settings of interaction for the production of scientific knowledge (Latour and Woolgar 1986). At a higher level of aggregation, Storper and Venables (2004, p. 367) consider cities a main stage where socio-cognitive proximities are sustained by making reference to their importance for "g*etting into loops which are associated with collocation*". Others have in this context pointed towards "*being there*" (Gertler 2003) and "*buzz*" (Bathelt et al. 2004) as organising principles for socio-cognitive systems that are bounded in space (see also Howells 2002).

Implications of globalisation

Globalisation impacts on the logic of proximity by affecting actual research practices via technological advancements in ICTs and mobility, and via the emergence of transnational institutional structures and globally operating organisations in which research practices become embedded. As has been argued in the previous section, technological advancement renders an extension of the spatial range of movement, while it also provides the possibility to substitute some moments of co-presence for time-sharing activities at a distance. This process of time-space compression is observed in this dissertation and in some related recent empirical work, although not in an unequivocal way. This dissertation shows for instance that within Europe the average distance over which research collaboration takes place has increased slowly with a maximum of 8 kilometers every year over the period 2000-2007, depending on the scientific field (Chapter 3). Jones et al. (2008) report an even more modest increase for collaborations within the United States that spanned on average 750 miles in 1975 and increased to 800 miles in 2005. On the global level the increase in the spatial span of research collaboration is more marked with an average growth of 47 kilometres per year (Waltman et al. 2011).

At the same time, the empirical evidence presented in this dissertation indicates that time-space compression does not necessarily make the need for physical proximity unnecessary for collaborative knowledge production. More specifically, physical distance between researchers continues to have a negative effect on co-publication activities even after controlling for a number of

alternative explanations (CHAPTER 2-4). These alternative explanations show independent significance and include amongst others the territorial effects of regional and national institutions (CHAPTER 2-4), language (CHAPTER 3-4), previous co-publication activities (CHAPTER 4), disciplinary specialisation profiles (CHAPTER 3) and funding schemes (CHAPTER 4). This outcome further corroborates earlier findings in the field of spatial scientometrics (Frenken et al. 2009) and recent work done by Hardeman et al. (2012) who show that physical proximity still matters for research collaboration after controlling for all other proximity dimensions that are proposed by Boschma (2005).

The ongoing importance of physical proximity between researchers is also indicated by the observation that collaborative research over larger physical distance is more likely to result in problems of coordination. Researchers foresee such problems when engaging in collaboration and they therefore reveal a preference to collaborate with physically proximate partners. This dissertation shows for instance that scientific leadership in large-scale research projects more often accrues to researchers that are located in relative close vicinity both to each other and to the sponsor of the study. This preference is even observed when distant collaboration partners are involved in the research (CHAPTER 5). Moreover, in case researchers choose to engage in longer-distance collaborations. they are more likely to make errors in the scientific publications they produce. This is possibly due to a relative lack of coordination activities in such distributed research projects (CHAPTER 7).

Given the process of time-space compression one can interpret the ongoing importance of physical proximity for research collaboration in at least two ways. *First,* it can be argued that in many research projects the necessary intensity and duration of co-presence is so high that the location of researchers vis-à-vis each other remains an important input in research collaboration, despite technological advancements. This explanation may be especially valid when one argues that the nature of problems being studied in contemporary science becomes increasingly complex. Such an increase in complexity may follow from the internal dynamic of science where it is necessary to create new forms of 'complementarities' between specialised fields of knowledge and heterogeneous groups of organisations (Bonaccorsi 2008). Increased complexity may also be driven by societal pressures to come up with solutions to 'grand challenges' (Gibbons et al. 1994; Nowotny et al. 2001). The implication of both perspectives is that contemporary research collaboration sustains more complex collaborative arrangements where the initial proximities between researchers are often lower, and the need for co-presence thus higher.

Second, even given a decrease in the functional need of co-presence, collaborations may still take place between researchers in close physical proximity because other reasons may exhibit gravitational force on their locations vis-à-vis each other.[5] These forces may stem from benefits associated with the spatial concentration of reward to which we will return in the next section. Potentially they may also be an outcome of localised preferences such as the attachment of researchers to particular places, localised settlement patterns of graduates after university training or spatially bounded patterns of labor mobility (Breschi and Lissoni 2009; Dahl and Sorenson 2010). Researchers may also concentrate around material infrastructure that facilitates communication and movement (e.g. airport, highways) not because of each other, but because it provides them with access to distant locations.

In addition to technological advancement, the impact of globalisation on research collaboration also operates through the emergence of transnational institutional structures and globally operating organisations. These overarching structures create alignments between researchers at distant locations, and make coordination relatively less dependent on 'traditional' territorial institutions such as nation-states and sub-national regions. Part of this structuring framework can be realised within multi-location organisations that establish affiliations across the globe and as such "*manage cross-fertilization of ideas from different locations*" (Singh 2008, p. 77). Yet, more important for scientific activities is the increased coordination of research activities by means of transnational institutions. These institutions may either be the outcome of a synchronisation of state-level regulations or may follow from the formulation of entirely new global standards.

The two cases studied in this dissertation very much bear the imprint of these new modes of governance. The first three empirical chapters of this dissertation (CHAPTER 2-4) focus on the process of European integration in science which involves the harmonisation of regional and national institutions in order to create a European research system. The latter three empirical chapters (CHAPTER 5-7) focus on the globalisation of clinical trial research which is made possible by the standardisation of research practices as envisaged in global guidelines such as the 'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use' and the 'Good Clinical Practice' guidelines (ICH 2012).

[5] These reasons do not follow from the importance of physical proximity expressed through other forms of proximities (e.g. national territorial institutions, local socio-cognitive systems), as we control for these factors in the presented analysis.

The empirical results presented in this dissertation indeed suggest that these alternative modes of governance increasingly facilitate cross-border research collaborations which goes at the expense of territorialised patterns of interaction within sub-national regions and nation-states. More specifically, co-publication activities in Europe show a gradual tendency towards European integration where the role of territorial borders as a determinant of co-publication activity decreases. When controlling for this harmonisation effect, the importance of physical distance for research collaboration is no longer decreasing over time (CHAPTER 3). Transnational funding schemes such as the European Framework Programmes (FPs) provide significant input in this process as they increase the likelihood of international research collaboration. More specifically, joint participation in the FP projects positively affects the spatial structure of research collaboration between international partners, but has no structuring effect on domestic collaborations (CHAPTER 4).

Clinical trial research has also shown an increased tendency towards multinational research, following the first publication of the Good Clinical Practice guidelines in 1995 (Petryna 2009). In this case large scale-research projects that involve many individuals are primarily supported by pharmaceutical companies. These companies increasingly outsource routine clinical activities to non-traditional research locations in emerging economies. Yet, at the same time they continue to rely on more physical proximate parties for the conduct of complex scientific activities such as the design of studies and the writing of manuscripts for publications (CHAPTER 5).

The empirical results do however not signal a complete withdrawal of the nation-state from the governance of scientific knowledge production. The effect of national institutions on research collaboration remains significant over time and is stronger in case of co-publication activity as compared to co-patenting activity (CHAPTER 2-4). In the medical sciences this is for for instance illustrated by the ongoing importance of large national research organisations (e.g. NIH, NHS) that have their own intramural research laboratories and also provide grants for the conduct of extramural research. Their funding schemes are often explicitly designed to support national priorities in health. In sum, although the nation-state has become less important for setting the 'rules of the game' in scientific knowledge production, its role still remains pronounced with respect to the funding of research. This is especially the case in those fields where research outcomes hold direct implications for national priorities.

1.4 LOGIC OF STRATIFICATION

There are many motivations for researchers to engage in research collaboration. Following the sociology of science one can argue that researchers are driven by a desire for recognition and reputation (Cole and Cole 1967; Merton 1973). Research collaboration is an important vehicle to gain and sustain this recognition as collaboration provides access to resources such as research infrastructure, information and training. Moreover, collaboration creates networks through which scientific knowledge and researchers' own reputation diffuses (Beaver and Rosen 1978). In doing so, the embeddedness of researchers in networks is a medium to mobilise 'allies' and to convince peers about the significance of research results (Latour 1987).

The structure of research collaboration that follows from these motivations can be considered an emergent, self-organising system insofar the selection of research partners relies upon choices made by the researchers themselves, irrespective of their location vis-à-vis each other and given the absence of any other type of incentive (Wagner and Leysdesdorff 2005). Such 'footloose' choices can however only be made when researchers have the means to organise the settings of interaction that are necessary in such research collaborations in the first place. It should be noted in this respect that the technologies that facilitate these interactions are not ubiquitous material properties. Urry (2002, p. 262) notes for instance that "*the power to determine the corporeal mobility of oneself or of others is an important form of power in mobile societies, indeed it may well have become the most significant form of power*", whereas for example an ongoing digital divide signals the differentiated access to ICTs that may hamper research collaborations involving less connected locations (Duque et al. 2005).

Science is a highly stratified institution in this respect. "*Power and resources are concentrated in the hands of a relatively small minority*" (Cole and Cole 1972, p. 368). Expressed in quantitative terms, the productivity of scientists follows a rank-size distribution where there are only a few scientists with very high productivity and many with low productivity (Price 1963). According to the sociology of science this unequal distribution of productivity reflects itself in the reward system that gives credit where credit is due, therefore effectively providing productive researchers with more recognition (Merton 1973). Such recognition is not an isolated property based on past achievement alone. Rather, it is part of a cumulative cycle of conversion that conditions "*scientist's abilities actually to do science*" (Latour and Woolgar 1986, p. 198). Within this cycle, recognition can be transformed in instrumental assets such as money, equipment and data.

Researchers 'invest' in these assets to produce new scientific knowledge with the intention of 'earning back' recognition with 'interest' after a complete cycle.

Merton (1973) however acknowledged that there are deviations from the perfect allocation of reward that skew its distribution towards researchers with an already achieved social status. Such misallocation of credit is known as the Matthew effect in science and holds that researchers with an established reputation are more likely to attain credit for their work than researchers who have not yet made their mark. In more general terms, the Matthew effect mimics a standard positive feedback mechanism which in different fields is known as cumulative advantage, preferential attachment, increasing returns or ratchet effect. One can argue that in the quasi-economic model of the cycle of credibility, the Matthew effect gives unequal interest rates to investments based on already established reputations of researchers.

The unequal distribution of rewards and its reinforcement through positive feedback mechanisms makes some researchers disproportionally attractive as collaborators. With regard to the geography of research collaboration this process 'pushes' reputable researchers to more distant collaboration partners and 'pulls' less reputable researchers towards more reputable ones. With respect to the former it can be argued that the unequal distribution of rewards provides researchers with differential means to access technology. It follows that spatial overlap between co-presence and co-location becomes relatively less of a concern for researchers with higher reputation as they have the resources to organise moments of co-presence on a temporal base. This renders their choice of research partners relatively more 'footloose'.

At the same time, reputable researchers also have the means to capitalise on their reputation by attracting other researchers that have a preference to be co-present with them (both for training and collaboration). This 'preferential attachment' is especially observed for early-career researchers and young talent (e.g. PhDs, post-docs). The minority of researchers with a high reputation are in this case like 'magnets' for the (yet) less reputable ones which makes it relatively easy for the former to hire new personnel, potentially over large distances. Mahroum (2000, p. 372 and p. 376) notes in this respect that "*mobility is a premier agent of scientific expansion* [where] *highly talented scientists flow to scientific institutions that are reputed for their excellence*". Hence, although reputable researchers have the means to collaborate over large distances, they can also create more favorable conditions to collaborate in close vicinity to their permanent location.

The location of researchers also contributes to the attractiveness of collaboration partners, because research collaboration at a distance relies on existing communication and transport infrastructures. These infrastructures are shaped by the spatially differentiated demand for communication and movement that does not follow from scientific activity alone but rather from the spatial concentration of advanced services and knowledge-based activities in general, including finance, insurance, advertising, legal services and real estate (Sassen 1991; Castells 1996). The connections that are made between the cities that host these functions take on a stratified network topology which is the outcome of a process of preferential attachment. More specifically, it is most effective in communication and transport networks to create links with already well connected cities which results in the generation of hub-and-spoke structure with dense connections between a small group of major world-cities (Friedmann 1986; Taylor 2004).

However, as scientific activity is a constituent part of this system it also self-organises demand for particular flows of communication and movement which endogenously shapes some of the material infrastructure that sustains research collaboration. As argued, this demand is higher for reputable researchers and differences between researchers may be further augmented due to self-reinforcing mechanisms. Merton (1973, p. 457-458) notes in this respect that self-reinforcing mechanisms associated with the Matthew effect are probably not limited to the contributions of individual researchers but also hold at the level of entire organisations which "*are allocated far larger resources for investigation*" and where prestige "*attracts a disproportionate share of truly promising students*". Empirical studies that are mainly based on citation counts as a particular form of reward have indicated that the stratified nature of scientific activity also holds at the level of cities and countries where only a few locations receive more citations than can be expected on the base of a random distribution, whereas many locations receive less citations (Bonitz et al. 1998; Batty 2003; Bornmann and Leydesdorff 2011).

The emergence of these spatial concentrations of reward can potentially be understood from an evolutionary perspective on spatial dynamics where historical accidents render a cumulative process of reward concentration in relatively few locations (Boschma and Frenken 2006). This process merely functions when researchers need to become physical proximate on a permanent base in order to collaborate which at least in an historical perspective seems to be an accurate description. Small historical accidents such as the location of one or a few reputable researchers in a particular location may in this case render increasing returns to reward which augment both the means to attract other

researchers to that location and to create demand for flows of movement and communication over larger distance. This internal dynamic of science may produce an endogenously sustained material infrastructure of communication and movement.[6]

The magnetic function of these spatial concentrations of reward can in this case also be understood from two additional localisation processes. *First*, groups of researchers can capitalise on their reputation by investing in facilities, or by more easily attracting them when they are provided by external funders. Depending on the technical requirements of the specific scientific field these facilities may range from large scale physical infrastructure (e.g. particle accelerators, telescopes) to the maintenance of specialised databases. They often rely on inert material properties that are likely to be 'grounded' at particular locations over longer periods of time. *Second,* researchers may create 'offspring' and transmit their reputation (and tacit knowledge) by training new PhDs and post-docs. When at least some of these newly trained researchers locate in close physical proximity to the original spatial concentration, localised cumulative advantages can be sustained over longer periods of time. This process is analogous to agglomeration in industrial dynamics that follow from spin-offs that locate in close physical proximity to their mother firm (Klepper 2010; Vaan 2012).

Implications of globalisation

Globalisation stratifies spatial structures of research collaboration which makes some researchers relatively more footloose than others, whereas it may also change the distribution of reward allocation. With respect to the former, there are on the one hand researchers with limited possibilities to make use of ICTs and transportation technologies. Due to these limitations, these researchers mainly engage in local collaborations. On the other hand there is a group of researchers that can operate relatively 'footloose' in space, but they still may have a preference to collaborate in close vicinity to their permanent location which is facilitated by the observation that they can more easily attract other researchers that prefer to be co-present with them. This smaller group of productive researchers finds a balance between the extent to which they pursue collaborations at a distance and the extent to which they collaborate in close

[6] Castells (1996, p. 444) provides the example of the city of Rochester, Minnesota. This small city has become a privileged hub in the medical sciences due to the location of the Mayo Clinic which initially only functioned as a small community hospital but grew out to a clinic hosting more than 3,000 researchers and attracting more than 2,000,000 visitors a year.

vicinity to their permanent locations. Hence, the outcome of this dissertation that physical proximity remains an important determinant of the spatial structure of research collaboration (CHAPTER 2-4) is driven by two different underlying processes.

Further advancement of ICTs and transportation technologies may thus both facilitate longer distance collaborations and at the same time result in an ongoing process of spatial concentration. Jones (2008, p. 1259) notes in this respect that the geography of research collaboration is "*not primarily driven by an increase in the distance between long-range collaborators but by an increase in the frequency of collaborations both near and far*". The findings in this dissertation corroborate this view and provide some further qualifications to this trend. It is shown for instance that catching-up countries in science actually start collaborating over shorter distances suggesting that the importance of physical proximity may increase when the pool of physically proximate collaborators is increasing (CHAPTER 3). These observations made in the context of European research have recently also been confirmed at a worldwide scale (Waltman et al. 2011).[7]

Although an overall tendency thus indicates that physical proximity remains important for research collaboration, the observation that more reputable researchers are relatively more 'footloose' is reflected in divergent spatial patterns to collaborate over larger distances. This may become reflected in matching of researchers on the base of similarity in productivity or access to resources and irrespective of their locations (Jones et al. 2008). Such collaboration patterns increasingly take on the form of more permanent network organisations in which data and material is shared among members, and common research and training programmes are developed. The entry barriers to participate in these networks can be substantial, both in terms of financial commitments as well as in terms of the reputation that is necessary for active engagement.

Matching of researchers on the base of social attributes and irrespective of their location is also visible in space where concentrations of productive researchers and resource-rich regions disproportionally link with each other (CHAPTER 2). Part of this stratification process simply follows from the location of researchers with respect to the material infrastructure that sustains the flows of

[7] There may actually be a process of spatial de-concentration of scientific publication activity in some countries which is driven by the rise of mass education in smaller cities (Grossetti et al. 2009). As education and research are still closely linked, the spatial pattern of research activities follows the spatial de-concentration of mass education.

communication and movement. This dissertation indicates for instance that researchers located in airport-supported regions are relatively more prone to collaborate (CHAPTER 3).

With respect to the emergence of transnational institutional structures, we observe a relative decrease in the importance of national and sub-national funding initiatives in comparison to the funding of scientific research at the international level. This process may skew the distribution of rewards itself, depending on the political choices that are made on the international level. It can be argued in this context that research funds allocated at the international level are mainly distributed on the base of global excellence rather than alternative political goals. If one accepts this premise, international funding is likely to augment the differences between researchers in the ability to connect with peers from other countries. This process creates stratified international collaboration patterns, where more productive researchers increasingly connect with each other. Potentially, it puts the often cited reason for international collaboration as a quality inducer (Narin et al. 1991; Frenken et al. 2010) in a different light because the observed collaborations between these researchers may be an outcome of a selection process where the researchers engaging in such collaborations are simply the more productive ones.

The Framework Programmes (FPs) as one of the largest international funding programmes in the world provide an important test-case in this respect. Allocation of these funds is said to be increasingly based on 'excellence', although alternative policy goals such as cohesion and 'juste retour' have also been a significant input in the design of earlier FPs (Sharp 1998). Against this background, the presented empirical results suggest that previous co-publication activity is only a minor consideration in the allocation of funding to collaborative projects. In addition, the FPs also turn out to be more effective in establishing ties between poorly connected regions than in further strengthening existing ties between more productive ones (CHAPTER 4). Thus, for what regards the FPs we do not observe a reinforcement of the logic of stratification. In this respect the FPs thus contribute to the cohesion objective of the European Union.

The enforcement of worldwide standards is also likely to influence the distribution of reward. Worldwide standards create a global level playing field where an increasing number of researchers follow the same rules of the game. Such standardisation does not imply however that each researcher has an equal chance of success. One empirical finding of this dissertation is that the creation of scientific standards routinises some aspects of scientific conduct and reduces as such the perceived reward that follows from these activities. Actual clinical

practices of enrolling patients and treating them in experimental settings is a specific example. Uniform definitions of Good Clinical Practice (GCP) harmonise experimental research by providing transnational standards for "*the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials*" (Petryna 2009, p. 108). It follows that patient-doctor interactions in clinical research are increasingly perceived as a routine practice, while the design of clinical experiments and the writing of manuscripts for publication are considered more creative tasks in scientific knowledge production (CHAPTER 5).

With respect to the geography of research collaboration, this process renders a spatial division of labor (Massey 1984) in large scale research where routinised activities become spatially decoupled from more creative tasks. The integration of different tasks in the research project in order to produce scientific knowledge can take place with a very limited need for actual co-presence. Routinised activities are as a result increasingly outsourced to non-traditional research locations, although they are often still managed from scientific centers. Examples of this process include patient enrolment in clinical research, the editing of scientific texts and programming and data collection tasks in information and computer sciences. In this, scientific knowledge production follows a logic that is similar to the economic pattern of globalisation where routine tasks in value-chains are often conducted in low-wage countries (Gereffi 1994).

Although the reward following from individual tasks in globalised research projects may be small, there is a perception that the overall research project benefits from the conduct of scientific tasks in a larger number of locations. In clinical research these quality standards are described by explicit grading systems which are promoted by the advocates of evidence-based medicine. According to evidence-based medicine standards, experimental research with patients from many locations signals that research findings are robust to geographical variation. Researchers anticipate on this when designing and publishing research. They are for instance more likely to publish findings in the scientific literature that stem from international research activities (CHAPTER 6). Thus, in this case global science becomes a constituent part of the reward system.

1.5 CASES AND OUTLINE OF THE THESIS

This dissertation consists of two parts both containing three empirical chapters. Five of these chapters have been collaborative efforts and the respective co-authors are mentioned at end of this dissertation. The empirical studies in this dissertation start from two abstract views on the science system that very much

bear the imprint of globalisation: the 'European Research Area' and 'Evidence-based medicine'. The actors that legitimise these concepts in the science system convey particular views on a desired organisation of scientific knowledge production and their views are enforced by virtue of the institutions they create (e.g. funding schemes, journals, training programmes). In the empirical strategy we focus on the elements of these abstract views that relate to the geography of research collaboration. In what follows, we introduce the two cases and derive some empirical starting points from written communication such as policy documents in the case of the European Commission and editorials in scientific journals that support an Evidence-based medicine perspective.

Part A: Towards a European Research Area?

The European Research Area (ERA) is the most important concept underpinning current research policies of the European Union (EU). Its launch shortly followed the initiation of the Lisbon Agenda in 2000 which is well-known for its catch-phrase goal to make Europe "*the most competitive and dynamic knowledge-based economy in the world*" (European Council 2000, I.A.5). During the nineties, the European Commission (EC) diagnosed weaknesses in Europe's research and industrial base vis-à-vis its main competitors (i.e. United States and Japan). Both the 1993 White Paper on Growth, Competitiveness and Employment (Commission 1993) and the 1995 Green Paper on Innovation (Commission 1995) summarised these weaknesses under three distinct headings. *"The first weakness is financial. The community invests proportionally less than its competitors in research and technological development (…). A second weakness is the lack of coordination at various levels of the research and technological development activities, programmes and strategies in Europe (…). The greatest weakness however, is the comparatively limited capacity to convert scientific breakthroughs and technological achievements into industrial and commercial successes"* (Commission 1993, pp. 86-87).[8] Against this background, both the initiation of the Lisbon Agenda and the creation of ERA are attempts to reorient Europe's main rationale from one based on economic integration alone towards one based on the concept of a knowledge society.

The original idea underlying ERA is that *"research activities at national and Union level must be better integrated and coordinated to make them as efficient and innovative*

[8] The reality of these weaknesses and their evolution over time is the focus of much academic debate. See on Europe's underinvestment in R&D (Pavitt 2000, Duchene et al. 2009); on lack of coordination (Luukonen 2009); on the 'European paradox' (Dosi et al. 2006).

as possible" (European Council 2000, I.A.12). This objective is further specified in a 2002 Communication of the EC which defines ERA as "*an 'internal market' in research, an area of free movement of knowledge, researchers and technology, with the aim of increasing cooperation, stimulating competition and achieving a better allocation of resources"* (Commission 2002, p. 4). Recently, the creation of an internal market for research has been further prioritised by dubbing it the "*fifth freedom of knowledge*" (European Council 2008a, p. 5) which is added to EU's four original principles of free movement of people, goods, capital and services.

Key to the creation of an area of free movement is overcoming "*fragmentation of research activities, programmes and policies across Europe"* (Commission 2007, p. 2). The exact desired levels of fragmentation remain elusive in this respect, although there seems to be a consensus that reducing current fragmentation fills a need for economies of scale and scope in order to make research activities less duplicative and more effective. Moreover, reducing fragmentation is also believed to contribute to "*re-focus R&D and innovation policy on the challenges facing our society, such as climate change, energy and resource efficiency, health and demographic change*" (Commission 2010, p.10).

The reduction of fragmentation can be understood as a process of removing "*barriers to the free flow of knowledge"* (European Council 2010, p. 5). Following the geography of research collaboration, we focus in this respect on fragmentation following from spatial barriers that hamper interactions between different 'areas' within Europe. The harmonisation of national institutional frameworks (e.g. funding schemes, research evaluation, etc.) enhance this process as it provides a common institutional framework under which European researchers can operate. In addition, several funding schemes promote research collaboration and the mobility of scientists at the European level. These schemes are expected to have an effect on the creation of ERA by changing the collaboration choices of researchers.

The emphasis on research collaboration in European policy provides a major justification for the European focus of this dissertation. From the discussed policy documents, no unequivocal definition of the spatial structures of research collaboration that would characterise ERA follows. However, the conditions for participation in the funding schemes such as the Framework Programmes (FPs) provide some tangible points of departure. The FPs are explicitly designed to facilitate the creation of ERA and are one of the worlds' largest transnational efforts to steer the organisation of scientific knowledge production by funding thousands of collaborative R&D projects. Ever since its initiation, the budget of the FPs has increased with a great leap following the launch of ERA. The current

running FP7 marks a clear increase over previous programmes (EUR50.521 billion, 2007-2013), while the budget is likely to grow further in the new research policy programme of the European Union called Horizon 2020.

Since the start of the FPs, one of the key requirements for participation on the FPs is that proposals for collaborative R&D projects must be submitted by at least two independent organisations established in different Member States. This implies that research collaboration within the FPs is inherently international and as such intends to reduce fragmentation that is due to the organisation of science at the level of nation-states and sub-national regions. In its most extreme form ERA can then be defined as an area in which the choices of collaboration partners are made irrespective of regional and national territories and of the borders that separate them. The underlying assumption for allocating funds to this pursuit holds that such an integrated research area does not yet exist. This assumption provides the starting point for the empirical analysis in Chapter 2 and Chapter 3.

RESEARCH QUESTION CHAPTER 2: *To what extent are the spatial patterns of research collaboration between European regions structured according to a logic of proximity and a logic of stratification?*

Chapter 2 provides initial empirical insights in the geography of research collaboration by studying the extent to which research collaborations are structured according to a logic of proximity and a logic of stratification. More specifically, we address the role of physical and institutional proximities (i.e. distance and territorial borders), as well as the role of elite structures among excellence regions and among capital regions.

We measure research collaboration using both scientific publications and patents with multiple addresses that are classified in 1,316 NUTS3 regions in 29 European countries. In doing so, one of the empirical novelties of the study is the detailed spatial level of analysis which roughly corresponds to labour market areas consisting of a major city and its commuting area. It can be argued that this is the most relevant unit of analysis for our theoretical arguments as interactions within such areas can rely on moments of co-presence on a daily bases.

Using gravity equations we show that the effect of geographical and institutional proximities is significant for co-publication activity as well as co-patenting activity. We also find evidence for the existence of elite structures, both between excellence regions and capital regions. Based on these findings we doubt the compatibility between the competiveness and cohesion objective of the European

Union. We do however not explicitly evaluate these policies in this chapter and return to this issue in Chapter 4.

RESEARCH QUESTION CHAPTER 3: *To what extent is the logic of proximity in research collaborations between European regions changing over time?*

In Chapter 3 we broaden the scope of analysis by studying the spatial structure of research collaboration over time and across a large range of scientific disciplines. Following the logic of proximity, our main argument holds that when considering changing spatial structures of research collaboration, one should distinguish between a possible changing effect of distance and a possible changing effect of territorial borders. Next to this general analysis we provide insight in differences between regions and countries in their propensities to collaborate with proximate and distant partners. We attribute this heterogeneity to spatial factors derived from the logic of stratification such as the unequal access to the material infrastructure that sustains communication and movement.

The main conclusion of Chapter 3 holds that the importance of regional and national borders is diminishing over time. Yet given this trend, physical proximity as a facilitator of moments of co-presence remains an important determinant of research collaboration. In the conclusion of this chapter we again attribute our findings to the possible effects of EU policies which reduce territorial fragmentation in research collaboration. In Chapter 4 we take up this suggestion further by studying the effect of the FPs on the geography of research collaboration.

RESEARCH QUESTION CHAPTER 4: *To what extent do the Framework Programmes influence the logic of proximity and the logic of stratification in research collaboration between European regions?*

In Chapter 4 we study the effect of FP participation on reducing the fragmentation in research collaboration that exists due to national borders. At the same time we address whether allocation and effect of the FPs is skewed towards already existing research collaborations between regions which may result in the creation of 'excellence structures' between European regions. The latter question is driven by the intention of the FPs to allocate research funds, not on the base of 'juste retour' or cohesion but "*based on the quality and relevance of research, thus gradually promoting the necessary specialisation and concentration*" (European Council 2008b, p. 6). This pursuit of excellence may be at odds with the goal of income convergence among regions and it may well stratify collaboration at the international level. To answer these research questions we link a regionalised

database on publication activity with a regionalised database on participation in the Framework Programmes. In order to link the two databases we establish a concordance based on acknowledgements in publications to FP projects.

The results of this chapter indicate that previous co-publication activity only has a minor effect on being funded in the FPs. We also find that the effect of FP funding on co-publication activity is especially significant for regional pairs that did not co-publish intensively before participation. The results suggest that the returns to FP funding are highest when involving scientifically lagging regions. Worries voiced in earlier chapters about potential incompatibilities between research and cohesion policy seem therefore unfounded at the regional level.

PART B: CLINICAL TRIALS AND EVIDENCE-BASED MEDICINE

The conduct of randomised controlled clinical trials is the key methodology to produce scientific evidence on the efficacy and safety of medical treatments in order to legitimate their release on the market. During the sixties it became a requirement for firms that medical treatments should be tested to be safe and effective before they could be marketed as such (Avorn 2003). The implementation of these new regulations converged around a standardised corporate drug testing process with well defined stages that ultimately results in the approval of an experimental compound on the market. More specifically, lab-based drug discovery results in the synthesis of new compounds that are tested in vitro and on animals. If the firm considers the drug promising enough both from a technological and economic perspective a compound is advanced in clinical trials on human subjects (Di Masi 2003). To start the clinical stage consisting of three standardised phases[9], an Investigational New Drug (IND) application needs to be filed and approved. The subsequent design and conduct of all clinical trials is overseen by an Institutional Review Board (IRB) and patient enrolment and data collection is conducted by researchers at academic institutions, hospitals or for profit clinics. If the drug proves to be effective and safe in all phases, a New Drug Application (NDA) can be filed which is reviewed

[9] The first phase of trials last about one year and aims to assess the safety of the drugs on small groups of healthy subjects. In a typical Phase II trials several hundred patients are involved and information is gathered on the efficacy of the compound and additional safety concerns are studied. Compounds that advance in Phase III are tested in large randomised controlled clinical trials which require thousands of patients and can last up to five years. It should be noted that there is also a fourth phase of post marketing clinical trials which are required by the FDA after the drug is approved on the market (Di Masi 2003; Fisher 2009).

by the U.S. Food and Drug Administration or the medicine authorities in other regions for approval of the compound on the market.

The increased use of clinical trials as a means to establish the safety and efficacy of medical treatment also provided the raw material for the rise of Evidence-based medicine as an organising principle of scientific knowledge production in the clinical fields. Evidence-based medicine de-emphasises *"intuition, un-systematic clinical experience and pathophysiologic rationale as sufficient grounds for clinical decision making" (*Evidence Based Working Group 1992, p. 2420) and advocates instead "*the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients*" (Sacket et al.1996, p.71). This novel approach to clinical medicine has gained remarkable support on the part of the academic community. Its specific implementation through a standardised package of scientific techniques (e.g. clinical trials, meta-analyses, systematic reviews, guidelines) and procedures (e.g. randomisation, concealment, control groups) has had a decisive impact on the epistemology of medical research and its associated normative structure. Recently, readers of the prestigious British Medical Journal chose the initiation of evidence-based medicine as one of 15 milestones of medicine since 1840 (Godlee 2007). Moreover, the methods of evidence-based medicine are now routinely taught in medical schools across the globe, and evidence-based thinking has extended its reach well beyond the domain of medicine to fields as diverse as education, policy-making and management (Mykhalovksiy and Weir 2004).

However, as clinical trial activities have become firmly embedded within evidence-based medicine, we observe major changes in the way clinical research is organised. More specifically, the large-scale research done in clinical trials is rapidly globalising which is facilitated by the harmonisation of clinical practices across the globe as envisaged in the ICH-GCP guidelines. These guidelines assure that the data resulting from global clinical trials are uniform, credible and accurate, and they also ensure that the rights and integrity of human subjects are protected wherever clinical research takes place. As argued in the previous sections, worldwide standardisation facilitates in this respect a process of globalisation.

RESEARCH QUESTION CHAPTER 5: *To what extent do we observe a spatial decoupling of management activities and clinical activities in clinical trial research?*

In Chapter 5 we focus on the globalisation of clinical trials and study under which conditions management and clinical activities in large-scale research collaborations become spatially decoupled. More specifically, pharmaceutical

clinical trials are mainly initiated by sponsors and investigators in the United States, Western Europe and Japan. However, more and more patients in these trials are enrolled in Central and Eastern Europe, Latin America and Asia. The involvement of patients in these new geographical settings raises concerns about proper trial design and outcome parameters, especially when knowledge of, and experience with, those settings is lacking at the level of clinical trial management.

We study this process by linking information on enrolment countries from clinical trial registrations to information on the spatial constitution of management teams that are listed on the primary publication following clinical trial conduct. The empirical results draw attention to a particular logic of stratification. In the field of clinical research some organisations and locations become specialised in the conduct of tasks to which a relatively minor amount of reward accrues. This 'spatial division of labour' follows well known patterns of economic development across the globe and has significant implications for the scientific and ethical integrity of clinical trial research.

Another influence of globalisation in clinical trial research concerns a redefinition of quality in science such as for instance envisaged in the explicit quality grading systems of evidence-based medicine. More specifically, international collaboration and the conduct of clinical research in different geographical settings is believed to make the obtained research results more robust. We turn our attention to this phenomenon in Chapter 6 where we study publication behavior of pharmaceutical companies and where we analyse amongst others whether spatial variation in research projects contributes to the willingness of firms to publish the results of clinical trials.

RESEARCH QUESTION CHAPTER 6: *To what extent is scientific publishing in clinical trial research dependent on the outcomes of the study and its clinical relevance?*

We frame the contribution of Chapter 6 against the background of ongoing debates about the publication behaviour of pharmaceutical firms. It is now well known that publication strategies from firms are characterised by a persistent bias to publish positive results. As a response to this bias, recent institutional reforms in clinical trial research now mandate that clinical trial protocols are registered before onset and basic results of trials are published after study completion.

We study the publication behaviour of pharmaceutical firms in this context of complete information disclosure where firms face the choice of publishing research results either in scientific publications or in web publications. We do so

by relying on a sample of diabetes clinical trials for which we establish a link between research protocols and subsequent result publications. The results indicate that under conditions of complete information disclosure firms do not publish less than not-for-profit researchers. However, firms strategically publish findings in scientific journals (as opposed to web reports) where they especially highlight favourable results and clinically relevant findings. With regard to the geography of research collaboration, the findings also suggest that firms are more likely to publish international studies although this effect decreases with the involvement of researchers from non-traditional research locations. Despite institutional reforms, publication bias thus persists in the scientific literature.

RESEARCH QUESTION CHAPTER 7: *To what extent is the detection of error in scientific publications dependent on the prestige of the research findings and the coordination modes of the research process?*

As argued in Chapter 2-5 physical proximity remains an important determinant of research collaboration, even after controlling for a number of alternative explanations. This finding begs the question whether scientific knowledge production has become standardised enough to facilitate effective mutual understanding and peer-control over large distances. We turn to this issue in Chapter 7 of this dissertation and study whether error in scientific publications is more likely to be present in spatially distributed research.

The last decade has witnessed a rapid increase in the number of mistakes that accompany scientific publications. Clinical trial research provides a unique opportunity to study this phenomenon as the field has become remarkably standardised in recent years. This facilitates the development of common reference frames against which inconsistencies can be more easily identified. We hypothesise that, in this context, the detection of error can be understood from coordination failure, as well as from the prestige of research. In the empirical strategy we link detailed information from protocols, publications and published errata of 4,777 clinical trials. All errata are classified based on the number and nature of mistakes.

Our findings indicate that corrections in the scientific literature depend amongst others on the expected impact of publications, academic peer-control, project size, funding sources and the geographical distance between researchers. We also observe significant differences between these factors depending on the nature of error. More specifically, the likelihood of content-related errors increases with the geographical distance between researchers, the project size and commenting by

peers, whereas the likelihood of deviations from institutional publishing norms increase with the number of authors and when the project is industry funded.

1.6 Concluding remarks

The next six chapters of this dissertation provide empirical insights in the geography of research collaboration from a variety of perspectives. Congruent with the two research questions, the first four chapters of this thesis study the spatial determinants of research collaboration (Chapter 2-5), whereas the latter four chapters analyse the influence of these determinants on scientific publishing (Chapter 4-7). The main conclusion of the first research question holds that changes in the contemporary geography of research collaboration are mainly visible in the harmonisation of scientific institutions across territories, rather than in a tendency towards a 'death of distance' per se. This paradoxical process creates a tension between prospects provided by worldwide standardisation, and an ongoing significance of physical proximity to make such prospects a reality in actual research practices. As a result we observe with respect to the second research question that globalised science reveals new publication practices that affect the reward system of science, authorship norms, the prevalence and correction of error in scientific publications and the conditions under which disclosure of research findings takes place. These changes require a rethinking of the dominant modes of governance in scientific knowledge production.

The ongoing process of worldwide institutional harmonisation is visible in many instances ranging from the rise of international funding schemes to the increased enforcement of uniform research practices and publication norms. A notable and timely example is the announcement of the United States' National Science Foundation to convene a summit in 2012 to develop "*global principles and procedures*" in order to reduce "*the most fundamental barriers to bilateral and multilateral international collaborations* [that] *are disparate standards for scientific merit review and differences in the infrastructures that ensure professional ethics and scientific integrity*" (Suresh 2011, p. 802).

First, the findings in this dissertation indicate that it would be too simple to assume that such territorial harmonisation of scientific institutions unambiguously results in a global level playing field where all researchers operate under the same rules of the game and where chances of success level off. In an age of globalisation, science remains a highly stratified institution. The differential allocation of reward is, for instance, anticipated in international funding schemes that often distribute funds on the base of 'global excellence' and

the tackling of 'grand challenges'. These competitive funding schemes have the potential of augmenting existing differences between researchers in their access to resources, making reputable researchers relatively more 'footloose' than less reputable ones. In doing so, stratified structures of research collaborations may emerge that have high entry-barriers and operate irrespective of the location of researchers vis-à-vis each other. At the same time, productive researchers may also contribute to ongoing spatial concentration of scientific activities in a few locations by attracting young talent and investments for scientific facilities to particular locations. The balance of this local-global nexus has received considerable attention in the field of geography, but their particular forms and effects have not yet been studied in the context of scientific knowledge production. One of the unanswered questions in this respect is to what extent science becomes more efficient in delivering technological innovation and providing policy solutions as a consequence of the emergence of stratified network structures. The dominant perspective in this case still holds that 'valorisation' of scientific knowledge is an outcome of 'localised knowledge spillovers' and the spatial concentration of star scientists in a small number of high-tech clusters. It remains to be seen whether changes in the geography of research collaboration will influence these interactions between science and innovation in the near future (see also Ponds et al. 2010).

Second, the findings in this dissertation suggest that the harmonisation of territorial institutions creates new divides. Standardisation of research practices and publication norms makes some scientific tasks increasingly routine. It follows that these tasks can be more easily managed at a distance facilitating a process of 'outsourcing' to locations where the costs of scientific conduct are lower and where institutions may be less strictly enforced. In this, the production of scientific knowledge follows economic patterns of globalisation and runs the risk of becoming more global without acknowledging the contributions of individuals across the globe. A notable counteracting development are the policy efforts of emerging economies (e.g. China, India, Brazil) to promote scientific knowledge production by training and funding an increasing number of scientists and by providing incentives to migrated scientists to return to their home-country. The spatial dynamics of this catching-up process and their organisational specificities remain a little studied topic until now and deserve more attention in further research. One important question holds to what extent these new scientific centers simply adapt to already existing scientific norms and institutions or whether their increased engagement will contribute to the emergence of new ways of doing science.

Third, the results of this thesis show that emergent global forms of scientific knowledge production put increasing pressure on scientific institutions to ensure the quality, transparency and integrity of individual research findings. New commercial and global contexts of doing research have often been cited as contributors to the quality, impact and practical application of research findings. The results of this dissertation do not argue with these findings but point at least to some potential 'side-effects' of the increased distributed nature of research, particularly with respect to the publication of research in scientific journals. Future studies could take changes in publication behaviour as a starting point in order to study to what extent editorial policies can effectively cope with them. Evaluations of the effectiveness of publication norms (e.g. data sharing, conflict of interest disclosure and peer-review) provide an interesting point of departure for these studies.

In general this dissertation sets out to contribute to the emergent field of spatial scientometrics (Frenken et al. 2009). In doing so we introduced proximity and stratification as two organising principles of research collaboration and mainly took a macro-spatial perspective to analyse their changing role. The main suggestion to improve the current analysis is therefore to lower the level of analysis as to document the time-space trajectories of individual researchers and research topics over their life-cycle. With regard to the role of proximity such an approach would provide the opportunity to study whether different forms of proximity can act as substitutes in space and time. For example, a new field may emerge from a single research institute where researchers develop a common socio-cognitive framework over time. When these researchers subsequently move to other organizations, physical proximity vanishes but the socio-cognitive proximity built up in the past allows them to continue to collaborate effectively. The notion of temporary proximity is central to such an analysis (e.g. conferences, guest scholarships) and requires more explicit attention in future studies as to extend the proximity framework from mere static to dynamic analysis. Furthermore the notion of proximity could also be used to study other settings of interaction in the science system such as those that take place between scientific manuscripts (e.g. referencing) and those that follow from labour mobility. Multiple settings of interaction can in this case also be conceptualized as being sequential. For example, particular referencing patterns between authors may render future research collaboration more likely and this may ultimately result in labour mobility and permanent co-location of researchers.

Suggestions for future research to understand processes of stratification are manifold as the spatial aspects of stratification remain little studied up to now. Our understanding of matching processes between researchers based on

similarity in their productivity and irrespective of their geographical locations is still limited. Documentation of the time-space trajectories of researchers and the topics they provide a starting point to assess the conditions under which we can expect such matching to occur. The increased prevalence of transnational funding initiatives should be taken into account in these analyses as such funding often explicitly tries to match researchers on the base of global excellence and irrespective of their locations. Furthermore, the field of geography has been traditionally concerned with the unequal spatial distribution of human activities but has only recently provided insight in the emergence and sustainment of spatial inequalities and their long-term implications for innovation and economic growth. Future studies can in this case explore how specific transmission channels of reputation and tacit knowledge between researchers enhance or weaken stratified patterns of scientific knowledge production.

In sum, this dissertation documents the contemporary geography of research collaboration and draws attention to related changes in scientific publishing that provide new challenges for the governance of scientific knowledge production. Given this development it is important to critically engage in debates about the nature of scientific knowledge production without automatically taking for granted particular norms and forms of scientific conduct. The six remaining chapters of this dissertation provide some points of departure for this endeavor.

2

The geography of collaborative knowledge production in Europe

2.1 Introduction

Knowledge production has become a central concern for firms and policy makers alike. In particular, the transformation towards a 'European knowledge society' rendered science and technology of particular importance to ensure the competitiveness of Europe. Against the background of this process, the 'Lisbon agenda' of the European Union can be considered an attempt to reorient Europe's main rationale from one based on economic integration alone towards one based on the concept of a common knowledge society. A major initiative in this direction has been to create a European Research Area (ERA).

The general idea underlying ERA is that *"research activities at national and Union level must be better integrated and coordinated to make them as efficient and innovative as possible"* (European Council 2000, I.A.12). Such an objective assumes that a European Research Area does not yet exist and that its creation requires action at several levels of spatial aggregation. Yet, studies assessing these assumptions are scarce and traditionally have focused only on the level of countries (see Narin et al., 1991; Glanzel 2001; Frenken 2002). Little is known about the regional dimension of collaborative knowledge production despite its supposed relevance in the light of regional, national and European policies.

The present study assesses the extent to which European inter-regional research activities are already integrated based on scientific publications and patents with multiple addresses. Using these data, we address the role of proximity and of elite structures in collaborative knowledge production. Our main research question holds to what extent geographical and institutional proximity, as well as

elite structures among excellence regions and among capital regions, explain the participation of regions in collaborative knowledge production.

Concerning proximity, the inter-regional perspective allows us to differentiate between geographical patterns in collaborative knowledge production within and between member states. By doing so, we can test to what extent geographical distance and institutional distance hamper collaboration, where geographical distance is expressed in terms of distance in kilometres between two regions and institutional distance is reflected in a dummy variable distinguishing between domestic and foreign collaborations. Geographical distance relates directly to the costs of collaboration, which increase with distance, while institutional distance relates to obstacles in collaboration due to different national institutions.

In our framework based on inter-regional collaboration, we also analyse elite structures that facilitate collaboration among favoured regions. More specifically, we focus on cognitive structures that explain why 'excellence regions' have a bias to network among them and on political structures that explain why capital cities have a bias to network among them.

This paper is organised as follows. In section 2 we discuss general trends in research collaboration. Section 3 introduces some theoretical concepts and derives a number of hypotheses. Data and methodology are presented in section 4 and the estimation results in section 5. In the final section we discuss EU policies in the light of our evidence.

2.2 PREVIOUS RESEARCH

If anything has characterised knowledge production in science and technology during the 20th century, it is the increased collaborative nature of knowledge production (Meyer and Bhattacharya 2004). In science, co-authorships accounted for less than 10 percent of all publications at the start of the 20th century, while co-authorships account for over 50 percent of all publications at the end of the twentieth century (Wagner-Doebler 2001).

The relevance of collaboration is evidenced by the fact that the number of citations that scientific articles receive increases with the number of contributing researchers (Katz and Martin 1997; Frenken et al. 2005). Similarly, the average number of inventors that contribute to a patent has increased over time during the past 20 years (Fleming and Frenken 2007). Both trends indicate an increased division of labour among researchers. With the universe of knowledge ever

expanding, researchers need to specialise to continue contributing to state-of-the-art knowledge production.

To encourage research collaboration, the European Union has always been concerned with funding international research projects and with removing barriers that currently hinder researchers in such projects, and its financial efforts in this direction have again been increased substantially in the 7th framework programme, which runs from 2007 to 2013 (Commission 2006).[10] European collaboration is expected to generate benefits in many ways. Economically, it provides opportunities to realise savings with regard to costs of training and sharing research infrastructures as well as to avoid duplication of research efforts. International collaboration is also expected to generate intellectual benefits from the cross-fertilisation of ideas that previously were unconnected. Indeed, scientific articles stemming from international collaboration projects, on average, receive more citations than national collaboration projects (Narin et al. 1991; Katz and Martin 1997). The European Commission's objective to create an ERA by stimulating research collaboration is therefore legitimate as long as barriers exist that impede European researchers from engaging in research collaboration.

Studies analysing collaborative knowledge production at the regional level have been mostly limited to particular countries only. Co-publications among regions have been analysed by Katz (1994) for the UK regions, Danell and Persson (2003) for Swedish regions, Liang and Zhu (2004) for Chinese regions, and Ponds et al. (2007) for Dutch regions. Co-inventorships among Swedish regions using patent data have been analysed by Ejermo and Karlsson (2006). At the European level, we know of only one patent study by Maggioni et al. (2007) who analysed the effect of geographical distance on inter-regional collaborations based on co-inventorships between NUTS2 regions for six countries. In line with studies done for particular countries, they also found that distance significantly affects the formation of inventor networks.

Our study takes three steps to improve the analysis of the geography of research collaboration. First, we have been able to cover a larger set of countries (EU27

[10] The total budget of the Seventh Framework amounts to EUR 50.521 million. The majority (64.1%) of the budget of the Seventh Framework is reserved for 'Cooperation'. Other important elements are labour mobility of researchers under the heading of 'People' (9.4%) and the enhancement of research and innovation infrastructures under the heading of 'Capacities' (8.1%) (Commission 2006).

plus Norway and Switzerland) at a lower level of spatial aggregation (NUTS3). Second, we will analyse not only the effect of geographical distance on the intensity of inter-regional collaboration, but we will also include other determinants (institutional proximity, elite structures) in the analysis. Third, since we collected both data on publications and patients we are able to differentiate between research collaboration in science and technology, respectively.

2.3 THEORETICAL FRAMEWORK

The rationales for collaborative knowledge production are straightforward: actors engage in collaborations to learn from each other and to make a stronger impact on the field than could be achieved individually. Indeed, collaborations are expected to increase the quality of the research output, but at the same time the pursuit of quality is restricted by several constraints. The time and money required to engage in collaboration are substantial, which forces researchers to be highly selective in choosing a collaboration partner. Thus, the strength of interaction between any two actors, and any two regions, will be dependent on the learning opportunities involved in collaboration at the one hand, and the time and money required to participate on the other hand.

Starting with the costs involved, we can distinguish between two forms of proximity that are expected to bring down costs and thus to increase the probability of interaction (Boschma 2005). First, the costs of collaboration increase as a function of geographical distance. As a result, we hypothesise that research collaborations between geographically proximate researchers are more likely to occur. Second, the costs of research collaboration increase with institutional distance as a common institutional framework brings costs down (Gertler 1995; Edquist and Johnson 1997).[11] In the case of knowledge production, the relevant institutional arrangements (funding, labour markets, intellectual property right regimes, common language) have a strong, although not exclusive, national component. Hence, our hypothesis therefore holds that two regions that belong to the same country are institutionally nearby and more inclined to collaborate, while two regions belonging to different countries are institutionally distant and more reluctant to collaborate.

[11] Institutional proximity can also be taken to refer to relations between organisations that operate in the same societal subsystem, like inter-university relationships, or inter-firm relationships, or inter-governmental relationships. On this, see Ponds et al. (2007).

Turning to benefits of collaboration, we distinguish between benefits for elite researchers and other researchers. Elite researchers working at the cutting edge of research are more inclined to collaborate with other elite researchers, since they learn much more from fellow elite researchers than from those less advanced. A fundamental observation in this context is that elites are remarkably concentrated in certain regions. This generates advantages as evidenced by the mean rate of citations received by scientific publications (Frenken et al. 2007; Tijssen 2007). Hence, in research collaboration, regional hierarchies are likely to emerge, with regions hosting the elite researchers – which we call 'excellence regions' – networking primarily among them and much less with less advanced regions.

Second, elite structures exist between researchers in terms of access to their resources. Collaboration requires resources, and differential access to resources will impact the propensity of actors to collaborate. Resources are concentrated in large cities - predominantly capital cities - where banks and funding agencies are concentrated. Furthermore, most national research institutes are located in capital cities, and these institutes are typically over-represented in multilateral programmes supported by multi-lateral government funding. Following this reasoning, we expect that, all else being equal, pairs of capital regions are likely to have stronger ties than pairs of any other type of regions.[12]

Summarising, we expect the inter-regional intensity of collaboration to be dependent on costs on the one hand and benefits on the other. The wish to minimise costs will lead researchers to be biased and to collaborate with geographically and institutionally proximate parties. Differential opportunities will be reflected in cognitive elite structures between excellence regions and political elite structures between capital regions.

2.4 Research design

Research on collaborative knowledge production has always been relying on partial indicators. Since knowledge is - by definition – intangible it cannot be measured and counted directly and unambiguously. Yet, many research collaboration efforts, have a tangible output: a text. Many of these texts reach the public domain in the form of publications in scientific journals or in the form of patents awarded by patent offices. Both publications and patents indicate a

[12] What is more, almost all capital regions also host the main airport in a country, providing an advantage in accessibility through air.

research activity of proven value. Publications in scientific journals have been peer-reviewed, which assures a certain minimum level of quality and originality. Patents are reviewed by patent examiners, who decide to grant a patent on the basis of the originality of the invention.

Scholars studying science and technology make extensive use of publications and patent data due to a number of advantages (Griliches 1990; Frenken et al. 2007):

1. Each publication and patent contains highly detailed information on content (title words and abstract), previous art (citations), researchers (name), organisations involved (institutional affiliation), and geographical location (address).
2. Systematic data collection on patents and publication goes back a long time.
3. The current 'stock' of patents and publications is large and ever growing.

However, we should also bear in mind that the use of these paper trails is not completely without limitations (Griliches 1990; Frenken et al. 2007). More specifically, we can identify three major drawbacks:

1. Research does not necessarily lead to publications or patents. Rejection by reviewers is one of the main reasons of research efforts not necessarily resulting in publications or patents. Other reasons include time/cost constraints of researchers to submit a report for publications or patenting and non-disclosure strategies by firms who value secrecy over property right.
2. Publications and patents do not necessarily contribute to our knowledge. Most publications and patents are rarely cited, if at all, which suggests that their added value to the knowledge system is small. And, regarding patents, the commercial value of patents varies widely.
3. Publication and patenting rates differ systematically across scientific disciplines and technology fields, respectively. This means that inter-regional comparisons can be misleading due to the differences in technological specialisation.

Despite these shortcomings we make use of both publications and patents as we consider these data appropriate given our purpose for a number of reasons. With regard to the first limitation, our research topic being the European Research Area renders the use of quantitative information almost indispensable. Alternative research methodologies, for example based on expert interviews, would be too limited in their scope. We address the second limitation by aggregating publications and patents to the regional level in order to minimise differences in quality. Furthermore, regarding publications, we distinguish between excellence regions and other regions as to control for quality differences. With regard to the third limitation, the separate analysis of various scientific

disciplines and technology classes allows us to avoid making conclusions that are biased by regional differences in scientific or technological specialisation.

DATA

Data on publications have been retrieved from *Web of Science (WoS)*, which is a product of Thomson Scientific. Web of Science is an electronic archive of scientific publications in most science journals. Though WoS does not contain all journals and tends to be biased towards English-language journals, it is widely considered the most comprehensive and reliable source covering all the major journals in the world.

Data on patents have been obtained from the *European Patent Office (EPO)* database. Our focus on the European Research Area provides a clear rationale for the use of this database. Moreover, using patent data from the European Patent Office rather than from national patent offices ensures that we deal with patents with, on average, a high expected commercial value, since applying to the EPO is more expensive and time-consuming than applying only to national patent offices.

We retrieved the information for scientific articles published between 1988 and 2004, since access to WoS is restricted before 1988. Hence, patents have also been obtained from 1988 onwards, but we did not extend the patent data beyond 2001, because there is a sudden drop in the total number of patents after 2001 at the time we retrieved the data. This drop reflects to backlog in the administration of patents awarded.

We did not retrieve all publications and patents, but limited the analysis to two science-based technologies: biotechnology and semiconductors.[13] These technologies had a revolutionary global impact during the last two decades and have long been thematic priorities in many European, national and regional policies. Patents are selected on the basis of the IPC classes biotechnology and semiconductors. Following Verbeek et al. (2002), we subsequently selected scientific publications on the basis of journals that are often cited in the patents. For biotechnology, the relevant scientific discipline becomes biochemistry and

[13] More details can be found in Frenken et al. (2007).

molecular biology, while for semiconductors we chose electrical and electronical as the relevant scientific discipline.[14]

With regard to the territorial breakdown, we decided to construct our data at the NUTS3 level covering the 27 countries of the European Union plus Norway and Switzerland. We consider the NUTS3 level of spatial aggregation to be relevant as it corresponds most closely to regional labour markets *in casu* 'regional innovation systems' (Cooke et al. 1998). Thus, all addresses occurring in publications and in patents have been assigned to one of the 1,316 NUTS3 regions in the aforementioned 29 countries in Europe.[15]

One major advantage of using publications and patents is that the addresses of researchers are systematically recorded in these texts. We make use of this information to construct our dataset on research collaboration by selecting all publications and patents with multiple addresses in more than one NUTS3 region.[16] In our dataset this phenomenon represents an inter-regional collaboration link. The collaboration intensity between region *i* and *j*, labelled I_{ij}, is then defined by the number of times addresses from these two regions co-occur in a publication or a patent. In doing so, we obtain our matrices of inter-regional collaboration patterns which serve as the basis of our empirical analysis. We thus use 'full counting' to derive the interaction strength between two regions. For example, if a publication contains three addresses in three different regions, the interaction count between each pair of regions is one. Alternatively, one can use fractional counting were a co-occurrence of two regions in a publication or patent divided by the total number of interactions. For example, if a publication contains three addresses in three different regions, the interaction strength between each

[14] Publications from Applied Physics are even more often cited than publications from electrical and electronical engineering, yet Applied Physics is rather broad as to account as a discipline.

[15] We were not able to locate the addresses within the greater urban areas of London and Manchester and as a result consolidated them into two new regions. Furthermore, we excluded some islands due to their remote locations and disproportional great geographical distances to other regions. These islands are: Guadeloupe Las Palmas (ES), Santa Cruz de Tenerife (ES), Guadeloupe (FR), Martinique (FR), Guyane (FR), Réunion (FR), Região Autónoma dos Acores (PT) and Região Autónoma da Madeira (PT). The outcome is a total number of 1316 NUTS3 regions instead of 1329.

[16] The address information in publication data refers to the address of the organisation where the researcher works. In contrast, the address information in the patent data we used refers to the home addresses of the researchers involved. This difference should always be kept in mind, as it precludes any comparison between the collaboration patterns that are reflected in publications and those that are reflected in patents.

pair of regions is one-third. The final matrix of inter-regional interaction strength based on full counting is very similar to the final matrix obtained by fractional counting.[17]

It is important to note here that the occurrence of publications and patents with multiple addresses may refer to several underlying mechanisms. In most cases, an inter-regional link represents a collaboration between two or more researchers or institutions. Yet, it may also be the case that a single researcher appears on a publication or patent with two or more addresses. This phenomenon also counts as a collaboration and denotes that the researcher works for two or more organisations or conducted a research for one organisation and subsequently moved to another organisation. Thus, the inter-regional collaboration networks refer primarily to the main pillar of the Framework Programmes (i.e. 'Cooperation'); to some extent, however they also reflect labour mobility mechanisms, which are another pillar of Europe's research policies under the heading of 'People'.

Gravity model

We analyse the determinants of the constructed inter-regional networks using a gravity model. Spatial interaction, the process whereby actors at different points in physical space make contacts, can be revealed by applying an analogical model of Isaac Newton's Theory of Universal Gravitation (Tinbergen 1962; Sen and Smith 1995; Roy and Thill 2004). In a gravity model, the gravitational force between two objects is assumed to be dependent on the mass of the objects and the distance between them. In our case this means that the interaction intensity of research collaborations in science and technology aggregated at the NUTS3 level is hypothesised to be dependent on the masses of the two regions and inversely dependent on the geographical distance between two regions. The basic gravity equation is therefore as follows:

$$I_{ij} = \alpha_1 \frac{MASS_i^{\alpha 2} MASS_j^{\alpha 3}}{DISTANCE_{ij}^{a4}} \tag{2.1}$$

Such a gravity model can be estimated using linear regression by taking a double log:

[17] Correlations between the full counting and fractional counting matrices are above 0.99.

$$\ln I_{ij} = \ln \alpha_1 + \alpha_2 \ln MASS_i + \alpha_3 \ln MASS_j + \alpha_4 \ln DISTANCE_{ij} \quad (2.2)$$

with $\alpha_2 > 0$, $\alpha_3 > 0$ and $\alpha_4 < 0$.

Since we deal with count data, we cannot rely on an OLS estimation procedure. The use of alternative regression techniques is appropriate (Burger and Van Oort 2007). Probably the most common regression model applied to count data is Poisson regression, which is estimated by means of maximum likelihood estimation techniques. In this log-linear model, the observed interaction intensity between region *i* and *j* has a Poisson distribution with a conditional mean (μ) that is a function of the independent variables.

$$\Pr[I_{ij}] = \frac{\exp^{-\mu_{ij}} \mu_{ij}^{I_{ij}}}{I_{ij}!}, \text{ where in our model}$$

$$\mu_{ij} = \exp(a_1 + a_2 \ln MASS_i + \alpha_3 \ln MASS_j + \alpha_4 \ln DISTANCE_{ij}) \quad (2.3)$$

In order to correct for overdispersion (conditional variance is larger than the conditional mean) and an excessive number of zero counts in our data set (the incidence of zero counts is greater than would be expected for the Poisson distribution as most regional pairs do not collaborate with each other), we make use of the zero-inflated negative binomial regression, which can be perceived as an extension of the Poisson model. Not correcting for the overdispersion and excess zero problem normally results in incorrect and biased estimates.

The zero-inflated negative binomial model considers the existence of two (latent) groups within the population: a group having strictly zero counts and a group having a non-zero probability of counts different than zero. Correspondingly, its estimation process consists of two parts. The first part contains a logit regression of the predictor variables on the probability that there is no interaction between two given regions at all. The second part contains a negative binomial regression on the probability of each count for the group that has a non-zero probability of count different than zero. A good technical discussion of the zero-inflated negative binomial model is provided by Long and Freese (2001).

COVARIATES

The gravity equation assumes that inter-regional interaction is dependent on the respective size or masses of the regions. In line with our count method for the interaction strength between regions, we use full counting for the masses and derive the total number of publications and patents, including single-authored

texts. Since collaborations are by definition undirected we only include the interaction between a pair of regions once. Due to this fact the size of the coefficient of the two masses may slightly differ.[18] Note also that we added 1 to all masses in order to allow for logarithmic transformation of observations without any publications or patents.

We account for our theoretical suggestions regarding the spatial context of research collaboration by introducing a number of independent variables. In concordance with basic gravity models we add *DISTANCE*, which is calculated between the central points of regions using GIS ('as the crow flies'). The covariate *COUNTRY* is a variable capturing institutional proximity between regions, coded one if regions belong to the same country and coded zero otherwise.

As explained, elite structures are accounted for by defining *EXCELLENCE* and *CAPITAL*. In our analysis, excellence regions are defined as those belonging to the top 25 most publishing regions and the top 25 most patenting regions. Size is treated here as a proxy for quality. Regions that host top institutes will typically grow and attract the best talent, while regions with poor institutes will have trouble growing and retaining their talent. The assumption that size and quality are closely correlated is also supported by the empirical finding that the mean citation rate for scientific articles in a region increases with the number of articles produced in that region (Frenken et al. 2007; Tijssen 2007). Defining capital regions does not need further explanations, although we should mention that as a result of the low level of aggregation we selected more than one NUTS regions as capital regions for some countries.[19] From this, we create two dummy variables that capture the elite structures between regions. Excellence structures are measured by a dummy for relations between two regions of excellence, and capital structures by a dummy for relations between two capital regions.

The extended gravity equation to be estimated is thus as follows:

$$\ln I_{ij} = \alpha_1 + \alpha_2 \ln MASS_i + \alpha_3 \ln MASS_j + \alpha_4 \ln DISTANCE_{ij} + \alpha_5 COUNTRY_{ij} + \alpha_6 EXCELLENCE_{ij} + \alpha_7 CAPITAL_{ij} + \varepsilon \quad (2.4)$$

[18] Alternatively, we may also subtract M_i and M_j to make a single new variable indicating the mass of both regions. Results of the regression models are similar and available on request.

[19] This is the case for Paris, France (5 regions) and Copenhagen, Denmark (2 regions). In all other countries we selected one NUTS3 region that corresponds to the capital city.

The zero-inflated negative binomial model allows for an estimation process in which the explanatory variable is predicted by two distinct processes. As we believe that in case of research collaboration the determinants predicting the chance of collaborating do not differ from the determinants that predict the intensity, we include the same variables in both parts of the regression model. The only exception in the model is the variable *EXCELLENCE*, which we only include in the negative binomial part. The reason for this is that estimating the probability that there is no interaction at all is irrelevant in this case, as we only included regions that belong to the 25 most publishing or patenting regions.

Table 2.1 reports some descriptive statistics on the variables of main interest. Because our analysis addresses all possible pairs of regions, and not individual regions, the total number of observations amounts to ½·1,316·1,315 = 865,270 observations. This also implies that the mean number of collaboration is very low as the large majority of inter-regional pairs do not collaborate at all (hence, our choice for the zero-inflated negative binomial regression model).

Table 2.1: *Descriptive statistics of inter-regional collaborations*

Publications Biotechnology	**Mean**	**SD**	**Min**	**Max**
1 Inter-regional collaborations	0.25	5.06	0	1671
2 Number of publications region$_i$	263.34	965.60	1	23694
3 Number of publications region$_j$	381.31	1410.67	1	23694
4 Inter-regional distance in km	1045.05	633.32	6.45	4195.56
Patents Biotechnology	**Mean**	**SD**	**Min**	**Max**
1 Inter-regional collaborations	0.04	1.60	0	609
2 Number of publications region$_i$	30.68	93.15	1	1332
3 Number of publications region$_j$	30.01	100.96	1	1332
4 Inter-regional distance in km	1045.05	633.32	6.45	4195.56
Publications Semiconductors	**Mean**	**SD**	**Min**	**Max**
1 Inter-regional collaborations	0.06	1.12	0	296
2 Number of publications region$_i$	74.99	260.97	1	4714
3 Number of publications region$_j$	117.54	350.29	1	4714
4 Inter-regional distance in km	1045.05	633.32	6.45	4195.56
Patents Semiconductors	**Mean**	**SD**	**Min**	**Max**
1 Inter-regional collaborations	0.06	1.12	0	296
2 Number of publications region$_i$	16.14	73.65	1	1518
3 Number of publications region$_j$	12. 274	71.71	1	1518
4 Inter-regional distance in km	1045.05	633.32	6.45	4195.56

2.5 RESULTS

Before discussing the results of the regression analysis, we present correlation matrices in Table 2.2 to identify possible multicollinearity in the covariates. All correlations are well within the allowed range and can be included in the regression analysis.

Tables 2.3, 2.4, 2.5 and 2.6 present the estimates for the regression models with all four regression models showing successively a negative binomial part (NBP), a zero inflated part (ZIP) and some general fit statistics.[20] The In each regression, Model A restricts the analysis to the respective mass of the regions and the geographical distance between them, while Model B adds institutional proximity (same country) and Model C the two elite structures related to excellence and capital regions. The results in all models show that mass and geographical distance are indeed powerful predictors of research collaboration in co-publications and in co-patents. Naturally, the mass contributes positively, indicating an increase in the change and intensity of collaboration between two regions if these regions accommodate a larger number of knowledge producing actors.[21] Distance also has a significant negative effect on the chance and intensity of collaboration. Regions that are further apart collaborate less than regions that are in closer proximity.

Institutional proximity as captured by the dummy variable *COUNTRY* is added in model B. The variable is significant in three of the four models and it has the expected positive sign, indicating that two regions belonging to the same country collaborate more frequently than two regions from different countries.

[20] It is essential to keep in mind that a positive sign in the zero inflated part indicates that with a one percent positive change in the predictor, the chance of belonging to the 'strictly zero group' increases, holding all other predictors constant. Thus, the coefficients in the zero inflated part should be interpreted in reverse in comparison to the negative binomial part: a positive value in the negative binomial part has the same meaning as a negative value in the zero-inflated part and *vice versa*.

[21] The effect of geographical distance tends to be stronger for patents than for publications possibly indicating the higher tacit content on technological knowledge compared to scientific knowledge. Yet, since address information in patent data refers to home address of inventors, while address information in publication data refers to addresses of the employer, strictly speaking, the two cannot be compared.

Table 2.2: *Correlation matrix of covariates*

Publications Biotechnology	**1**	**2**	**3**	**4**	**5**	**6**
1 Mass origin (ln)	1.000					
2 Mass destination (ln)	0.011	1.000				
3 Distance (ln)	0.036	0.067	1.000			
4 Same country	-0.025	-0.128	-0.616	1.000		
5 Excellence	0.048	0.043	0.000	-0.002	1.000	
6 Capital	0.050	0.042	0.009	-0.009	0.113	1.000
Patents Biotechnology	**1**	**2**	**3**	**4**	**5**	**6**
1 Mass origin (ln)	1.000					
2 Mass destination (ln)	0.005	1.000				
3 Distance (ln)	-0.121	-0.121	1.000			
4 Same country	0.051	-0.003	-0.616	1.000		
5 Excellence	0.050	0.053	-0.011	0.000	1.000	
6 Capital	0.040	0.035	0.009	-0.009	0.090	1.000
Publications Semiconductors	**1**	**2**	**3**	**4**	**5**	**6**
1 Mass origin (ln)	1.000					
2 Mass destination (ln)	0.011	1.000				
3 Distance (ln)	0.016	0.058	1.000			
4 Same country	0.007	-0.125	-0.616	1.000		
5 Excellence	0.052	0.043	0.000	-0.002	1.000	
6 Capital	0.049	0.040	0.009	-0.009	0.070	1.000
Semiconductors patents	**1**	**2**	**3**	**4**	**5**	**6**
1 Mass origin (ln)	1.000					
2 Mass destination (ln)	0.011	1.000				
3 Distance (ln)	-0.161	-0.165	1.000			
4 Same country	0.144	0.039	-0.616	1.000		
5 Excellence	0.057	0.071	-0.014	0.005	1.000	
6 Capital	0.025	0.027	0.009	-0.009	-0.009	1.000

Table 2.3: *Zero-inflated negative binomial regression model on interaction intensity of co-publishing in biotechnology for the period 1988-2004*

	Model A	Model B	Model C
	Negative Binomial Part		
Mass origin (ln)	0.640 ***	0.649 ***	0.621 ***
	0.006	0.005	0.006
Mass destination (ln)	0.591 ***	0.636 ***	0.609 ***
	0.005	0.005	0.005
Distance (ln)	-0.734 ***	-0.367 ***	-0.367 ***
	0.009	0.010	0.010
Same country		1.160 ***	1.146 ***
		0.022	0.022
Excellence			0.832 ***
			0.056
Capital			0.475 ***
			0.052
Constant	-2.363 ***	-5.401 ***	-5.040 ***
	0.067	0.086	0.087
	Zero Inflated Part		
Mass origin (ln)	-0.760 ***	-0.770 ***	-0.787 ***
	0.009	0.009	0.009
Mass destination (ln)	-0.764 ***	-0.779 ***	-0.794 ***
	0.009	0.009	0.009
Distance (ln)	0.739 ***	0.359 ***	0.362 ***
	0.017	0.021	0.021
Same country		-1.395 ***	-1.394 ***
		0.048	0.046
Capital			-0.974 ***
			0.233
Constant	4.458 ***	7.366 ***	7.593 ***
	0.112	0.165	0.162
Overdispersion (a)	1.098 ***	0.881 ***	0.848 ***
Vuong-statistic	27.43 ***	27.25 ***	27.85 ***
Log Likelihood	-102712	-99775	-99546
Mc Fadden's Adj. R^2	0.442	0.458	0.459
AIC	0.237	0.231	0.230
N	865270	865270	865270
Nonzero observations	25589	25589	25589

Notes. **** p < 0.01; ** p < 0.05; * p < 0.1*

Table 2.4: *Zero-inflated negative binomial regression model on interaction intensity of co-publishing in semiconductors for the period 1988-2004*

	Model A	Model B	Model C
	Negative Binomial Part		
Mass origin (ln)	0.550 ***	0.533 ***	0.504 ***
	0.010	0.009	0.010
Mass destination (ln)	0.526 ***	0.552 ***	0.525 ***
	0.010	0.010	0.010
Distance (ln)	-0.565 ***	-0.301 ***	-0.299 ***
	0.013	0.016	0.016
Same country		0.824 ***	0.836 ***
		0.036	0.036
Excellence			0.626 ***
			0.073
Capital			0.450 ***
			0.076
Constant	-2.091 ***	-4.064 ***	-3.763 ***
	0.103	0.133	0.135
	Zero Inflated Part		
Mass origin (ln)	-0.844 ***	-0.851 ***	-0.866 ***
	0.013	0.013	0.013
Mass destination (ln)	-0.810 ***	-0.832 ***	-0.845 ***
	0.013	0.014	0.014
Distance (ln)	0.739 ***	0.423 ***	0.426 ***
	0.021	0.027	0.026
Same country		-1.112 ***	-1.098 ***
		0.059	0.058
Capital			-1.146 ***
			0.232
Constant	4.535 ***	6.999 ***	7.150 ***
	0.145	0.202	0.201
Overdispersion (a)	1.502 ***	1.333 ***	1.302 ***
Vuong-statistic	20.30 ***	20.41 ***	20.46 ***
Log Likelihood	-52192	-51302	-51202
Mc Fadden's Adj. R^2	0.429	0.439	0.440
AIC	0.121	0.119	0.118
N	865270	865270	865270
Nonzero observations	12531	12531	12531

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$

Table 2.5: *Zero-inflated negative binomial regression model on interaction intensity of co-patenting in biotechnology for the period 1988-2001*

	Model A	Model B	Model C
	Negative Binomial Part		
Mass origin (ln)	0.411 ***	0.419 ***	0.414 ***
	0.013	0.013	0.013
Mass destination (ln)	0.376 ***	0.387 ***	0.381 ***
	0.013	0.013	0.013
Distance (ln)	-0.572 ***	-0.503 ***	-0.499 ***
	0.015	0.018	0.018
Same country		0.275 ***	0.296 ***
		0.053	0.053
Excellence			0.046
			0.115
Capital			0.453 ***
			0.153
Constant	0.417 ***	-0.187	-0.180
	0.105	0.147	0.148
	Zero Inflated Part		
Mass origin (ln)	-0.740 ***	-0.769 ***	-0.765 ***
	0.013	0.014	0.014
Mass destination (ln)	-0.678 ***	-0.771 ***	-0.769 ***
	0.013	0.014	0.014
Distance (ln)	1.458 ***	0.951 ***	0.961 ***
	0.022	0.025	0.025
Same country		-1.750 ***	-1.743 ***
		0.055	0.054
Capital			-1.390 ***
			0.219
Constant	-0.859 ***	3.360 ***	3.292 ***
	0.124	0.172	0.172
Overdispersion (a)	2.022 ***	1.880 ***	1.865 ***
Vuong-statistic	22.22 ***	19.08 ***	12.12 ***
Log Likelihood	-31660	-30738	-30703
Mc Fadden's Adj. R^2	0.369	0.387	0.408
AIC	0.073	0.071	0.027
N	865270	865270	865270
Nonzero observations	6078	6078	6078

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$

Table 2.6: *Zero-inflated negative binomial regression model on interaction intensity of co-patenting in semiconductors for the period 1988-2001*

	Model A	Model B	Model C
	Negative Binomial Part		
Mass origin (ln)	0.424 ***	0.427 ***	0.421 ***
	0.020	0.020	0.021
Mass destination (ln)	0.452 ***	0.448 ***	0.443 ***
	0.023	0.022	0.023
Distance (ln)	-0.585 ***	-0.614 ***	-0.612 ***
	0.027	0.031	0.031
Same country		-0.233 **	-0.239 **
		0.113	0.114
Excellence			0.131
			0.166
Capital			-0.627
			0.734
Constant	0.206	0.567 **	0.596 ***
	0.163	0.224	0.228
	Zero Inflated Part		
Mass origin (ln)	-0.616 ***	-0.590 ***	-0.593 ***
	0.021	0.021	0.021
Mass destination (ln)	-0.533 ***	-0.597 ***	-0.599 ***
	0.021	0.021	0.021
Distance (ln)	1.570 ***	1.180 ***	1.186 ***
	0.034	0.037	0.037
Same country		-1.654 ***	-1.672 ***
		0.094	0.095
Capital			-2.305 ***
			0.837
Constant	-2.243 ***	1.069 ***	1.076 ***
	0.184	0.240	0.241
Overdispersion (a)	1.690 ***	1.647 ***	1.635 ***
Vuong-statistic	13.52 ***	12.24 ***	12.12 ***
Log Likelihood	-11996	-11757	-11751
Mc Fadden's Adj. R^2	0.396	0.408	0.408
AIC	0.028	0.027	0.027
N	865270	865270	865270
Nonzero observations	2196	2196	2196

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$

Comparison of the results of Model A and Model B also reveals that the inclusion of the *COUNTRY* variable diminishes the estimate of the *DISTANCE* variable, as there is considerable correlation between geographical distance and belonging to the same country. However, though its influence diminishes, geographical distance remains significant in all cases, indicating an independent effect of both geographical distance and institutional distance.

In the final model (Model C), we add the two elite variables to denote possible elite structures in research collaboration. Taken as a whole, these models are more accurate predictors of the determinants of research collaboration, indicated by the better fit expressed in the log likelihood, AIC and adjusted R^2. However, outcomes for publications differ from the outcomes for patents. In the publication system the coefficients of collaborations between excellence regions and capital regions are all positive and significant.[22] For the patenting system, we only find a bias between capital regions for biotechnology.

2.6 DISCUSSION

In this study we adopted a gravity framework to analyse inter-regional collaboration based on scientific publications and patents with multiple addresses. More specifically, we addressed the role of proximity and elite structures in collaborative knowledge production. The results for 1,316 European regions indeed showed that these two determinants affect the formation of inter-regional collaborative networks. By doing so, we confirmed the role of geographical proximity as found by other studies, yet extended our understanding of other barriers to collaborate including national borders and elite structures stemming from cognitive and political structures.

Our results bear significant implications within a European policy context.[23] The outcomes with regard to the importance of proximity indicate that the European Union is far from having created an area in which '*research efforts at national and union level are integrated*' (European Council 2000, I.A. 12). In such a research area the choice for a collaboration partners should be based solely on scholarly ground, while we found that this choice is significantly impeded by geographical

[22] This finding is in line with a recent study by Tijssen (2007) who found that regions with higher quality of research (indicated by the mean citation rate) have a higher propensity to collaborate internationally.

[23] For a more detailed policy discussion, see Frenken et al. (2007).

barriers. Hence, there is a clear need to further harmonise the national research systems, including the alignment of labour market regulations, diploma systems and property rights. The current spatial heterogeneity explains why most researchers are still heavily biased towards domestic collaboration, even though European collaboration could offer more opportunities in many cases. As there is evidence that the effect of geographical proximity exists independently of national borders, the process of integration within member states is incomplete too. This implies that the research policy efforts to promote international collaboration under the heading of the Seventh Framework Programme should be complemented with efforts of member states to integrate their own national research systems.

Next to the significance of proximity in collaborative knowledge production, we also found evidence for elite structures in which regions that host quality scholars or financial resources are more inclined to network among themselves. This finding is not incompatible with the definition of ERA, as promoting elite structures is part of the agenda. With the recent emphasis in the Seventh Framework Programme on frontier research, both by individual researchers and in collaboration networks, the gap between these regions is expected to increase rather than decrease in the future.

Thus, our results suggest that within the European context facilitating research collaboration *per se* will not necessary contribute to increasing cohesion at the regional level. Rather, ERA policy will remove barriers related to geography thereby fostering integration and reinforcing the centralisation of knowledge flows among already well-connected excellence regions and capital regions. Reading from the Commission's recent green paper on ERA (Commission 2007) such an outcome should be considered as intended. Yet, if the objective of the EU is to implement an inclusive policy that promotes active participation of peripheral locations in the European Research Area, it should be more specific in their policies. Stimulating linkages between elite regions and peripheral regions is such an inclusive instrument. In this way, less connected regions profit from access to knowledge in the elite regions. At least for peripheral locations such a strategy seems more effective than local research policies, even if the two strategies are not mutually exclusive.

3

Research collaboration at a distance: changing spatial patterns of scientific collaboration within Europe

3.1 Introduction

Human activities are known to cluster in space. Scientific research is no exception. As a general rule, researchers that are in close vicinity interact more intensively than those at a distance. However, with recent advances in information and telecommunication technologies some have declared an end to 'the tyranny of distance' (Castells 1996; Cairncross 1997). In the specific context of scientific collaboration this trend has been evidenced by an increase in long distance collaboration activities (for a survey see Frenken et al. 2009).

A better understanding of the observed trend towards collaboration at longer distance is important for at least two reasons. First, research collaboration generates benefits in several ways (Katz and Martin 1997). It provides opportunities to realise savings in the costs of research infrastructure and the training of personnel. Collaboration also generates intellectual benefits through the cross-fertilisation of ideas. These benefits are expected to increase with the distance over which collaboration takes place, as relevant partners are more easily found within a greater radius. Indeed, scientific articles stemming from international collaborative projects are cited more frequently, on average, than publications from national collaborative projects (Narin et al. 1991). Second, significant public expenditures are used to foster long distance collaboration. As a prime example, the European Union's member states attempt to develop a European Research Area (ERA) that is dedicated to improving the internal

coherence within the European research landscape by coordination of regional, national and EU research activities.[24] The Framework Programmes constitute one of the centrepieces of those activities. They are specifically designed to pool resources and promote R&D cooperation between the EU member states in order to improve the communication and collaboration among researchers, scholars, engineers and other technical support staff.

The present study aims at uncovering some of the changing spatial patterns of research collaboration by examining co-publication activities over time. Previous studies in this area (Narin et al. 1991; Katz. 1994; Hicks and Katz 1996; Gheorgiou 1998; Glänzel et al. 1999; Glänzel 2001; Okubo and Zitt 2004; Adams et al. 2005; Wagner and Leydesdorff, 2005; Jones et al. 2008) have all been descriptive. What is more, these studies analysed *either* the changing effect of geographical distance on co-publication activities *or* the changing effect of regional or national boundaries, therefore possibly confounding both effects. Given the heterogeneity of the European geographical landscape, a systematic comparison between the effect of distance and territorial borders is required to analyse the (changing) spatial patterns in research collaboration. We do so by explaining the co-publication intensity between 313 regions in 33 European countries by the physical distance between regions and by regional, national and linguistic border effects. We draw conclusions regarding the observed changes in spatial patterns of research collaboration and the extent to which these changes are in line with EU policy objectives. Doing so, we are not able to directly evaluate Europe's policy efforts as we lack data on the inputs provided by the European Union. Rather, we analyse trends in the publication system towards a desired 'European science system' and leave aside whether a possible change is brought about by the interventions of the European Union, by other factors or by a combination of both.

The remainder of this paper is organised as follows: in section 2 we discuss the role of geography in research collaborations with a special focus on the European context; section 3 describes the data collection from Thomson Reuters' *Web of Science* database and introduces the statistical model employed in our study which is derived from the gravity equation; key results of our statistical analysis

[24] The concept of the 'European Research Area' centres around the idea of mobilizing a more coherent overall policy framework conducive for European research through mobilizing critical mass, reducing costly overlaps and duplications and making more use of coordination and integration mechanisms involving all levels of policy intervention in the European Union" (Commission 2007, p. 93). Achieving more coherence at the level of regions within member states is one of the key policy foci (Commission 2001).

on co-publication intensities among EU regions are reported in section 4, while in the final section we interpret these empirical results in the light of both theory and EU's policy objectives.

3.2 THE GEOGRAPHY OF RESEARCH COLLABORATION

Although scientific practice still invokes images of the *"lone, long-haired genius, mouldering in an attic or basement workshop…motivated by the flame burning within him"* (Price 1963, p. 3), scientific knowledge creation is increasingly dependent on collaborative efforts. The rise in research collaboration is most commonly measured by the increasing number of authors on research papers as noted in early work (Price 1963; Narin and Carpenter 1975). Since, escalating costs of research and an increasing division of intellectual labour among researchers seem to have accelerated collaboration tendencies (Katz and Martin 1997). We did not yet observe the 'virtual demise of the lone researcher' (Beaver and Rosen 1979), but shares of collaborative research now lie well above 50% of all research activities in many countries and research organisation (Wutchy et al. 2007).

The increasing level of collaboration in scientific research worldwide has gone hand in hand with increasing levels of inter-organisational collaboration, international research collaboration and intra-EU collaboration (Adams et al. 2005; Tijssen and Van Leeuwen 2007; Tijssen 2008; Mattson et al. 2008). Technological improvements in transportation and communication technologies are held responsible for these trends as they ease the process of research collaboration, decrease the costs and time of travel and facilitate distant communication. Furthermore, 'big science' has been widely supported by political strategies at multiple levels where (international) collaboration is often a requirement for funding.

In the event that travelling and communication at a distance would not require time and resources such political strategies would not be necessary; research partners would be matched based on a 'fit' between their research questions, irrespective of their geographical location. In the most extreme case we would observe a completely random spatial pattern of research collaboration that is solely guided by differences in the amount and focus of research inputs. In this study, such a system would be regarded a perfectly integrated system.

Yet, as with all human activities, physical co-presence remains important in carrying out the complex tasks associated with scientific research (Collins 2001). Face-to-face interaction offers the possibility of having intense and complex

forms of interaction in which not only language is involved but the entire behavioural complex. Contrary to modern communication media (e.g. e-mail, video conferencing) this enables the unique establishment of common reference frames through amongst others rapid feedback, pointing and referring to objects in real space, subtle communication, informal interaction and a shared local context (Olson and Olson 2000). All these factors facilitate the creation of a common language, shared meaning within a research team and the passing on of knowledge that cannot easily be expressed in words or visualisations (Collins 2001; Urry 2002).

Such moments of co-presence between researchers do not necessarily have to be permanent, but can also be organised on a temporary base (Torre 2008). Regular meetings at well-decided stages of a research project may be sufficient to coordinate tasks and allocate responsibilities effectively. Geographically dispersed research collaborations, however, impose search and coordination costs for bridging geographic distance and institutional differences (Hinds and Bailey 2003; Adams et al. 2005; Cummings and Kiesler 2007). Due to these costs, multi-institute collaborations tend to have less frequent and less effective coordination (Cummings and Kiesler 2007). Spatially dispersed collaborations also more often experience conflict, free-riding, lack of monitoring and diverging interests (Hinds and Bailey 2003).

The bridging of physical distance between collaborating researchers imposes two types of costs. In general, researchers require more information about the research interests of physically proximate partners. This is because researchers' embeddedness in social networks decays with physical distance (Breschi and Lissoni 2009). It follows that the search costs for a research partner are expected to be a function of the geographical distance separating researchers. Second, coordination activities within collaborative projects tend to involve physical mobility of researchers, especially activities such as seminars, meetings, exchange of personnel, and sharing lab facilities. This imposes travel costs and time upon a collaborative project. Given that these costs tend to increase with distance, the incidence of collaborative research projects involving intensive face-to-face interaction tend to be inversely related with the physical distance between researchers' permanent locations (Adams et al. 2005).

Given the decreased costs and time of travelling, and advances in communication and information technology, one may assume that hampering effects of physical distance is diminishing - all else being equal. Indeed, for the top 110 universities in the United States a study by Adams et al. (2005) reports an increase in the mean distance over which collaboration takes place in the period 1981-1999.

Moreover, the many initiatives of the European Commission, such as the Framework Programmes, to support transnational research networks and to integrate infrastructural networks one may assume that this also has contributed positively to shrinking distances. Summarising, our first hypothesis investigated in this paper is:

HYPOTHESIS 1: *Physical distance impedes research collaboration in Europe yet its effect is decreasing over time in importance.*

Apart from physical distance acting as a barrier to collaborate, spatially dispersed research teams also need to bridge institutional differences. In the particular case of cross-border collaborations it becomes more difficult to align incentives among researchers due to differences in for instance funding schemes, institutional frameworks and norms and values. In the following, we distinguish between institutional differences on three spatial levels.

First, research activities within regional science systems are subject to policy initiatives that support regional collaborative projects (Cooke et al. 1997). Those policies are often complemented by long term collaborative contracts between institutes (i.e. universities, laboratories, firms) around localised sites with large scale supportive infrastructure. Economic geographers have emphasised the ease of collaborative efforts at such regional sites owing to continuous monitoring, comparing of activities, and due to the ease of receiving and updating information about ongoing activities (Bathelt et al. 2004). One can therefore expect co-publication activities to be partly concentrated in regional science systems and to be less likely when crossing regional borders.

Second, national borders separating researchers will render collaboration less likely as researchers operating under different national systems will generally find it more difficult to align incentives. As remarked above, the vast majority of funding is still allocated at the national level. This means that one can safely expect most of the research collaborations to take place at national rather than international levels. Yet, even if funding would be truly global, advantages exist to collaborate at national levels as the nation-state provides a common and familiar institutional framework facilitating distant research collaboration. For example, property rights issues, university regulations, research assessment criteria, and – more generally – shared norms and values all render research projects easier to coordinate at national levels than at the international level. What is more, in some scientific fields the nation-state may be an object of study. In all, national borders within the European Union are expected to result in a

European network of collaboration that is rather fragmented along national dimensions.

Third, the primacy of language for structuring our understanding of the world and communicating it to others is well understood (Balconi et al. 2007). Coordination activities require complex and sensitive modes of communication that are easier when researchers speak the same language. Despite the fact that English has become by far the most dominant language in publishing results of research projects, those who are more familiar in speaking another (native) language are expected to do so if they share this language (Liang et al. 2006). Although researchers speaking a common language are not necessarily located within a single geographical area, especially given the internationalisation of the labour market of researchers, we will treat common languages as being confined to specific geographical areas, primarily to indicate those European areas where one particular language is dominant. Within the context of Europe, in which many different languages are being spoken, different linguistic areas are thus expected to add to the fragmentation of European research networks.

Similarly to the impact of distance we expect that institutional differences reflected by territorial borders impede research collaborations between Europe's regions, yet are getting less important over time as the European unification process proceeds. Next to a general tendency towards internationalisation of research, European research policies aim to harmonise regional and national institutional frameworks. The increased budgets for collaboration within the Framework Programmes provide an additional incentive to collaborate across national (hence regional) borders. This leads us to formulate a second general hypothesis:

HYPOTHESIS 2: *Regional, national and linguistic borders impede upon research collaboration yet their effect is diminishing over time in importance*

With barriers to research collaboration diminishing in importance, there is no reason to believe that future spatial collaboration patterns will become entirely random across the European landscape. Indeed, it has been found that even the collaborative networks created by the Framework Programmes are subject to distance decays (Scherngell and Barber 2009). A random collaboration pattern can only be expected if researchers across Europe have equal possibilities of finding relevant research partners and equal possibilities of successful participation in collaborative projects. Opportunities and successful participation in funded projects however, are unequal for at least two reasons.

First, most funding is still allocated on a national and regional base (Banchoff 2002) with funding opportunities being unequal across Europe. Researchers in Western and Northern Europe as the 'core' areas are much better funded than researchers in the European 'periphery' (Dosi et al. 2006). This indeed biases collaborative research activities to core areas, especially when funding primarily intends to serve the interests of national or regional research performing entities.

Second, access to European funding may be equal in terms of eligibility, yet peer review favours more talented and more experienced researchers over the less talented and less experienced ones. The emphasis on proven research quality and scholarly excellence has only become stronger over the past decade, especially with respect to the performance of research active universities. As research quality is not equally distributed within Europe, the increase in the European budget for research excellence over the successive Framework Programmes does not necessarily render the European collaboration networks more equally distributed across the EU27.

Next to funding opportunities, European regions are also highly heterogeneous in terms of size, specialisation, reputation, quality of research, supporting infrastructure, as well as in their specific historical trajectories. Those differences are important drivers of research collaboration patterns across Europe. Our statistical analysis cannot fully capture all regional and national heterogeneity. Hence, we prefer not to formulate specific hypotheses concerning their impact within the scope of this study. Nonetheless, we acknowledge their importance, and introduce these factors in our explanations of the differences in propensities to collaborate – both at the level of countries as a whole (SECTION 3.4) and regions within countries (SECTION 3.5).

3.3 DATA AND METHODOLOGY

DATA

The empirical data used in this study were extracted from research articles published within scientific journals that are indexed by the *Web of Science* database (WoS). The WoS is a bibliographical database produced by *Thomson Reuters*, indexing approximately 9,000 journals worldwide and considered to be one of the most comprehensive and reliable sources of information on basic

research activity across all countries and fields of science.[25] Its indexed research articles all occur in peer-reviewed journals. These sources are selected on the basis of a minimum quality assessment carried out by *Thomson Reuters*. As such, the database can be considered representative of all scientific research that exceeds some minimum quality threshold.

We analyse all research articles contained in the WoS that were published in the period 2000-2007, and list at least one author-affiliation address (an 'institutional' address) that refers to a European country, including all 27 current member states of the European Union (see Appendix A). All selected publications are assigned to one of six broad fields of science that are defined by *Netherlands Observatory of Science and Technology* (NOWT 2010; see Appendix A) based on the journal categories listed in WoS.[26]

All institutional addresses listed in the by-line of the research articles are uniquely assigned to European NUTS2 regions based on the corresponding city names and postal codes.[27] In most countries these intra-national regions have some institutional authority, although for nine small countries they are defined at the national level (see Appendix B).

We define the key concept 'research collaboration' as a pair of unique institutional and regional addresses occurring in any research publication

[25] The two major limitations of WoS are its bias towards English-language journals, and the fairly low coverage of research in the social sciences and humanities. The latter in particular may influence the results with respect to the spatial structure of collaboration, especially when research publications are not disseminated by the international peer-reviewed scholarly journals that are WoS-indexed. Non-WoS journals are expected to be 'local' or 'domestic', publishing their research publications in a native language where the underlying research activities differ significantly from work published in WoS journals (notably, less collaborative and collaboration being more sensitive to spatial biases). Hence we are likely to underestimate the spatial biases in those disciplines within our WoS-based analysis.

[26] A research publication can be assigned to more than one field of science. Moreover, we did not assign the multidisciplinary journals to a field. Hence, counts for the total number of publications are not equal to the sum of individual fields.

[27] In most cases both city names and postal codes were used to ensure reliable classification. In case of doubt or conflicting information, priority was given to the postal codes. In our final classification less than 2% of all addresses could not be assigned (unambiguously) to a region. We were not able to locate the addresses within the greater urban area of London and consolidated the two London regions into one new NUTS1 region.

contained in our dataset.[28] Each publication with two or more different institutional addresses is defined as an 'institutional co-publication'. Publications with addresses referring to the same main institution (e.g. university, research institute, firm) are excluded from analysis. A publication may contain multiple region pairs in the by-line depending on the number of different regions related to author addresses, yet the counts exclude multiple occurrences of similar region pairs within the same publication. The aggregate count of all co-publication frequencies is stored in a region-by-region array, where each cell denotes the number of co-publications between region *i* and region *j* in year *t.* These co-publication counts are computed for each broad field of science. The co-publication frequencies for the intra-regional pairs, located on the main diagonal of the array, are included. Since these symmetric arrays contain "undirected" data on research collaborations, the dataset used for analysis contains 49,141 unique regional pairs [((313²-313)/2)+313)] for every year in the time period 2000-2007.

MODEL AND VARIABLES

The spatial structure of research collaboration is modeled in analogy to Newton's law of universal gravitation. Its use to explain social processes dates back to the early years of geography's quantitative revolution (Isard 1954) and states that the gravitational force between two entities is dependent on their masses and the distance between them. The gravity model and its extensions have become a workhorse for the statistical analysis of aggregate compositions of human interactions ranging from trade, traffic flows and telephone calls, to marriages, museum trips and money flows. In the context of research collaboration, the gravity model has been used to explain the intensity of co-publications among regions in The Netherlands (Ponds et al. 2007), China (Scherngell and Hu 2009) and the European Union (CHAPTER 2).

Mathematically, gravity models are best written as the following general formulaic expression (Sen and Smith 1995):

$$C_{ij} = A_i B_j F(d_{ij}) \tag{3.1}$$

[28] This definition is not restricted to co-authored publications *per se* as in a small but non-negligible fraction of the cases the same person can be associated with more than one institution and list multiple affiliations in the author address (Katz and Martin 1997).

where C_{ij} denotes the directional interactions between any two entities, A_i and B_i are origin and destination masses and $F(d_{ij})$ is a factor that measures the separation between the two entities. An empirical specification of this general expression that fits our dataset is: [29]

$$C_{ijt} = \alpha_0 + P_{it}^{\alpha_1} P_{jt}^{\alpha_2} \exp[\sum_{k=1}^{K} \beta_k d_{ij}^{(k)}] + \varepsilon_{ijt} \quad (3.2)$$

In this specification C_{itj} denotes the count of co-authored research publications between any regional pair i and j in year t, including those pairs where $i = j$. α_0 is a constant. The masses associated with the origin and destination of the collaborations are P_{it} and P_{jt} which represent the total number of publications in region i and region j, respectively. Indeed, the co-publication output frequency for each pair of regions is directly related to their publication activities. Hence, the product of the weight functions can be interpreted as the number of distinct collaborations that are possible between any two regions. Estimates of the weight parameters α_1 and α_2 are therefore expected to be significant and close to one.

The exponential term of Equation 3.2 is the separation function. This function indicates that the choice of collaboration partners is not randomly based on the possible number of collaborations itself, but also on the geographic location of region i compared to region j (i.e. on the separation between them). From a modelling point of view we hypothesise that in a perfectly integrated and cohesive European research system, research collaboration patterns could be solely explained by the number of publications and the existence of specialisations. However, from a spatial perspective separation measures may systematically bias the frequency count of collaborations between region i and j. We use a multivariate function in which there are $K=5$ separation measures of d_{ij} and in which β_k are their parameters to be estimated. The error ε_{ijt} in the expression is assumed to be independent and identically distributed (i.i.d.).

The spatial measures are hypothesised to explain the count of co-publication activities between regional pairs and take two forms. The first form is a continuous variable measuring the physical distance in terms of the kilometric

[29] Similar specifications and estimation techniques are present in another study dealing with co-patenting (Maggioni and Uberti 2007) and studies dealing with patent citations (LeSage et al. 2007; Fischer et al. 2008). In the Newtonian gravity model the exponents $\alpha_1 = \alpha_2 = 1$, and the included distance parameter $\beta=2$.

distance between the central points of region i and j.[30] The second form is a set of binary variables representing whether two regions belong to the same geographic area and is set to 0 if they do, and 1 if not. In the various specifications we distinguish between collaborations that take place within regions (0) and between regions (1); collaborations that take place within countries (0) and between countries (1), and, collaboration that take place within linguistic areas (0) and between linguistic areas (1). The binary variables measure the resistance of a research collaboration to cross a regional, national or language border. A negative sign thus indicates that research collaboration likelihood decreases when a territorial border is crossed.

As we are interested in the effect of spatial separation on research collaboration, it is important to control for non-spatial separation measures that may impact upon the spatial distribution of research collaboration. We therefore include a fifth separation measure. Scientific disciplines are not equally distributed across regions and certain research specialisation profiles are likely to be geography-dependent due to for instance historic legacies (e.g. chemistry in Germany) or subject specificity (e.g. polar research). Regions with comparable profiles may therefore be located near each other and failing to control for this might result in overestimating the effect of geography. For that reason, we include a separation measure of profiles between any two regions by constructing a 'discipline vector' that describes the distribution of publications in each region across the 36 disciplines. In so doing we follow Peri (2005, p. 315) and calculate a noncentered correlation measure of similarity in disciplinary specialisation. Two regions that publish exactly in the same proportion in each discipline have an index equal to one, while two regions publishing only in different disciplines have an index equal to zero. By subtracting from one we obtain the 'cognitive' separation measure of research profiles.

We fit Equation 3.2 to the research collaboration data by estimating the unknown parameters for the number of publications as well as the five separation measures. In so doing, we cannot rely on a log-normal specification of Equation 3.2 in which the parameters can be estimated by Ordinary Least Squares (OLS) regressions. This is because one would generate estimates of the logarithms of the dependent variable, rather than of C_{ijt} which would lead to the under-prediction of large C_{ijt} quantities and of the C_{ijt} total (Flowerdew and Aitkin 1982). Moreover,

[30] In case of intra-regional collaborations we use $d_{ij}^{(1)} = (A_i / \pi)^{1/2}$, in which the intra-regional distance is two thirds of the radius of the presumed circular area A_i. See Bröcker (1989) for an overview and the exact derivation.

since the log normal specification cannot deal with zeroes, we would also have to omit the inter-regional co-publication frequencies that take the value of zero, or use C_{ijt} + 1 instead,. Most importantly, the data does not meet the general assumption that counts of C_{ijt} are log-normally distributed around their mean value with a constant variance. To overcome the deficiencies of the log-normal specification, it is more appropriate to specify predictions of C_{ijt} as discrete counts that follow a Poisson-like distribution. The family of Poisson models solves the above shortcomings of OLS techniques while allowing for straightforward maximum likelihood estimations in which the parameters can be interpreted as elasticities (see Fischer et al. 2008). More specifically we choose the negative binomial variant as co-publication count data between any regional pair may deviate from a standard Poisson data-generation process.[31] We tested whether this choice of the negative binomial model is appropriate. For all regressions below, the likelihood ratio tests of over-dispersion (i.e. the alpha-parameter) is indeed significant, indicating that our count data follows a negative binomial distribution and that we should favour this model over a Poisson model.

We estimate models for the aggregate of all broad fields, and for the six fields separately. In the estimation technique there are two minor differences between the two analyses. First, in case of the aggregate of all fields we include the described non spatial separation measure of research specialisation. Second, some regions do not publish in a particular field and therefore we always add one publication to all regional masses, enabling the computation of natural logs. By contrast, at the aggregate level only four regions did not publish in any one of the years 2000-2007 and we therefore discarded from further analysis: Ciudad Autónoma de Ceuta (ES), Ciudad Autónoma de Melilla (ES), Réunion (FR), and Mardin (TR). As a result, the six fields span a total of 49,141 regional pairs, whereas the aggregate includes 47,895 pairs.

Our empirical analysis consists of five parts. We first present some descriptive statistics and maps suggestive of spatio-temporal trends in co-publication

[31] In the expected distribution of co-publication data the conditional variance is not equal to the conditional mean, i.e. there is overdispersion. This is because all heterogeneity in the data that influence the prediction of inter-regional co-publication occurrences cannot be captured by the specified independent variables. We therefore use a negative binomial model which specifies an additional parameter that allows the variance to exceed the value of the expected mean (see Long and Freese 2001). Based on the excess amount of zeroes in the data we could also have chosen to use a zero-inflated variant of the negative binomial model. The estimation results of a zero-inflated model, available upon request – did not change the results.

activities between regional pairs. In the next two sections we examine whether co-publication patterns are spatially biased and to what extent this bias changes over time. The last two sections are devoted to shedding light on the position of specific European countries and regions within Europe's collaboration patterns.

3.4 Empirical results

Descriptives

Table 3.1 displays the descriptive statistics for all sciences and for the six broad fields separately: the total number of interregional co-publications; the average distance of a co-publication count; and the respective shares of the number of co-publications that occur within intra-national regions, countries and linguistic areas. We document aggregate numbers for the period 2000-2007, alongside the first and last year for this time series.

The dataset contains 3,768,086 unique intra-regional and interregional co-publication counts for the total period and the yearly counts increase from 408,622 in 2000 to 524, 155 in 2007. Medicine is the largest field in terms of co-publication counts followed by physical sciences, life sciences, engineering, social sciences and humanities. With the exception of the humanities, co-publication counts for all fields increase over time.

The main focus of the analysis is on the spatial distribution of co-publication occurrences and changes therein over time. Table 3.1 marks the variation in these occurrences in the variables that measure spatial separation between regions. It is striking to observe that for all sciences in 2007 almost 60% of all co-publications between institutes still take place within regional borders, more than 80% within country borders and also more than 80% within linguistic areas. Over time we observe a decreasing share of co-publications within regions, nations and linguistic areas, suggesting that there is an increasing tendency to co-publish across borders. This trend is accompanied by a tendency to co-publish with long distance partners. The average distance involving co-publication activities within Europe has steadily increased from approximately 230 km to 280 km in the period 2000-2007.[32]

[32] Interestingly, a comparison with Adams et al. (2005) and Jones et al. (2008) suggests that collaborations in the US research system are less sensitive to distance.

Table 3.1: *Descriptive statistics by scientific field*

	# of co-publications			mean distance			% within region			% within country			% within lingual		
	Total	**2000**	**2007**	**Total**	**2000**	**2007**	**Total**	**2000**	**2007**	**Total**	**2000**	**2007**	**Total**	**2000**	**2007**
Total	3,768,086	408,622	524,415	260	231	284	62%	66%	59%	83%	84%	81%	84%	86%	83%
Physical sciences	1,210,089	132,808	156,818	284	261	304	62%	64%	59%	77%	79%	75%	80%	82%	78%
Life sciences	699,144	74,250	99,777	275	241	302	58%	64%	55%	78%	81%	75%	82%	85%	80%
Medicine	1,525,266	157,890	216,973	261	222	289	56%	62%	52%	80%	84%	79%	85%	87%	82%
Engineering	179,275	19,068	26,056	168	148	183	75%	79%	73%	88%	91%	86%	90%	92%	89%
Social sciences	134,616	14,000	21,908	134	105	152	76%	82%	72%	90%	94%	88%	93%	95%	91%
Humanities	61,030	8,147	7,396	72	53	75	93%	95%	92%	97%	99%	96%	97%	99%	97%

Apparent variations in the spatial distribution of co-publications exist when considering the six scientific fields. Researchers in physical sciences and life sciences collaborate on average over the longest distance and have the lowest shares of domestic co-publications and co-publications within linguistic areas. Medical researchers collaborate least within their own region, but have a stronger national and linguistic bias than researchers in physical sciences and life sciences.

Collaboration in engineering, social sciences and especially the humanities are most heavily biased on all spatial dimensions. In 2000, 99% of all co-publications within the humanities still took place within linguistic areas. Nonetheless, like in all other fields, their co-publication activities have become ever more distributed in space across the years 2000-2007.

Maps of the spatial distribution of researchers' co-publication activities in Europe for the aggregate of all sciences and years are shown in Figure 3.1 and Figure 3.2. Figure 3.1 shows all inter-regional co-publication pairs that produced at least 1000 co-publications. Co-publication activities within Europe are clearly dominated by a group of 'core' countries - mainly Northern and Western European countries within the European Union, plus Switzerland. Important European city regions within these countries are: Berlin, London, Munich, Stockholm, Paris, Madrid and Milan, while the Randstad area in the Netherlands (i.e. Amsterdam, Rotterdam, The Hague and Utrecht) also features prominently.

Figure 3.2 displays a graphic representation based on the 'association strength' index (Van Eck and Waltman, 2009) to control for the fact that regions with high number of co-publications will automatically have numerically stronger links with other regions.[33] When displaying all inter-regional pairs that have an (arbitrary) minimum association strength of 0.000007, we clearly observe the dominance of national co-publication systems over international co-publication linkages.

[33] The number of co-publications between two regions can be seen as the result of two independent effects, a similarity effect and a size effect. The association strength corrects for the size effect in order to measure the similarity between two regions (Van Eck and Waltman 2009). The 'assocation strength' index is defined as follows: $I_{ij} = copub_{ij} / (pub_i * pub_j)$ where $0 \leq I_{ij} \leq 1$, $copub_{ij}$ is the total number of co-publications of region i with region j, pub_i is the total number of publications of region i and pub_j is the total number of publications of region j.

Figure 3.1 (upper panel): *Absolute number of inter-regional co-publication counts (threshold ≥ 1,000).*

Figure 3.2 (lower panel): *Co-publication linkage strengths between regions (Association strength-index; threshold ≥ 0.000007).*

DO PHYSICAL DISTANCE AND BORDERS IMPEDE ON EUROPEAN RESEARCH COLLABORATION?

We hypothesised that research collaboration patterns in Europe are affected by physical distance and territorial border effects after controlling for publication intensities of regions and the (dis)similarities between regional research portfolios. Table 3.2 reports the estimates of the empirical specification of Equation 3.2 for an aggregate across the years 2000-2007.[34] We present the findings for all sciences jointly and for the six scientific fields separately. We include all four spatial separation measures (e.g. physical distance, regional border, country border and language border) simultaneously in this model.

A number of general conclusions can be drawn from the model coefficients and their standard errors as displayed in Table 3.2.

- *First*, all coefficients are always significant and have the expected sign. The positive coefficient for the number of publications indicates that the higher the publication activities of regional pairs, the higher their co-publication activities. The coefficient of disciplinary specialisation is negatively related to co-publication intensities (only included for the aggregate of all sciences) suggesting that the larger the differences in research portfolios, the less co-publication activity occurs. The coefficients of the four spatial separation measures are negative and significant for the aggregate of all sciences as well as for the six scientific fields. Thus, co-publication intensity decreases with physical distance and is higher within regional, national and linguistic areas after controlling for the size of regions and their research specialisation profiles. Since all four spatial separation measures are included in the model the spatial effects are additive. Thus, an effect of country borders exists even after controlling for the fact that international collaboration tends to take place over longer distances. Moreover, we still find a linguistic border effect after taking into account the fact that most co-publications occurring within linguistic areas are also domestic collaborations.[35]
- *Second*, regional border effects appear to be the strongest impediment to co-publication activities when considering the aggregate of all fields. This suggests relatively strong agglomeration effects, where local clusters and

[34] All statistical analyses were performed using the software package STATA 9.2.

[35] In comparison to a similar study dealing with the spatial structure of research collaborations within the Framework Programmes those coefficients are rather high (Scherngell and Barber 2009). Collaborations within the FPs are not impeded by country borders and have a much lower coefficient of distance (-0.278).

networks of universities, non-universities and other research partners exert a pull on within-city or within-region collaboration propensities. What is more, the effect of country borders tends to be stronger than linguistic borders even when taking into account 95% confidence intervals.

- *Third*, conclusions can be drawn from comparing the coefficients between the broad fields. The coefficient of publications for physical sciences, life sciences, medicine and engineering is much larger than for the social sciences and for the humanities, suggesting that given a certain amount of publication output, co-publication intensities in the latter two fields are much lower than in the former four. As for the spatial measures, the negative effect of distance on collaboration intensity is at its lowest within the physical sciences and the humanities, and most pronounced within the social sciences. In the case of the humanities, this finding is in contrast to the descriptive findings which ranked this field as the one most prone to collaborate over short distances, a paradox explained by the strong regional border effects within this field. Regional borders are also relatively important for engineering and the physical sciences, which reflect the fact that research in those fields is often concentrated around sites with large-scale research facilities. The relatively strong effect of country borders within the field of medicine indicates that European medical sciences are primarily organised along the lines of national research systems.

Are effects of distance and borders diminishing over time?

To test whether the effect of distance and territorial borders diminishes over time we estimate the same model for each year separately and compare their parameters over time. In comparison to the previous model (Table 3.2) we only omit the variable 'language' because its effect strongly overlaps with the effect of the variable 'country' judging from a Pearson correlation of 0.83. The results of the analyses are presented in Table 3.3, for all fields together and for the six fields separately. For reasons of concision we only show the coefficients of the relevant spatial variables. We observe that all coefficients remain significant and show the expected sign, confirming again that the spatial structure of co-publication activities is subject to both a distance effect and several border effects across all years.

Turning to the changes of the coefficients over time, we simultaneously observe a significant decrease in the importance of regional or national borders and a significant increase in the importance of distance; for the aggregate of all sciences, as well as for all six fields separately. When applying a 95% confidence interval for coefficient in the year 2000, we find little overlap with the coefficient in later

Table 3.2: *Determinants of inter-regional collaboration counts by scientific fields for period aggregates*

	All	Physical sc.	Life sc.	Medicine	Engineering	Social sc.	Humanities
Publications	0.869 ***	0.915 ***	0.912 ***	0.888 ***	0.934 ***	0.456 ***	0.644 ***
	0.003	0.004	0.005	0.004	0.008	0.006	0.012
Specialization	-0.111 ***	---	---	---	---	---	---
	0.038	---	---	---	---	---	---
Distance	-0.570 ***	-0.587 ***	-0.710 ***	-0.810 ***	-0.747 ***	-0.903 ***	-0.563 ***
	0.008	0.012	0.012	0.012	0.022	0.024	0.033
Region	-3.342 ***	-4.042 ***	-3.418 ***	-2.731 ***	-4.321 ***	-2.020 ***	-4.642 ***
	0.063	0.086	0.081	0.082	0.112	0.128	0.119
Country	-1.645 ***	-1.148 ***	-1.111 ***	-1.498 ***	-0.939 ***	-0.946 ***	-1.015 ***
	0.034	0.046	0.042	0.040	0.071	0.072	0.094
Language	-0.969 ***	-1.116 ***	-1.235 ***	-1.308 ***	-1.044 ***	-1.448 ***	-1.066 ***
	0.030	0.041	0.036	0.035	0.065	0.064	0.091
Constant	-5.173 ***	-4.609 ***	-3.799 ***	-3.679 ***	-2.869 ***	2.745 ***	-0.208 ***
	0.080	0.102	0.099	0.098	0.146	0.160	0.188
Alpha	0.906 ***	1.586 ***	1.356 ***	1.431 ***	2.264 ***	3.924 ***	2.103 ***
AIC	5031	3406	2731	3264	1088	0.988	0.390
N	47895	49141	49141	49141	49141	49141	49141

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$

years, suggesting that the effect of regional borders is diminishing over time. This applies to all fields together, as well as the life sciences, medicine, and the social sciences. We also observe a decreasing importance of co-publishing activities within countries in the case of the physical sciences, engineering, social sciences, and humanities.[36]

Turning to the formulated hypotheses regarding the changing effect of physical distance (Hypothesis 1) and territorial borders (Hypothesis 2), we can conclude the following. Hypothesis 1 is partially confirmed - we observe that physical distance impedes research collaboration, but we did not find evidence that its importance has been declining over during the years 2000-2007. Hypothesis 2 however is fully confirmed - we find that territorial borders impede research collaboration and that their effect has declined over time. The finding that distance is increasingly important while territorial borders are not, is a surprising outcome. After all, in Table 3.1 we observed that the average distance over which researchers collaborate has indeed increased.

To further explore this paradox we computed the mean distance of co-publication activities per country and changes over time. We can draw two conclusions from this analysis (Table 3.4). First, researchers in countries in Europe's periphery tend to be the long-distance collaborators, whereas researchers in countries closer to Europe's core are less so. This is understandable because peripheral countries are naturally inclined to collaborate over longer distance if relevant proximate partners are lacking. Second, some countries see their mean distance of co-publication activities decreasing over time in one or more fields. This group of countries includes all 14 accession countries - of which 10 became member in 2004 and another two in 2007 – as well as peripheral EU and non-EU members including Greece, Portugal, Iceland, Finland and Ireland. Previous studies have shown that the EU accession countries and some peripheral EU countries are indeed 'catching-up' in terms of publication and co-publication activities (Tijssen and Van Leeuwen 2007; Mattsson et al. 2008). We conclude that over time these

[36] We repeated the analysis reported in Table 3 using robust standard errors (not shown), in which case the major results still hold but become slightly less pronounced. More specifically, the significant increase of the effect of distance disappears in case of physical sciences and social sciences, whereas the decreasing effect of regional borders vanishes in case of humanities; the decreasing effect of country borders also disappears in case of engineering and physical sciences, but it becomes significant in case of medicine. Furthermore, the same results as reported in Table 3 continue to hold when applying a 90% confidence interval, with the exception of the decreasing effect of country borders in case of engineering.

countries now also tend to collaborate over shorter distances. Most probably, the relative growth of their science systems enables them to co-publish more and more with partners at closer vicinity. [37]

To further validate this conclusion we ran the same regression analysis as in Table 3.3 for all regional pairs within EU15 (EU member states in 2000) and for all regional pairs within EU14 (accession member states in 2000) separately.[38] Although the effect of geographical distance has been increasing for both the EU14, and the EU 15, the decreasing effect of territorial borders has been particularly strong in the EU15 and – although still clearly observable - less so for EU14. These results indicate that next to the general trends (Table 3.3), the integration process proceeds at a faster pace within EU15 than within EU14.

NATIONAL DIFFERENCES

Having analysed the general impact of spatial constraints on co-publication activities, we examined to what extent researchers within specific countries differ in terms of their bias to collaborate with domestic partners. Thus, rather than measuring the general effect of country borders using a single zero/one dummy variable as in Table 3.2 and Table 3.3, we now include a dummy for each country separately. To prevent identification problems of these dummies we include a dummy for only those countries that have more than eight regions. The remaining region-pairs are grouped into three variables: domestic regional pairs within EU15 countries (Denmark, Finland, Ireland, Luxembourg, Sweden); domestic pairs within the 14 accession countries (Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Romania, Slovenia, Slovakia); and domestic pairs within other non-EU countries (Iceland, Norway and Switzerland).

Table 3.5 shows the results for the aggregate data for the period 2000-2007. The United Kingdom has the highest propensity to co-publish internationally followed by Germany and the Netherlands, while Turkey and Greece exhibit the strongest propensities for domestic co-publication activities. The effect of the domestic science base on regional partnering is relatively minor in the case of other EU15 countries, as well as the group of three other non-EU countries.

[37] Indeed, the growth of co-publication activities between the accession countries surpasses the growth between the accession countries and the EU15 and also surpasses the growth among the EU15 member states (Tijssen and Van Leeuwen 2007).

[38] Results are not shown for reasons of concision and can be obtained from the authors.

Table 3.3: *Determinants of inter-regional collaboration counts per year*

	2000	2001	2002	2003	2004	2005	2006	2007
	All							
Distance	-0.535	-0.544	-0.567	**-0.599**	**-0.603**	**-0.615**	**-0.642**	**-0.635**
	0.011	0.011	0.011	**0.010**	**0.010**	**0.010**	**0.010**	**0.010**
Region	-3.519	-3.438	-3.316	**-3.146**	**-3.108**	**-3.007**	**-3.034**	**-3.020**
	0.062	0.063	0.062	**0.060**	**0.059**	**0.061**	**0.060**	**0.059**
Country	-2.233	-2.182	-2.222	-2.261	-2.212	-2.266	-2.179	-2.183
	0.026	0.025	0.025	0.024	0.024	0.024	0.023	0.023
	Physical Sciences							
Distance	-0.666	-0.686	-0.640	-0.644	-0.723	-0.728	**-0.733**	**-0.777**
	0.017	0.017	0.016	0.016	0.016	0.016	**0.015**	**0.015**
Region	-3.880	-3.772	-3.755	-3.785	-3.653	-3.602	-3.655	-3.649
	0.097	0.096	0.092	0.097	0.096	0.095	0.092	0.096
Country	-1.740	-1.629	-1.675	-1.737	-1.610	-1.640	-1.643	**-1.535**
	0.041	0.041	0.040	0.042	0.040	0.040	0.038	**0.039**
	Life Sciences							
Distance	-0.734	**-0.831**	-0.746	**-0.907**	**-0.884**	**-0.892**	**-0.961**	**-0.926**
	0.019	**0.019**	0.019	**0.019**	**0.018**	**0.017**	**0.017**	**0.017**
Region	-3.581	**-3.173**	-3.332	**-2.945**	**-2.954**	**-2.943**	**-2.656**	**-2.691**
	0.097	**0.106**	0.102	**0.105**	**0.100**	**0.100**	**0.101**	**0.096**
Country	-1.670	-1.591	-1.793	-1.660	-1.808	-1.698	-1.540	-1.704
	0.043	0.045	0.046	0.043	0.043	0.040	0.040	0.040
	Medicine							
Distance	-0.828	**-0.921**	**-0.968**	**-0.968**	**-0.924**	**-0.973**	**-0.950**	**-0.895**
	0.017	**0.017**	**0.017**	**0.016**	**0.016**	**0.016**	**0.015**	**0.015**
Region	-2.881	-2.721	-2.508	**-2.312**	**-2.502**	**-2.171**	**-2.263**	**-2.324**
	0.093	0.099	0.099	**0.095**	**0.095**	**0.095**	**0.095**	**0.093**
Country	-2.310	-2.096	-2.187	-2.186	-2.203	-2.282	-2.212	-2.247
	0.039	0.039	0.038	0.037	0.036	0.036	0.035	0.035

Notes. Regressions include a constant and the number of publications. Total also includes specialization. The effect in 2000 is baseline. Significant deviations using 95% confidence intervals are marked in bold. All variables are significant at the 1% level.

Table 3.3: *Determinants of inter-regional collaboration counts per year (continued)*

	2000	2001	2002	2003	2004	2005	2006	2007
	Engineering							
Distance	-0.680	-0.699	**-0.834**	**-0.927**	**-0.984**	**-0.938**	**-0.876**	**-0.951**
	0.035	0.035	**0.038**	**0.034**	**0.034**	**0.032**	**0.032**	**0.032**
Region	-4.246	-4.079	-4.029	-4.060	-3.774	-3.837	-3.786	-4.019
	0.132	0.140	0.140	0.149	0.144	0.141	0.141	0.146
Country	-1.600	-1.566	-1.525	**-1.227**	-1.339	-1.498	-1.439	-1.364
	0.073	0.074	0.076	**0.073**	0.073	0.070	0.070	0.070
	Social Sciences							
Distance	-0.914	-0.988	-0.918	**-1.144**	-0.887	**-1.118**	**-1.127**	**-1.138**
	0.039	0.038	0.037	**0.036**	0.036	**0.035**	**0.035**	**0.034**
Region	-2.359	-2.228	-2.195	**-1.692**	-2.193	**-1.799**	**-1.682**	**-1.599**
	0.124	0.132	0.127	**0.132**	0.134	**0.135**	**0.142**	**0.141**
Country	-2.217	-1.963	-2.027	**-1.845**	-2.066	**-1.716**	**-1.679**	**-1.598**
	0.080	0.080	0.077	**0.073**	0.077	**0.073**	**0.073**	**0.072**
	Humanities							
Distance	-0.312	-0.315	**-0.144**	-0.327	**-0.523**	**-0.675**	**-0.196**	**-0.590**
	0.041	0.046	**0.036**	0.045	**0.045**	**0.049**	**0.034**	**0.053**
Region	-4.908	-4.886	-5.335	-4.744	**-4.483**	**-4.411**	-4.735	-4.526
	0.102	0.105	0.099	0.107	**0.119**	**0.110**	0.084	0.116
Country	-2.818	**-2.109**	-2.711	-2.608	**-1.045**	**-1.371**	-2.850	**-1.527**
	0.128	**0.114**	0.123	0.124	**0.100**	**0.115**	0.104	**0.122**

Notes. Regressions include a constant and the number of publications. Total also includes specialization. The effect in 2000 is baseline. Significant deviations using 95% confidence intervals are marked in bold. All variables are significant at the 1% level.

Table 3.4: *Change in average distance of inter-regional collaborations per country*

	1		2		3		4		5		6		7	
	2000	2007	2000	2007	2000	2007	2000	2007	2000	2007	2000	2007	2000	2007
AT	319	394	435	557	449	528	492	563	187	231	73	250	57	138
BE	271	305	340	385	349	382	420	438	69	233	85	124	18	51
BG	616	713	874	978	350	711	657	**605**	131	222	798	**687**	-	-
CH	283	334	438	471	379	453	416	445	247	326	106	291	97	171
CY	1153	**1137**	1311	**1060**	750	1337	1119	**1062**	-	-	1732	**842**	-	-
CZ	274	310	284	296	240	291	303	345	196	**190**	63	**52**	19	84
DE	257	322	283	336	275	340	225	297	188	244	132	210	79	82
DK	409	485	505	515	397	492	416	486	393	**313**	183	288	99	315
EE	507	641	509	**479**	450	452	496	890	284	325	-	-	-	-
ES	435	523	467	545	396	505	402	540	297	299	253	296	103	115
FI	567	662	675	796	517	619	515	631	504	**438**	220	385	153	480
FR	322	383	358	405	308	387	282	348	225	262	175	244	67	95
GR	644	**642**	658	**579**	669	**601**	510	622	350	355	466	620	61	271
HR	207	248	207	291	151	199	193	243	150	207	74	**74**	-	-
HU	415	466	461	471	374	398	386	453	253	335	315	431	186	**62**
IE	433	485	486	617	456	509	390	443	252	297	296	**273**	77	107
IS	1180	1466	1164	1265	1185	**1123**	1096	1645	-	-	714	**641**	-	-
IT	358	411	357	401	333	399	326	403	227	242	324	364	137	180
LI	302	**294**	361	**251**	-	-	-	-	-	-	-	-	-	-
LT	543	**534**	-	-	-	-	-	-	-	-	-	-	-	-
LU	387	411	221	377	467	473	290	373	-	-	-	-	-	-
LV	559	641	696	**462**	517	531	641	798	-	-	-	-	-	-
MT	638	1246	1053	**886**	-	-	675	1381	-	-	-	-	-	-
NL	248	287	273	308	251	312	215	261	180	223	121	136	41	101
NO	480	597	575	638	416	612	416	602	280	309	174	293	125	125
PL	359	366	362	**352**	278	295	336	374	215	222	612	**391**	126	166
PT	685	700	571	618	806	**581**	823	945	254	322	505	**420**	146	783
RO	684	728	498	591	922	**682**	582	905	553	719	-	-	67	72
SE	488	579	487	585	467	590	451	599	271	422	218	286	139	241
SI	251	290	235	245	256	312	233	286	96	142	185	**107**	-	-
TR	340	**299**	413	**327**	504	**310**	214	224	217	**190**	217	**193**	56	95
SK	280	366	295	322	178	298	321	402	165	336	52	186	30	**22**
UK	264	356	336	403	296	396	220	324	188	236	114	187	41	62

Notes. 1 All; 2 Physical Sciences; 3 Life Sciences; 4 Medicine; 5 Engineering; 6 Social Sciences; 7 Humanities. Decreases in the average distance of co-publication activities are shown in boldface. Observations that did not co-publish within a specific field during one of the years under study are indicated with a dash.

Table 3.5: *Determinants of inter-regional collaboration counts by scientific fields for period aggregate (2000-2007)*

	COEF		SE
Publications	0.482	***	0.015
Specialization	-0.646	***	0.009
Distance	-1.293	***	0.047
Region	-2.778	***	0.052
Language	-1.014	***	0.027
Constant	28.515	***	0.509
	Country Dummies		
AT	-2.165	***	0.117
BE	-1.720	***	0.102
DE	-1.138	***	0.040
ES	-1.505	***	0.072
FR	-2.183	***	0.055
GR	-2.394	***	0.103
IT	-1.672	***	0.060
NL	-1.301	***	0.095
PL	-2.011	***	0.079
TR	-3.907	***	0.064
UK	-0.555	***	0.046
Other EU15	-1.751	***	0.089
Other EU14	-2.396	***	0.075
Other Non EU	-2.071	***	0.103
Region dummies	YES		
Alpha	0.493	***	
AIC	4.738		
N	47195		

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$

Judging from Table 3.5, with the exception of France, the six European countries which have the highest publication output (i.e. United Kingdom, Germany, Italy, Spain, The Netherlands) also tend to be the most internationalised countries. This finding may be due to the availability of specialised scientific knowledge or facilities within those countries, rendering them especially attractive research partners (Frenken 2002).

REGIONAL DIFFERENCES

In order to further explore the effects of territorial heterogeneity we also included a dummy variable every time a region occurs within a regional co-publication pair. [39] This set of variables measures the strength of the regional science system in terms of co-publication propensities given all other included determinants of co-publication activities. Figure 3.3 shows a graphic representation of the European regions depicting the relative importance of regional effects on co-publication intensity. The map represents the 50 regions with the highest dummy-values (depicted in black) and the regions with a dummy coefficient ranked 51-100 (in grey). The hatched regions are excluded from the analysis as these regions do not co-publish at all (see section 3) or not outside regional, national or linguistic borders, thus creating problems of multi-collinearity within the regression analysis.

In contrast to Figures 3.1 and 3.2, a clear-cut spatial 'core-periphery' structure of co-publishing activities is no longer visible, as we now control for the effect of geographical distance and borders. Collaboration-prone regions appear to be scattered across the European research landscape. Turning to the well performing regions, the observed pattern can be explained by three structural determinants: [40]

- RESEARCH OUTPUT: Although we control in our models for publication output, regions with relatively large numbers of publications and co-publications are overrepresented on the map (e.g. Paris, London, Milan, Madrid, Rome and Berlin). This is also the case for peripheral regions which publish less according to European standards, but are still intensive publishers according to national standards (e.g. Warsaw, Krakow, Budapest and Sofia). This suggests that researchers based in these city agglomerations

[39] In the estimation procedure we only included regional dummies for 301 regions instead of 308 regions as some regions only co-published within their own region, within their own country or within their own lingual area, resulting in no additional explanatory power of the regional dummies and perfect collinearity with other separation measures.

[40] We did not include those variables in the regression because we wanted to conclude on additional effects in all regions without specifying the nature of these effects beforehand.

are attractive partners, possibly reflecting their access to dense local or regional research networks.

- SCIENTIFIC QUALITY: Regional science systems of international scientific quality tend to attract relatively many research partners from outside the region. The possible hidden effect of 'research quality' as a determinant was examined by incorporating data on research performance rankings of major European universities (CWTS 2008) that are located within those regions. The degree of research quality of each university was measured in terms of the field-normalised average citation rate across all fields of science (Moed et al., 1995). This indicator assigns 47 out of the top 50 universities to the coloured regions (e.g. Oxford, Cambridge, Lausanne, Zürich and London). In short, most of these collaboration-prone regions appear to be among Europe's scientific leading regions.
- INTERNATIONAL ACCESSIBILITY: Collaboration-prone regions benefit from accessibility to other scientific centres. As we opted for measuring distance along a straight line we are likely to overestimate its effect for those regions that are well-connected through (inter)national airports. Comparing our map with a list of the 27 largest airports within the EU15 plus Switzerland and Norway (Burghouwt and Hakfoort 2001), we find indeed that all 27 'airport-supported regions' also have high propensities to collaborate. What is more, relatively well connected regions within non-EU15 countries also tend to be more prone to collaborate too (e.g. Bratislava, Budapest, Bucharest, Prague, Sofia and Warsaw).

Clearly these three determinants reflect an underlying factor: a region's general state of socio-economic development. These determinants however fail to explain the high co-publication propensities of the regions with much lower levels of output, quality and accessibility. Most of these 'disadvantaged' regions (e.g. Iceland, Cyprus, Malta, Estonia, Northern Norway and Northern Sweden) are in geographically peripheral locations and, judging from our co-publication data, often tend to be relatively long-distant international collaborators. Their co-publication performance might well result from their peripheral location, which renders long-distance collaboration a necessity, but it may also be an effect of specific regional or national policies geared at creating and sustaining international collaborative scientific networks.

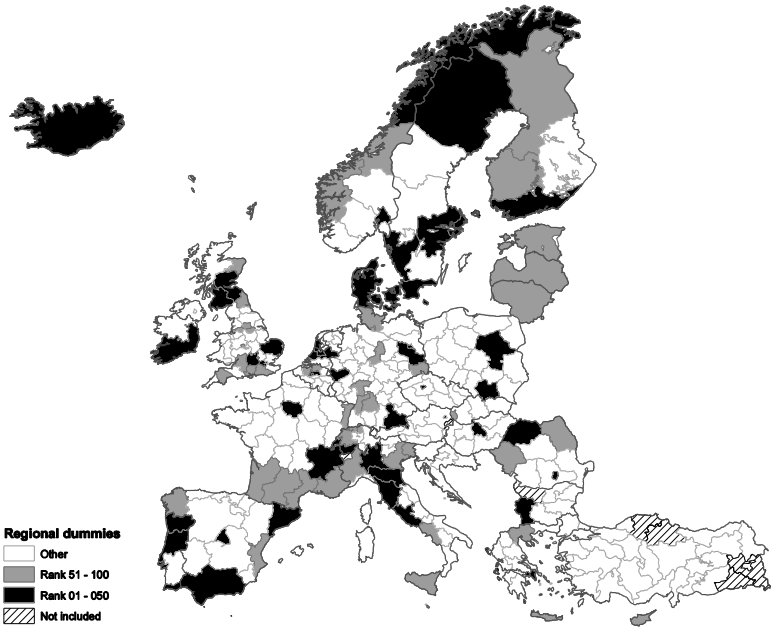

Figure 3.3: *Coefficient values of regional dummy variables*

3.5 DISCUSSION

Research collaboration has always been influenced by a dynamic interplay of economic, scientific, cultural and geographical factors. However, the pervasive shift towards collaborative scientific knowledge production raises questions related to the spatial structure underlying scientific practice within Europe. On the one hand, research partners and collaborators can easily travel back and forth between distant places, thus rendering it easier to find the best available partners. On the other hand, joint research efforts will still benefit from close physical proximity, as well as from regional, national and linguistic communalities, which may improve effectiveness of research as well as limit costs of search, coordination and communication activities. The key question is how these contrasting pressures affect spatial patterns of research collaboration within a dynamic and highly heterogeneous European science landscape, which has been dominated by national research systems during the 20th century and is now expected to move toward a more integrated European Research Area.

In order to obtain a better, evidence-based understanding of these issues we analysed co-publication patterns and trends among European regions for the

period 2000-2007. Deriving our research collaboration data from the subset of publications with multiple author affiliations we focused our statistical analyses on three issues: (i) spatial patterns in co-publication activities; (ii) the changing sensitivity of co-publication activities to physical distance and territorial borders, (iii) regional and national specificities in propensities to collaborate. Our results clearly show that co-publication patterns are geographically localised. Physical distance has a negative effect on co-publication activities, even after controlling for differences in disciplinary specialisation profiles. Apart from physical distance acting as a barrier to collaborate, co-publication activities are also more likely to occur within the same sub-national region, within the same country, and within the same linguistic area. These effects occur concurrently, suggesting that a mixture of simultaneous processes driven by a distance logic and a territorial logic.

The results of our analysis also point out that Europe is to some extent breaking down geographical barriers and is moving away from localised 'gravity holes'. The macro-level trends and broad patterns described in this paper reveal traces of 'Europeanisation', albeit weak and mixed. Overall, a gradual convergence is taking place toward a more integrated and interconnected European science system. One of our main conclusions holds that the effect of geographical localisation on co-publishing activities is indeed diminishing over time, which is most clearly observed by a decreasing importance of territorial borders in explaining co-publication activities. Given that such territorial borders are getting less important, physical distance effects are relatively stable over time and in some cases even increasing in importance. At first sight this result may seem surprising as we would expect internationalisation to go hand in hand with a decreasing effect of distance. Yet, it seems that the trend to collaborate over longer distance can be fully explained by the decreasing effect of crossing borders, Furthermore, in an ongoing integration process where the importance of territorial borders fade, researchers seem to (re)-orient themselves mainly towards physically proximate, yet cross-territorial, partners. This observation particularly holds for the new member states of the European Union which are currently catching up at a rapid pace.

Obviously, the co-publication indicators applied in this paper constitute a partial and incomplete description of research collaboration characteristics. Nonetheless, this unique information source provides useful comparative empirical evidence, and when used with appropriate caution reveals valuable new insights that are both compelling and politically informative. Despite this study's time-frame of only eight years, these findings may have evaluative implications for the design of policies and large scale programmes to promote international research

collaboration within the EU. Our statistical findings suggest possible effects of EU policies in terms of diminishing the role of 'artificial' territorial borders within the European Union. Having said this, the observed decrease in the importance of territorial borders does not imply that researchers are now more inclined to randomly search for the most appropriate research partners across the European landscape. To the contrary, the effect of physical distance seems to be increasing for some regions and disciplines. EU funded research projects may therefore run the risk of being dominated by partners from outside the region or country, albeit in close physical proximity.

We also found that propensities to collaborate vary greatly across regions. In particular, accessible regions with large research outputs of high quality tend to be collaboration prone. This outcome suggests that the European science system is still far from being a level playing field in terms of equal possibilities for collaboration. Given current differences in research quality and unequal access to (European) funding meant to enhance such quality, it seems unlikely that current ERA-policies will suffice to create a truly cohesive European Research Area. Nonetheless, we observe that some science centres in the periphery are becoming more involved as collaborators in the European scientific landscape.

A final policy remark concerns the observed differences in spatial patterns between scientific fields. Judging from our data, the physical sciences and life sciences are in a more advanced stage of Europeanisation. Research budgets to promote collaboration may therefore have its largest added value within the fields of medicine, engineering, social sciences and humanities. Having said that, one should bear in mind that each scientific field may well have its own specific 'spatial requirements' due to their research topics or their reliance on large infrastructures. The finding that the engineering sciences and physical sciences exhibit a high level of regional embeddedness raises the question whether these two fields need more budget to promote cross-border collaboration, or whether those fields are perhaps better served by promoting high-quality research within research agglomerations.

APPENDIX A: Classification of disciplines according to NOWT (www.nowt.nl)

Natural sciences
Astronomy & Astrophysics
Chemistry & chemical engineering
Computer Sciences
Earth Sciences & Technology
Mathematics
Physics & Materials Science
Statistical Sciences

Life sciences
Agriculture & Food Science
Basic Life Sciences
Biological Sciences
Environmental Sciences & Technology

Medicine
Basic Medical Sciences
Biomedical Sciences
Clinical Medicine
Health Sciences

Engineering
Civil Engineering & Construction
Electrical Engineering & Telecommunication
Energy Science & Technology
General & Industrial Engineering
Instruments & instrumentation
Mechanical Engineering & Aerospace

Social Sciences
Economics and Business
Educational Sciences
Information & Communication Sciences
Management & Planning
Political Science & Public Administration
Psychology
Social & Behavioral Science, Multidisciplinary
Sociology & Anthropology

Humanities
Language & Linguistics
Law & Criminology
Literature
History, Philosophy & Religion
Creative Arts, Culture & Music

APPENDIX B: Country abbreviations and number of regions

AT; Austria (10)
BE; Belgium (11)
BG; Bulgaria (6)
CH; Switzerland (7)
CY; Cyprus (1)
CZ; Czech Republic (8)
DE; Germany (41)
DK; Denmark (1)
EE; Estonia (1)
ES; Spain (19)
FI; Finland (5)
FR; France (26)

GR; Greece (13)
HR; Croatia (4)
HU; Hungary (7)
IE; Ireland (2)
IS; Iceland (1)
IT; Italy (21)
LI; Liechtenstein (1)
LV; Latvia (1)
LU; Luxembourg (1)
LT; Lithuania (1)
MT; Malta (1)
NL; Netherlands (12)

NO; Norway (7)
PL; Poland (16)
PT; Portugal (7)
RO; Romania (9)
SE; Sweden (8)
SK; Slovakia (4)
SI; Slovenia (1)
TR; Turkey (26)
UK; United Kingdom (37)

4

Acquisition of European research funds and its effect on international scientific collaboration

4.1 Introduction

Despite pervasive trends towards the globalisation of knowledge production, research policy is still driven mainly by national budgets and objectives. One of the major exceptions is the European Union, where at the Lisbon Council in 2000, the Heads of State signed up to develop a European Research Area (ERA). The objective of ERA policy is to improve the competitiveness and coordination of research activities at regional, national and EU levels. The Framework Programmes (FPs) of the European Commission (EC) constitute the main instrument to achieve this goal. They are specifically designed to pool resources and promote international R&D collaboration between EU member states by enabling and intensifying interactions among researchers. The final goal is to stimulate knowledge creation and diffusion which are prime sources for sustainable economic growth in the long run (Romer 1990; Foray 2004).

From its inception, there has been much concern that the policy objective to create ERA would compromise the cohesion objective of the European Union (Sharp 1998; Begg 2010). After all, Europe's research policies are not intended to intervene in the European scientific and technological landscape at large, but to bundle resources with the purpose of supporting collaborative efforts between 'excellent' researchers in a few strategic scientific fields. Following common perceptions about the instrumentality of research collaboration (Katz and Martin 1997; Sonnenwald 2004), this strategy is expected to induce economies of scale, to

avoid duplication of research efforts, and to enhance the competitiveness of the European territory as a whole vis-à-vis its main global competitors.

Given the current unequal spatial distribution of scientific and technological capabilities across the European landscape, Europe's research policy may well disproportionally support high-performance core regions in the North-West of Europe, possibly even at the expense of the development of peripheral regions. Scientific and technological activities show strong natural tendencies to concentrate in geographical space (Audretsch and Feldman 1996; Moreno et al. 2005), and collaborations between regions also tend to be geographically bounded (CHAPTER 2; Adams et al. 2005; Maggioni and Uberti 2009). In Europe these forces are arguably particularly strong, as distinct national and regional systems persist and countries maintain their own strategies next to the European-wide policy agenda with core regions receiving more domestic R&D support than peripheral regions (Banchoff 2002; Crescenzi et al. 2007). A lack of support for research in peripheral regions may not only slow down the development of scientific and technological capabilities, but is also likely to weaken the absorptive capacity of these regions to reap the benefits of knowledge produced outside their regions in the context of their own industry specialisations (Foray et al. 2009). This means that European research funding is expected to increase the differences in the rates of knowledge production and utilisation across European regions.

The tension between agglomeration economies and regional convergence has been a more general concern over the last ten years among scholars and policymakers alike (Puga 2002; Scott and Storper 2003; Crescenzi et al. 2007; Farole et al. 2011). In Europe, this debate has been recently reinvigorated due to the 'Lisbonisation' of the European policy agenda and proposed reforms of EU cohesion policy (Barca 2009). Much of the empirical research in this direction has however focused on the effect of cohesion policies on inter-regional income convergence (for a recent overview, see Farole et al. 2011), while the territorial impact of Europe's research policies, apart from descriptive analysis (Sharp 1998; Clarysse and Muldur 2001), has not yet been investigated systematically. The question whether the FP funding scheme is disproportionally to the benefit of a group of core regions is therefore still an open one.

This study aims to fill this gap in our understanding by analysing the territorial impacts of Europe's research policy. We do so by relating participation in the FP funding scheme to co-publication output as an indicator of collaborative knowledge production. The objective is first, to investigate whether existing scientific co-publication activity is conducive for the acquisition of FP funding,

and second, to measure the effects of FP funding on subsequent co-publication activity between EU regions. Should peripheral actors indeed have difficulties in connecting to more central ones, we will observe that the acquisition of European research funds and its effect on scientific collaboration is disproportionally concentrated in the scientific 'core' regions in North-West Europe.

We address these research objectives by exploiting a unique time-series in which FP participation and FP network structures – as captured by joint participation of organisations in FP projects – are linked to publication output and co-publication networks at the macro level of 254 regions within 25 European countries. We develop a thematic concordance between scientific fields and FP thematic areas, which is needed to establish the link between FP networks and co-publication networks in different thematic fields, Using this concordance, we analyse for three broad thematic programmes running in the Fifth Framework Programme (FP5) and Sixth Framework Programme (FP6) to what extent existing co-publication networks predict subsequent FP funding acquisition, and to what extent FP funds, in turn, affect subsequent co-publication patterns.

The remainder of the paper is organised as follows. In the next section, we develop a geographical perspective on the role of sub-national regions in Europe's research policies by focusing in particular on the compatibility of the FPs with Europe's cohesion objective. We subsequently describe the data and our empirical setting in section 3, followed by an introduction of the concordance scheme between scientific fields and FP thematic areas in Section 4. Section 5 spells out the empirical modeling approach, before in section 6 we present our results. Finally, in section 7 we discuss the implications of our findings, limitations of our study and potential directions for further research.

4.2 A GEOGRAPHICAL PERSPECTIVE ON THE EUROPEAN RESEARCH AREA

The emergence of a systematic Research and Technological Development (RTD) policy at the European level can be traced back to the 1980s when the first multi-annual Framework Programme was implemented. As the name suggests, the FPs are conceived as a common *framework* under which EU RTD policies should be organised and as *programmes* that last several years to enable long term investments in specific strategic areas such as ICTs, sustainable development, biotechnology and energy. From its inception, an essential role of the FPs has been to provide funds for transnational networks of researchers in order to overcome impediments to international research collaboration.

At the Lisbon Council in 2000, it was decided to concentrate Europe's RTD policies around the mobilising concept of the 'European Research Area' (ERA) with the aim of creating a space in which '*researchers, technology and knowledge freely circulate*' (Commission 2002). The justification for ERA policy is that European scholars produce top research in a wide range of fields, yet research activities are often fragmented and the presence of valuable expertise is not always sufficiently known across Europe. The integration of these researchers in self-organised research consortia should therefore facilitate the creation of critical mass that possesses a collaborative attitude and that converges on strategic goals (Breschi and Malerba 2009).

From a geographical perspective, the goal of ERA policy is first and foremost to tackle the problem of fragmentation in the research system by aligning a wide variety of institutions and agencies that govern research activities in Europe. Nation-states in particular are responsible for this fragmentation as national policies still define the key institutional settings in research funding schemes, research infrastructures, education systems, intellectual property regimes and labour markets, amongst others (Lundvall 1988; Crescenzi et al. 2007). The emphasis on regional competiveness as an important policy goal has also contributed to a plethora of regional institutions that promote knowledge-based activities at the sub-national level (Bristow 2005). Research activities have become strongly engrained in these governance modes which renders the process of knowledge creation to be primarily dependent on localised interactions within regions (Cooke et al. 1997; Morgan 1997). However, local territorial embeddedness (Rodriguez-Pose and Crescenzi 2008) also impedes effective research collaborations across regions and countries, which is visible in the 'spatial barriers' to collaborative knowledge production. More specifically, research collaborations are impeded by regional, national and language borders effects, even after controlling for the effect of geographical distance (CHAPTER 2 AND CHAPTER 3). The goal of ERA policy then becomes to reduce the significance of these spatial barriers in cases where knowledge creation has a European-wide value added.

At the same time, the EC aims to reduce inequalities between scientific and technological leading and lagging regions as to increase equal participation in the European Research Area. This objective is to a large extent financed by the Structural Funds (SFs) that provide resources to Europe's poorest regions (i.e. less than 75% of average European GDP). Over the years, an increasing proportion of this budget has been allocated to RTD policies in order to strengthen the innovation capabilities and the absorptive capacity of these cohesion regions

through various instruments focused on research infrastructures, network development and technology transfer (Musyck and Reid 2007; Begg 2010).

One can argue that there is a functional division of labour between EC's cohesion policy and research policy. The SFs provide the necessary conditions for more equal participation in ERA, whereas the FPs intend to reduce the spatial barriers to collaborative knowledge production in order to actually realise ERA. Such a division of labour, however, also necessitates synergies and complementarities between the two policy objectives which was also acknowledged by the European Commission shortly after introducing the ERA concept (Commission 2001). This implies that in case the SFs provide the necessary funding for increasing the participation of peripheral actors in ERA, the EC also needs to make sure that these capabilities can be effectively exploited in ERA (Sharp 1998). Yet, the task of involving peripheral actors in ERA mainly rests on the shoulders of the FPs and their mandate to reduce fragmentation does not necessarily involve the creation of a more cohesive ERA. Rather, it is more likely that in the current funding scheme acquisition of FP funding and its effect are structured in such a way that they disproportionately benefit scientific leaders. This would imply that much of the language of European policy suggesting that it is possible to maximise scientific competitiveness and related innovation potential while at the same time achieving convergence in research capabilities, is rather ill-informed. In our view, there are no less than four reasons for possible incompatibilities between the competitiveness and the cohesion objectives in the context of research policy in Europe.

First, with regard to the allocation of FP projects, it follows from the rationales and goals of the FPs that the cohesion objective should not play a role in the selection of FP projects that are being funded and those that are not (Sharp 1998; Breschi and Malerba 2009). The outcome of research funded by the FPs should be a European wide public good that maximises the research and innovation potential of the European territory as a whole. It follows that over the successive FPs, funding has become increasingly based on criteria of research quality (i.e. scientific excellence), socio-economic relevance (i.e. tackling societal challenges and innovation potential) and critical mass, rather than on a redistribution criterion[41]. Our data - which is described in the next section - strongly suggests

[41] Sharp (1998) found that funding in FP3 and FP4 favored core regions only in absolute terms. Peripheral countries still managed to acquire more funding relative to their total R&D capacities in line with the cohesion objective of FPs at the time. Given the turn towards excellence we expect that these findings do no longer hold in FP5 and especially not in FP6.

that at a macro-level these criteria of research activity are very unevenly spatially distributed in Europe, even more so than economic activity (see Frenken et al. 2007; Matthiessen et al. 2010).

- Scientific publication output per capita (Figure 4.1) is concentrated in a group of 'core' regions located in a Western European axis stretching south-east from London towards Rome, in Scandinavian regions and in some large city-regions located in other parts of Europe (e.g. Berlin, Budapest, Glasgow/Edinburgh, Madrid, Vienna).
- Scientific collaboration networks as proxied by co-publication counts (Figure 4.2) are especially dense in national systems and over short-distances. The Western European national systems are connected by a small group of leading city-regions (e.g. Berlin, London, Paris, the Randstad Region).
- High impact science – as measured by mean citation rates – is especially produced in Germany, the Netherlands, Switzerland, the UK and the Scandinavian countries, and average citation rates are much lower in the new member states of the European Union (Figure 4.3).

Given these unequal distributions of research activities one can reasonably infer that competitive FP funding is likely to favour the European core of research performing entities. In the analysis that follows we test this hypothesis by estimating whether the number of previous co-publications between two regions is predictive of acquisition of FP funding by these two regions.

Second, it seems difficult for unconnected actors to acquire a central position in the FP funding networks. Breschi and Cusmano (2004), Autant-Bernard et al. (2007) and Wanzenböck et al. (2012) analyse the social network structures among FP participants and find that the funded collaboration networks are dominated by a small *'oligarchic core'* (Breschi and Cusmano 2004, p. 748) of research actors, whose central network positions in the programme have only strengthened over the successive funding rounds. This implies that participants are much more likely to acquire FP funding when they were already participating in previous FPs (Paier and Scherngell 2011), and that peripheral participants experience difficulties to enter the FP networks. The latter observation is also confirmed in various studies concluding that - despite the intended European character – the number of links between organisations in the in the FPs tends to decay with geographical distance and language barriers (Scherngell and Barber 2009, 2011; Maggioni and Uberti 2009; Balland 2011). Although these spatial structures are not determining future collaboration *per se*, they signal that the FP funding scheme largely reproduces, or even reinforces, already existing spatial network structures. We also analyse this by estimating whether joint past acquisition of funding by two regions is predictive of joint acquisition of funding in FP6.

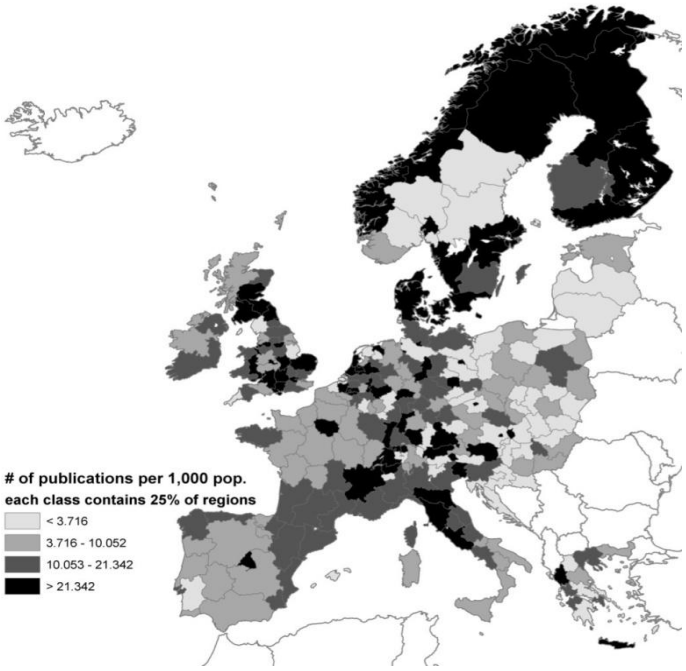

Figure 4.1: *Total number of publications per capita in the period 2000-2007.*

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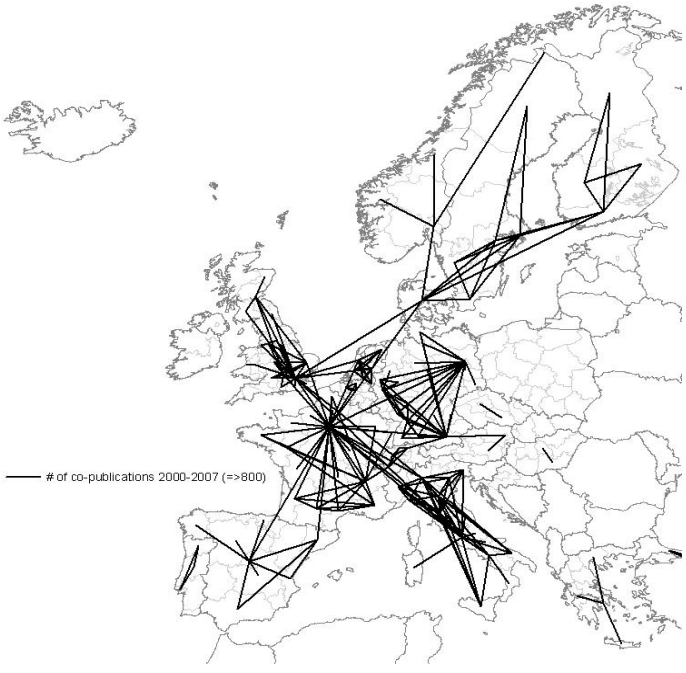

Figure 4.2: *Total number of co-publications in the period 2000-2007.*

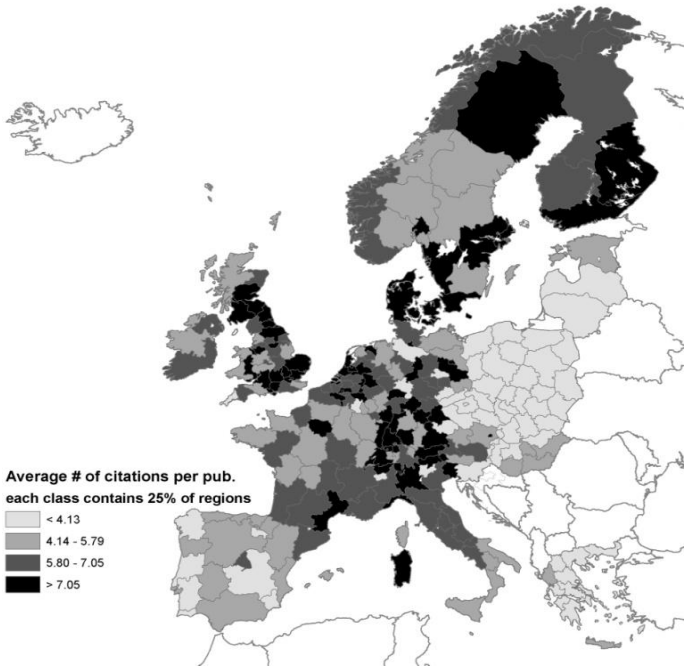

Figure 4.3: *Average number of citations in the period 2000-2007.*

Third, turning to the effects of FP funding we may safely assume that the volume of FP funding will have at least some positive effect on co-publication activity because the FP funding scheme provides 'behavioural additionality' (Luukonen 2000). The additionality of FP funding is apparent from the fact that most research collaborations take place over short distances and within the same country (CHAPTER 2; Adams et al. 2005). In the European context these proximity barriers tend to be quite pervasive and have only partially broken down over the last decade (CHAPTER 3). Collaboration networks that require to be organised in international large-scale R&D consortia are therefore very unlikely to emerge in a similar structure without strategic interventions.[42] The question thus becomes not

[42] This observation is confirmed by the experience of participants who often mention the establishment of international partnerships as a main benefit of participation in the FPs (Luukonen 2000). Effects of FP funding on international scientific collaboration networks might also be substantial due to a number of other reasons. Among them are matching requirements by national governments or research organisations, which alone may double the volume of funding. It has also been documented that in some successful cases the FPs have played an agenda setting role, which may have induced multiplier effects on domestically funded research (Arnold et al. 2005). Moreover, a micro level study has

whether FP funding has an effect on scientific activity *per se* but rather whether there are differences between the effect of FP funding on structuring the knowledge activities of scientific leading and lagging regions. Due to the need for face-to-face interaction in collaborative projects and the institutional embeddedness of research practices, knowledge will circulate more easily within research agglomerations than between them (Malmberg and Maskell 2002; Storper and Venables 2004). The mediators of these localised processes are both informal social ties and contractual channels (Botazzi and Peri 2003; Breschi and Lissoni 2009). This implies that researchers located in core regions may, on average, be better able to transform acquired FP funding in relevant knowledge outputs.

Fourth, and finally, core regions may also benefit from their central position in global exchange networks of people, capital and ideas (Castells 1996; Bathelt et al. 2004; Moodysson 2008). Such geographically dispersed networks have been highlighted by urban geographers in their work on globalisation (Derudder 2006) and provide actors within regions with complementary resources and variation in knowledge (Owen-Smith and Powell 2004; Gertler and Levitte 2005). Indeed, recent work using a knowledge production framework shows that long-distance collaborations, both of the formal and the informal type, carry knowledge spillovers (Maggioni et al. 2007; Breschi and Lissoni 2009; Ponds et al. 2010; Marrocu et al. 2011). Regions that reap the benefits of these knowledge spillovers are often well-positioned in stratified networks that are shaped by cumulative mechanisms (e.g. preferential attachment, network retention) of individual and organisational behavior (Glückler 2007). These mechanisms have a tendency to result in disproportional concentration of resources and ideas in a few nodes, effectively creating a network core-periphery structure that materialises in physical space (Sassen 1991; Castells 1996). In science, such stratified structures are evidenced by the observation that over time organisations producing high quality science increasingly start to collaborate with each other (Jones et al. 2008). The observed network logic is central to the European policy discourse which intends to create dense collaboration structures between *"virtual centres of excellence"* (Commission 2007a, p. 15). Because of these mechanisms and political intentions based upon them, we expect that the effects of FP funding on structuring scientific collaborations are especially significant for those inter-

shown the importance of FP funding in stimulating the productivity and collaborative behavior of researchers as captured by co-publications (Defazio et al. 2009). Given these observations, we might observe evolving international scientific collaboration networks that are closely associated with funding provided by the FPs.

regional channels through which resources and ideas already abundantly flow and less so for peripheral regional pairs where collaboration structures have not yet emerged.

4.3 DATA

To test how acquisitions and effects of FP projects are distributed over the European territory, we link data from two different sources: (i) research articles indexed by the *Web of Science* database, (ii) FP project participations extracted from the *EUPRO* database.

The *Web of Science* database (WoS) is a bibliographical database produced by Thomson Reuters, indexing approximately 12,000 sources worldwide and considered to be one of the most comprehensive and reliable sources of information on basic research activity across all countries and fields of science. Its indexed research articles all occur in peer-reviewed journals. The journals are selected on the basis of a sufficient quality assessment carried out by *Thomson Reuters*. We analyse research articles contained in the WoS, published in the period 2000-2007 and containing at least one European author-affiliate address. All publications are assigned to 22 scientific fields based on aggregations of the journal categories listed in WoS as defined by Netherlands Observatory of Science and Technology (NOWT).[43]

The *EUPRO* database comprises data on funded FP projects and participating organisations.[44] *EUPRO* contains systematic information on project objectives and achievements, project costs, project funding and contract type as well as on the participating organisations including the full name, the full address and the type of the organisation (Roediger-Schluga and Barber 2006). Currently, data for FP1 to FP7 are complete. For this analysis, we choose to extract all projects that run in FP5 and FP6. Because of the specific time-series on publications we focus on all projects that have been funded in the period 2000-2005.

We further restrict the analysis to the thematic areas in FP5 and FP6. The rationale for this focus is threefold: (i) the thematic areas receive the lion's share

[43] NOWT Science and Technology Indicators reports are available at www.nowt.nl. We exclude the thirteen social science and humanities disciplines because the coverage of ISI is less in this domain and because their contribution to the FPs is rather small.

[44] EUPRO has been constructed and maintained by AIT Austrian Institute of Technology.

of funding within the FPs. More specifically, in FP5 they mutually make up 72.5% of funding, whereas in FP6 63.3% of funding is allocated within those themes (Arnold et al. 2009), (ii) one of the major goals of the thematic areas is their scientific and technological impact, implying that scientific publications can be considered a significant and meaningful output of the funded projects[45], and (iii) knowledge production within the thematic areas explicitly concentrates on collaborative actions which allows for a sound comparison not only with the activity of regions but also with their scientific collaboration networks.

As we adopt a geographical perspective, we are interested in the locations involved in research production and collaboration. Accordingly, all institutional addresses on research articles and FP project description are uniquely assigned to European regions on the basis of city names and postal codes. More specifically, regions are defined by the hierarchical NUTS classification with each organisation being assigned to one out of 254 NUTS2 regions in 25 countries in Europe (COM 2007b). The 25 countries include all countries of the European Union plus Norway and Switzerland, but excluding Romania, Bulgaria, Cyprus and Malta. In most countries the NUTS2 regions have administrative authority, although for five small countries they are defined at the national level.

Research collaboration is defined as a pair of different main organisations that co-occur in the same research article or on the same FP project description, but are located in different sub-national regions. In our procedure, we count each region-pair that occurs simultaneously in the author address by-line of a research article or on a FP project description. Obviously, a co-publication or a project may contain multiple region pairs depending on the number of different regional addresses that appear in the byline of a publication or project description. [46] We subsequently aggregate the count of all inter-regional collaborative activities in the datasets into region-by-region matrices that denote the number of collaborations between region i and region j ($i, j = 1, \ldots, n; i \neq j$) in scientific field s and year t. As collaborations are undirected, the final dataset contains 32,131 unique regional pairs for every scientific field s and year t.

[45] The number of publications may in the future also be used as an indicator for the evaluation of projects.

[46] The counts exclude multiple occurrences of the same regions within the same article or project description.

4.4 CONCORDANCE

The funded projects within the FPs tend to focus on specific broad thematic areas such as life sciences, sustainable development and ICTs. A systematic study of acquisition and effect of FP funding in which total FP participation is juxtaposed with total research collaboration activity therefore runs the risk of serious estimation biases, because FP participation in a particular thematic area is not randomly distributed over scientific fields and because the spatial distribution of scientific activity tends to differ considerably between scientific fields (CHAPTER 3).

In order to correct for this bias, we established a concordance that indicates the extent to which different scientific fields are targeted by particular thematic areas of the FPs. The concordance consists of a set of scientific publications that are - at least partly - an outcome of funding within the FPs. As of 2009, the indexed publications in the various citation databases that are part of *Web of Science* can be searched on grant activity and funding acknowledgements (i.e. funding agencies and grant numbers). We use this tool to develop a query that searches in the funding acknowledgement texts for names and abbreviations related to European institutions, European Commissions' RTD policies and the FPs. The developed methodology provides a unique opportunity to characterise scientific output that follows from FP funding, although the specific data sample should be taken with caution due to limited coverage and sampling bias.[47]

We first retrieved the funding acknowledgement text and the journal source for every identified publication. We subsequently searched in the acknowledgements of the retrieved publications for unique grant numbers and call abbreviations of FP projects, which are available in the *EUPRO* database. The search included names of the various sub-programmes and parts of 'model case' structures of grant numbers in FP5 and FP6, which contain a unique programme identifier, a year and a contract number. In case we linked a publication to a particular FP thematic area, we checked manually whether the match was correct. Based on this procedure, 8,235 publication records could be assigned to a

[47] The data is only available for the year 2009 and it is unclear how the mentioning of funding acknowledgements differs between organisations, scientific fields and locations. In addition, FP funding is often used in combination with other funding sources which makes it difficult to disentangle the exact contribution of the FPs to a specific research project. Due to these reasons we decided to only use this sample of publications to establish a concordance between FP thematic areas and scientific fields, and not to use the FP funded publications directly in the final analysis.

specific thematic area within FP5 or FP6. It turns out that the FPs are acknowledged in many scientific publications with even the thematic areas of FP5 – running from 1998 to 2002 – still being acknowledged in almost 1,400 publications in 2009 (Table 4.1).

WOS classifies all journals in at least one journal category (with a maximum of 6) based on their titles and citation relations (see for an overview and critique Leydesdorff and Rafols 2009). Journal categories can be uniquely assigned to one out of 22 scientific fields as defined by the NOWT classification introduced in section 3. This structure allows us to aggregate all publications that acknowledge a FP thematic area to a particular scientific field. A fractional counting method is used in which every publication is counted as one. Accordingly, the scientific fields to which publications are assigned receive a fractional count equal to one divided by the total number of scientific fields to which the publication can be assigned.[48] In doing so, we obtain for every FP thematic area a distribution of acknowledged publications over scientific fields.

By correlating these distributions between thematic areas, we assess (dis)similarities in scientific focus between the thematic areas in FP5 and FP6. Following this procedure, we observe three distinct broad thematic areas that both run in FP5 and FP6:

1. SUSTDEV: Consisting of the programmes FP5-EESD and FP6-SUSTDEV (r=0.95, P<0.01) and for which scientific output is particularly concentrated in Earth Sciences and Technology and Environmental Science and Technology.
2. LIFESCIENCE: Consisting of FP5-QOL and FP6-LSH (r=0.88, P<0.01) and for which scientific output is particularly concentrated in Basic Life Sciences, Clinical Medicine and Biomedical Sciences.
3. ICT: Consisting of FP-IST which is a continuing programme in FP5 and FP6 and for which scientific output is particularly concentrated in Physics and Material Science, Computer Science and Electrical Engineering and Telecommunication.

The number of acknowledged publications and its distribution over scientific fields is used to compute a weight for every scientific field per broad thematic programme. This weight captures the relevance of a scientific field to each of the three programmes (i.e. SUSTDEV, LIFESCIENCE and ICT). More specifically, we divide for every programme the number of acknowledged publications in each

[48] A scientific field is always counted once even if a publication is assigned to more than one journal category belonging to the same scientific field.

scientific field by the total number of acknowledged publications in that thematic programme. As our dataset contains 22 scientific fields, the computed shares of acknowledged publications per scientific field are multiplied by 22 to obtain weights that are smaller/greater than one in case the scientific field contributes less/more than 1/22 to a thematic programme. All scientific field specific (*i*, *j*)-region collaboration counts are subsequently weighted and the adjusted collaboration counts are aggregated over the 22 scientific fields. By using this simple adjustment method, co-publication counts between region *i* and *j* approximate the total number of co-publications between region *i* and *j*, but are now weighted for the relevance of scientific fields to each of the three programmes. The weights are reported in Table 4.1.

Table 4.1: *Weights used for computing publication and co-publication counts*

	SUSTDEV			LIFESCIENCE			ICT	
	FP5	**FP6**	**W[a]**	**FP5**	**FP6**	**W[a]**	**FP5-6**	**W[a]**
Total number of publications	430	1028		865	2800		1081	
Biomedical Sciences	3.0	25.9	0.44	130.2	622.7	4.52	60.6	1.33
Basic Life Sciences	19.8	52.3	1.09	174.8	1007.5	7.10	44.0	1.04
Biological Sciences	68.5	77.2	2.20	81.8	71.9	0.92	22.3	0.47
Chemistry & Chemical Eng.	19.7	124.9	2.18	15.3	105.9	0.73	66.1	1.36
Clinical Medicine	1.8	17.6	0.29	252.2	745.0	5.99	33.5	0.80
Computer Sciences	1.7	4.5	0.09	2.0	8.1	0.06	194.6	3.96
Earth Sciences & Tech.	130.5	268.8	6.03	4.8	1.0	0.04	4.0	0.08
Environmental Sciences	118.8	287.8	6.13	50.5	3.4	0.32	4.3	0.09
Physics & Materials Science	10.5	58.5	1.04	4.2	45.8	0.30	323.2	6.58
Electrical Engineering	5.0	6.8	0.18	0.0	2.0	0.01	193.9	3.95
Other	50.7	103.7		149.2	186.7		134.6	
Correlation[b]		r=0.95 p<0.01			r=0.88 p<0.01			

Notes. [a] only weights greater than one for at least one thematic priority are shown.

[b] results of correlations between 22 scientific fields are shown.

4.5 Research Design

Model 1: Acquisition of FP funding

The first empirical objective of the paper is to investigate whether existing scientific collaboration networks – as captured by co-publications in scientific journals – are conducive for the acquisition of FP funding. Accordingly, we set out to explain the number of joint acquisitions of FP6 projects between region *i* and region *j* by employing a cross-sectional spatial interaction model of the gravity type. Spatial interaction models are extensively used for understanding aggregate compositions of interactions in geographical space, and they also have been used to explain the intensity of research collaboration among European regions (Chapter 2 and Chapter 3; Maggioni and Uberti 2009; Scherngell and Barber 2009; 2011). Appendix C provides a description of the mathematical situation we are considering and the concrete empirical specification of Model 1. Variables are summarised in Table 4.2.

Following common practice in spatial interaction models, we first randomise the model by including origin and destination variables for the total number of FP links of region *i* and the total number of FP links of region *j*. In case the acquisition of FP projects would be perfectly random between regions only these mass terms would become significant with a value approximating one. This implies that we can interpret all other significant effects as deviations from complete random acquisition of FP funding between European regions The variable of central interest that is expected to result in deviations from random acquisition of FP funding is the number of co-publications between region *i* and region *j* in the three years prior to the start of FP6. Our main hypothesis in this model holds that a disproportional amount of funding is allocated to existing channels of scientific interaction. Hence, we expect a positive effect of these co-publications networks on the likelihood that region *i* and *j* acquire FP funding.

In addition, we estimate whether FP funding networks follow repetitive structures by measuring whether joint previous FP participations of region *i* and region *j* deviate FP6 funding from randomness (see Paier and Scherngell 2011). In doing so, we include a variable denoting the number of times the (*i*, *j*)-region pair previously participated in a thematically related FP5 projects, and the number of times the (*i*, *j*)-region pair previously participated in a thematically unrelated FP5 projects.

We finally include common spatial separation measures as controls in our model. These controls are the geographical distance between two regions *i* and *j* as

measured in terms of the natural logarithm of the great circle distance, a dummy whether two regions *i* and *j* are located in the same country (0) or not (1), and a dummy whether two regions *i* and *j* are located in the same language area (0) or not (1).

Model 2: Effect of FP funding

The second empirical objective of this paper is to measure the effects of FP funding on the occurrence of scientific collaboration networks between region *i* and *j*. More specifically, in a panel-data setting we explain the number of inter-regional co-publications after joint participation in FP projects, while controlling – amongst other factors – for the number of inter-regional co-publications before joint participation. The mathematical derivation and econometric specification of Model 2 is presented in Appendix D, variables are summarised in Table 4.3.

Similar to Model 1 we randomise the model by including the total number of publications of region *i* and the total number of publications of region *j* as origin and destination variables. In addition we also include the same spatial control variables for geographical distance, national borders and language borders, as we expect that these measures of geographical proximity have an effect on the number of co-publication counts between region *i* and *j* (Chapter 3).

The variable of main interest in this model is the amount of FP funding that region *i* and *j* received, which is measured as the cumulative number of joint acquisitions of FP funding of the (*i*, *j*)-region pair in a three year moving window prior to the observation of co-publication output. Indeed, we expect this variable to have a positive and significant effect on the number of inter-regional co-publications.

One can also expect that significant amounts of co-publication activity take place on the basis of previously established connections. In our estimation framework, we therefore include a measure of past performance that controls for the cumulative number of co-publications between region *i* and *j* in a three year moving window before we observe inter-regional co-publication output. Our variables of central interest however relate to whether the effects of funding are equally distributed over the European territory. We first distinguish between the effect of acquisition of FP funding by regions *i* and *j* that are located in the same country, and regions *i* and *j* that are located in different countries by introducing an interaction term that captures international funding. In line with the objective of the FPs to stimulate international scientific collaboration we expect that this interaction term will become positive and significant possibly at the expense of

the main funding term. This would suggest that it is FP funding provided to international collaborations rather than FP funding *per se* that increases co-publication activity between regions.

Most importantly, however, we measure the differential effect of FP funding on the European territory by including an interaction term between the amount of funding and already existing scientific collaboration networks in the three years prior to the observation of co-publication output. In line with our hypothesis we expect this interaction term to become positive which would imply that better connected regional pairs indeed profit more from the acquisition of FP funding than less connected regional pairs.

4.6 RESULTS

MODEL 1: ACQUISITION OF FUNDING

Table 4.4 reports descriptive statistics and correlations for the included variables. Both the number of existing co-publication relations and the acquisition of FP5 funding are positively correlated with the acquisition of FP6 funding. The acquisition of FP6 funding also decays significantly with distance and when a language border is crossed.

We present the cross-section Poisson regression explaining the number of acquisitions of joint projects in which both region *i* and region *j* participate in Table 4.5. Model 1A shows that in two of the three thematic programmes (i.e. SUSTDEV and ICT) the number of existing co-publication relations exerts positive and significant influence on the amount of funding regional links receive, albeit with a very small coefficient. Previous co-publication relations are not a significant input for joint acquisition of FP projects in LIFESCIENCES. We also confirm that participation in FP6 tends to decay with geographical distance and that there is some evidence that FP participation decreases when either a country or a language border is crossed (see Scherngell and Barber 2009, 2011).

In Model 1B we estimate whether previous participation in FP5 has an independent and significant effect on FP6 participation. Regional links that already participated in FP5 have a higher likelihood of participating in FP6 for all thematic programmes. In addition, we show that this is especially the case for participation in related programmes, whereas experience in unrelated programmes does not influence FP6 participation.

Table 4.2: *List of variables included in Model A (acquisition of FP projects)*

	Description
Dependent variables	
FP6 $LINKS_{ij}$	number of funded participations in FP6 between $region_i$ and $region_j$
Independent variables	
FP6 $WEIGHT_i$	number of funded participations of $region_i$ in FP6
FP6 $WEIGHT_j$	number of funded participations of $region_j$ in FP6
$COPUB_{ijt-3}$	number of copublications between $region_i$ and $region_j$ in 2000-2002
FP5 RELATED $LINKS_{ij}$	number of funded participations in related 5^{th} FP between $region_i$ and $region_j$
FP5 UNRELATED $LINKS_{ij}$	number of funded participations in unrelated 5^{th} FP between $region_i$ and $region_j$
$DISTANCE_{ij}$	straight line distance between $region_i$ and $region_j$
$COUNTRY_{ij}$	dummy whether $region_i$ and $region_j$ are located in the same
$LANGUAGE_{ij}$	dummy whether the same language is spoken in $region_i$ and

Table 4.3: *List of variables included in Model 2 (effect of FP funding)*

	Description
Dependent variables	
$COPUB_{ij}$	number of copublications between $region_i$ and $region_j$
Independent variables	
main variables	
$FUND_{ijt-3}$	number of FP projects in which a regional pair has participated in previous 3 years (mean centered)
International $FUND_{ijt-3}$	number of FP projects in which an international regional pair has participated in previous 3 years (mean centered)
$COPUB_{ijt-3}$	number of copublications between $region_i$ and $region_j$ in previous 3 years (mean centered)
$FUND_{ijt-3}COPUB_{ijt-3}$	product of $FUND_{ijt-3}$ (mean centered) and $COPUBij_{t-3}$ (mean centered)
control variables	
PUB_i	number of publications of $region_i$ in previous 3 years
PUB_j	number of publications of $region_j$ in in previous 3 years
$DISTANCE_{ij}$	straight line distance between $region_i$ and $region_j$
$COUNTRY_{ij}$	dummy whether $region_i$ and $region_j$ are located in the same country (0) or not (1)
$LANGUAGE_{ij}$	dummy whether the same language is spoken in $region_i$ and $region_j$ (0) or not (1)

Table 4.4: *Descriptive statistics and correlations for Model 1 (acquisition of FP funding)*

	SUSTDEV	**Mean**	**SD**	**Min**	**Max**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	FP6 $LINKS_{ij}$	1.032	2.803	0	65	1.000								
2	FP6 $WEIGHT_i$	4.504	1.920	0.000	7.847	0.328	1.000							
3	FP6 $WEIGHT_j$	4.463	1.962	0.000	7.847	0.343	-0.004	1.000						
4	$COPUB_{ijt-3}$	1.117	1.492	0.000	8.075	0.481	0.345	0.382	1.000					
5	FP5 RELATED $LINKS_{ij}$	0.490	0.740	0.000	4.357	0.667	0.414	0.428	0.606	1.000				
6	FP5 UNRELATED $LINKS_{ij}$	0.710	0.938	0.000	5.808	0.651	0.443	0.440	0.673	0.743	1.000			
7	$DISTANCE_{ij}$	6.830	0.702	2.397	8.250	-0.057	-0.038	-0.085	-0.377	-0.095	-0.091	1.000		
8	$COUNTRY_{ij}$	0.924	0.266	0.000	1.000	-0.012	0.013	-0.037	-0.433	-0.052	-0.062	0.521	1.000	
9	$LANGUAGE_{ij}$	0.890	0.313	0.000	1.000	-0.023	-0.002	-0.058	-0.424	-0.068	-0.078	0.554	0.805	1.000
	LIFESCIENCE	**Mean**	**SD**	**Min**	**Max**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	FP6 $LINKS_{ij}$	0.633	2.312	0	96	1.000								
2	FP6 $WEIGHT_i$	3.449	2.313	0.000	7.591	0.295	1.000							
3	FP6 $WEIGHT_j$	3.591	2.300	0.000	7.591	0.284	-0.003	1.000						
4	$COPUB_{ijt-3}$	1.445	1.876	0.000	8.941	0.443	0.416	0.424	1.000					
5	FP5 RELATED $LINKS_{ij}$	0.463	0.740	0.000	5.004	0.561	0.412	0.417	0.627	1.000				
6	FP5 UNRELATED $LINKS_{ij}$	0.730	0.936	0.000	5.576	0.512	0.453	0.442	0.633	0.731	1.000			
7	$DISTANCE_{ij}$	6.830	0.702	2.397	8.250	-0.080	-0.111	-0.089	-0.401	-0.071	-0.105	1.000		
8	$COUNTRY_{ij}$	0.924	0.266	0.000	1.000	-0.016	-0.023	-0.033	-0.467	-0.040	-0.068	0.521	1.000	
9	$LANGUAGE_{ij}$	0.890	0.313	0.000	1.000	-0.031	-0.045	-0.056	-0.465	-0.055	-0.085	0.554	0.805	1.000
	ICT	**Mean**	**SD**	**Min**	**Max**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	FP6 $LINKS_{ij}$	1.094	3.371	0	129	1.000								
2	FP6 $WEIGHT_i$	4.629	1.680	0.000	8.087	0.320	1.000							
3	FP6 $WEIGHT_j$	4.709	1.672	0.000	8.087	0.329	-0.003	1.000						
4	$COPUB_{ijt-3}$	1.227	1.639	0.000	8.776	0.456	0.387	0.402	1.000					
5	FP5 RELATED $LINKS_{ij}$	0.450	0.749	0.000	5.384	0.690	0.447	0.454	0.619	1.000				
6	FP5 UNRELATED $LINKS_{ij}$	0.740	0.930	0.000	5.384	0.566	0.458	0.466	0.642	0.730	1.000			
7	$DISTANCE_{ij}$	6.830	0.702	2.397	8.250	-0.056	-0.072	-0.058	-0.369	-0.087	-0.096	1.000		
8	$COUNTRY_{ij}$	0.924	0.266	0.000	1.000	-0.022	-0.009	-0.032	-0.415	-0.065	-0.055	0.521	1.000	
9	$LANGUAGE_{ij}$	0.890	0.313	0.000	1.000	-0.032	-0.033	-0.053	-0.406	-0.078	-0.074	0.554	0.805	1.000

Table 4.5: *Model 1 explaining inter-regional acquisition of FP funding*

	Model 1		Model 2	
SUSTDEV	**COEF**	**SE**	**COEF**	**SE**
	SUSTDEV			
FP6 WEIGHT$_i$	0.986 ***	0.007	0.941 ***	0.008
FP6 WEIGHT$_j$	0.983 ***	0.007	0.938 ***	0.008
COPUB$_{ijt-3}$	0.029 ***	0.005	0.012 **	0.006
FP5 RELATED LINKS$_{ij}$			0.102 ***	0.009
FP5 UNRELATED LINKS$_{ij}$			-0.012	0.009
DISTANCE$_{ij}$	-0.050 ***	0.009	-0.054 ***	0.009
COUNTRY$_{ij}$	0.034	0.029	0.014	0.029
LANGUAGE$_{ij}$	-0.054 **	0.025	-0.068 ***	0.025
CONSTANT	-10.68 ***	0.071	-10.15 ***	0.095
LOG-LIKELIHOOD	-22902		-22846	
N	32131		32131	
	LIFESCIENCE			
FP6 WEIGHT$_i$	1.012 ***	0.008	1.001 ***	0.008
FP6 WEIGHT$_j$	1.003 ***	0.008	0.991 ***	0.009
COPUB$_{ijt-3}$	0.009 *	0.005	0.000	0.006
FP5 RELATED LINKS$_{ij}$			0.043 **	0.010
FP5 UNRELATED LINKS$_{ij}$			-0.012	0.008
DISTANCE$_{ij}$	-0.037 ***	0.010	-0.045 ***	0.010
COUNTRY$_{ij}$	0.020	0.032	0.009	0.032
LANGUAGE$_{ij}$	-0.006	0.027	-0.018	0.027
CONSTANT	-10.53 ***	0.081	-10.34 ***	0.098
LOG-LIKELIHOOD	-14768		-14762	
N	32131		32131	
	ICT			
FP6 WEIGHT$_i$	0.989 ***	0.007	0.905 ***	0.010
FP6 WEIGHT$_j$	0.995 ***	0.006	0.912 ***	0.009
COPUB$_{ijt-3}$	0.015 ***	0.005	-0.002	0.005
FP5 RELATED LINKS$_{ij}$			0.113 ***	0.010
FP5 UNRELATED LINKS$_{ij}$			0.014	0.009
DISTANCE$_{ij}$	-0.061 ***	0.009	-0.068 ***	0.009
COUNTRY$_{ij}$	-0.055 **	0.027	-0.052 *	0.027
LANGUAGE$_{ij}$	-0.043 *	0.023	-0.047 **	0.024
CONSTANT	-10.64 ***	0.076	-9.73 ***	0.114
LOG-LIKELIHOOD	-24189		-24110	
N	32131		32131	

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.$ 1. All regressions are estimated with robust standard errors

Most importantly, we also note that in Model 1B the effect of existing co-publication activity on FP participation vanishes, with the exception of SUSTDEV showing a small coefficient of 0.012. The marginal effect of existing co-publication activity is much smaller than the marginal effect of previous participation in FP5 on participation in FP6, even when comparing the coefficients of existing co-publication activity in Model 1A with the coefficient of previous FP participation in Model 1B. The main outcome of the analysis thus suggests that within the FP funding scheme, experience in previous FPs is especially important for receiving FP funding, whereas previous co-publications only have a minor effect, if any, on being funded in FP6.

This result implies that better networked regions in science are not disproportionally selected into the FP funding scheme. This is important given that in our subsequent analysis we need to make sure that potential effects of the FPs are indeed due to funding and not just to the selection of better performing regions (see Busom 2000). Since regional pairs that perform better in terms of co-publication output do not seem to receive disproportionally more funding, we can safely assume that the effect of funding on subsequent co-publication activity is independent from previous funding.

Model 2: Effect of FP funding

The objective of Model 2 is to estimate the effects of FP funding on co-publication activity. To understand the basic intuition of the model, Figure 4.4 reports on a descriptive analysis for a subsample of peripheral regional pairs without any previous co-publications in the period 2000-2002. We show the evolution of average numbers of co-publications after 2002, given that different amounts of funding are allocated to these regional pairs. Reading from Figure 4.4, funding seems to have a positive effect as regional pairs with FP funding produce more joint publications than regional pairs without FP funding.

The effect of FP funding on co-publication activity, however, should be assessed taking into account a number of control variables. In particular, we take into account the total publication activity in each region, their joint co-publication activity and their geographical position to other regions as measured by distance, national border and language effects. Descriptive statistics and correlation matrices of these variables are presented in Table 4.6, and regression results in Tables 4.7, 4.8 and 4.9.

In Model 2A we explain the number of co-publications between region *i* and *j* by including the amount of funding and previous co-publication activity, next to the

publication and geographical controls. Signs and coefficients of the amount of funding are positive and significant which confirms a positive effect of participation in the FPs on the creation of new scientific research collaborations. This result holds after controlling for the observation that much co-publication activity is repetitive as indicated by the positive and significant coefficient of previous co-publication activity. In line with previous studies (CHAPTER 2 AND CHAPTER 3; Maggioni and Uberti 2009; Scherngell and Barber 2009; 2011) the controls also exhibit highly significant effects on the number of co-publications that are produced between regional pairs. The higher the number of publications in region *i* and in region *j*, the higher the likelihood that scientific research collaborations will follow between the regional pairs. The creation of research collaborations is also explained by spatial effects. More precisely, the the number of times that regional pairs co-publish decays with geographical distance, and decreases when both a country border and a language border is crossed.

To test whether the effect of funding differs when giving to regional pairs located in the same country as compared to regional pairs located in different countries, we estimate the size and significance of international funding by introducing an interaction term between the effect of funding and the effect of international collaboration on co-publication activities. We find in Model 2B that the funding variable is not significant in this case and funding is only positively significant when provided to international regional pairs. The result holds irrespective of the thematic area.

Our main analysis tests whether funding has a differential effect on co-publication activity between regional pairs, according to their previously established co-publication relations. We therefore include in Model 2C an interaction term between funding and previous co-publications. All variables are centered on the mean, which implies that we should interpret the coefficient of funding as the effect of funding, when regional pairs had average levels of co-publication activity and *vice versa*.

The coefficients of funding and previous co-publications are again positive and highly significant, yet the marginal effect of FP funding has increased in comparison to earlier models and now approximates a value of 0.3. Turning to the sign and significance of the interaction term, we show that it is negative and significant for all three broad thematic programmes. This outcome suggests that the more a regional pair co-published in the past, the less is the impact of FP funding on subsequent co-publication activity. That is, for regional pairs that already intensively co-published, FP funding does not provide much additionality, but rather acts as a substitute for other sources of funding.

In Model 2D we verify the results of Model 2C by only focusing on international regional pairs. Because regional pairs that intensively co-published in the past are disproportionally located in the same country, it may well be that the observed substitution effect is driven by the insignificance of funding between regions within the same country. However, Model 2D shows that this is not the case as the effect of funding is still positively significant and equal in its size. Moreover, the interaction term remains negatively significant, suggesting that the substitution effect of FP funding is also present in international collaborations between regions.

We also carried out three robustness checks. First, we repeated the analysis on intervals of the data in which we distinguish between groups of regional pairs with approximately similar amounts of co-publication activity. In this case funding only becomes positively significant for group of regional pairs that have low numbers of previous co-publication activity, whereas funding becomes insignificant or sometimes even negatively significant for samples with high numbers of previous collaborations. Second, we separated the dataset in a sample of regional pairs within the same country and in a sample of international regional pairs, and estimated separate regressions. Third, we estimated models with moving windows of up to five years (i.e. funding and co-publication relations in the five years before measurement of co-publication activity), because in some cases the production of a co-publication might take longer than three years after the start of a FP project. The results obtained from these analyses did not change the outcomes of the main analysis.

4.7 Discussion

Research collaboration across territories is believed to be beneficial for the production and diffusion of knowledge. Yet, long distance collaboration is still significantly hampered by the dominance of national and regional research systems. In the European context, the Framework Programmes (FP) have been designed to overcome fragmentation by funding transnational collaboration networks between researchers. The main objective of these European research policies is to increase Europe's R&D-based innovation capacity as to render Europe more competitive. However, serious concerns have been voiced over the possibility that research funds are disproportionally absorbed by established institutes in the core research agglomerations in North-West Europe. If so, it can be argued that in the pursuit of competitiveness, the cohesion objective of the European Union is compromised.

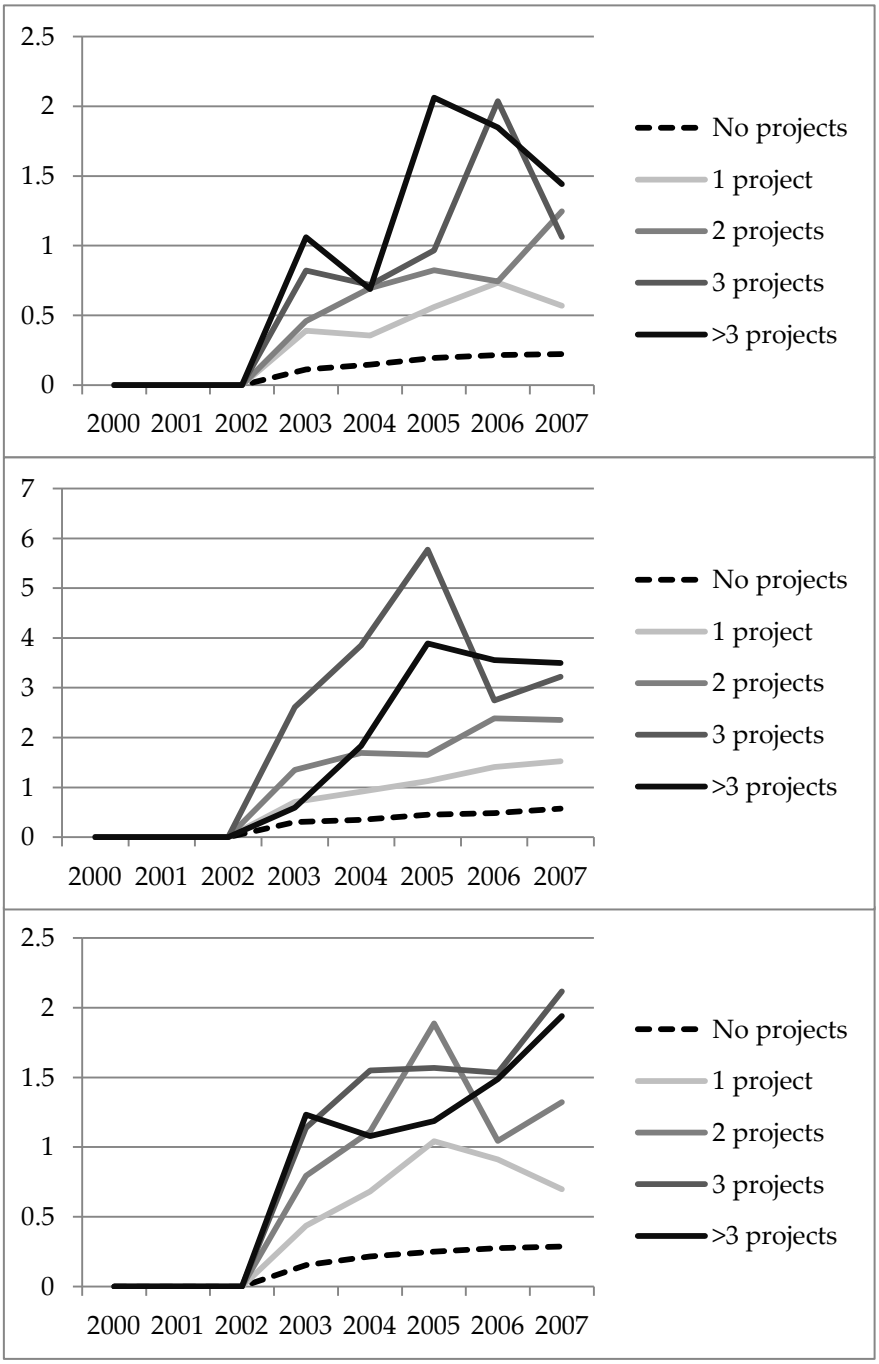

Figure 4.4: *Average number of co-publications (y-axis) for regional pairs that did not co-publish before joint participation in the FPs. SUSTDEV (upper), LIFESCIENCE (middle) and ICT (low).*

Table 4.6: *Descriptive statistics and correlations for Model 2 (effect of FP funding)*

	SUSTDEV	**Mean**	**SD**	**Min**	**Max**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	$COPUB_{ij}$	6.824	31.409	0.000	1368.51	1.000							
2	$FUND_{ijt-3}$	0.000	0.704	-0.446	3.923	0.342	1.000						
3	$COPUB_{ijt-3}$	0.000	1.539	-1.199	7.100	0.507	0.590	1.000					
4	PUB_i	8.572	1.545	0.860	12.555	0.177	0.396	0.442	1.000				
5	PUB_j	8.443	1.666	0.860	12.555	0.185	0.400	0.466	0.002	1.000			
6	$DISTANCE_{ij}$	6.830	0.702	2.397	8.250	-0.270	-0.090	-0.376	-0.061	-0.040	1.000		
7	$COUNTRY_{ij}$	0.924	0.265	0	1	-0.317	-0.041	-0.432	-0.021	-0.059	0.521	1.000	
8	$LANGUAGE_{ij}$	0.890	0.313	0	1	-0.318	-0.058	-0.429	-0.033	-0.032	0.554	0.805	1.000
	LIFESCIENCE	**Mean**	**SD**	**Min**	**Max**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	$COPUB_{ij}$	21.197	96.434	0.000	3466.76	1.000							
2	$FUND_{ijt-3}$	0.000	0.633	-0.351	4.539	0.381	1.000						
3	$COPUB_{ijt-3}$	0.000	1.940	-1.562	7.633	0.509	0.602	1.000					
4	PUB_i	9.375	1.726	3.224	13.722	0.192	0.406	0.464	1.000				
5	PUB_j	9.346	1.752	3.224	13.722	0.203	0.410	0.467	-0.004	1.000			
6	$DISTANCE_{ij}$	6.830	0.702	2.397	8.250	-0.283	-0.087	-0.401	-0.094	-0.067	1.000		
7	$COUNTRY_{ij}$	0.924	0.265	0	1	-0.373	-0.037	-0.466	-0.033	-0.060	0.521	1.000	
8	$LANGUAGE_{ij}$	0.890	0.313	0	1	-0.363	-0.055	-0.469	-0.054	-0.048	0.554	0.805	1.000
	ICT	**Mean**	**SD**	**Min**	**Max**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	$COPUB_{ij}$	9.647	43.103	0.000	2603.02	1.000							
2	$FUND_{ijt-3}$	0.000	0.661	-0.373	5.011	0.381	1.000						
3	$COPUB_{ijt-3}$	0.000	1.688	-1.321	7.620	0.505	0.582	1.000					
4	PUB_i	8.861	1.696	2.331	13.193	0.196	0.387	0.463	1.000				
5	PUB_j	8.849	1.771	2.331	13.193	0.198	0.384	0.469	0.001	1.000			
6	$DISTANCE_{ij}$	6.830	0.702	2.397	8.250	-0.248	-0.077	-0.366	-0.095	-0.043	1.000		
7	$COUNTRY_{ij}$	0.924	0.265	0	1	-0.291	-0.049	-0.409	-0.029	-0.061	0.521	1.000	
8	$LANGUAGE_{ij}$	0.890	0.313	0	1	-0.296	-0.064	-0.406	-0.047	-0.031	0.554	0.805	1.000

Table 4.7: *Model 2 explaining the number of co-publications after inter-regional acquisition of FP-funding for Sustdev*

	Model 1 **All**	**Model 2** **All**	**Model 3** **All**	**Model 4** **International**
$FUND_{ijt-3}$	0.097 ***	0.010	0.265 ***	0.247 ***
	0.005	0.008	0.008	0.009
International $FUND_{ijt-3}$		0.130 ***		
		0.010		
$COPUB_{ijt-3}$	0.203 ***	0.198 ***	0.227 ***	0.211 ***
	0.005	0.005	0.005	0.006
$FUND_{ijt-3}COPUB_{ijt-3}$			-0.062 ***	-0.074 ***
			0.002	0.003
Control Variables				
PUB_i	0.647 ***	0.642 ***	0.626 ***	0.698 ***
	0.006	0.006	0.006	0.007
PUB_j	0.647 ***	0.643 ***	0.625 ***	0.688 ***
	0.006	0.006	0.006	0.007
$DISTANCE_{ij}$	-0.308 ***	-0.309 ***	-0.307 ***	-0.336 ***
	0.008	0.008	0.008	0.009
$COUNTRY_{ij}$	-1.284 ***	-1.329 ***	-1.255 ***	
	0.024	0.024	0.024	
$LANGUAGE_{ij}$	-0.464 ***	-0.460 ***	-0.479 ***	-0.498 ***
	0.020	0.020	0.021	0.022
CONSTANT	-8.755 ***	-8.634 ***	-8.382 ***	-10.62 ***
	0.083	0.083	0.084	0.106
LOG-LIKELIHOOD	-234600	-234511	-234251	-191413
N	160655	160655	160655	148395

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$. All regressions are estimated with robust standard errors.

Table 4.8: *Model 2 explaining the number of co-publications after inter-regional acquisition of FP-funding for Lifescience*

	Model 1 All	Model 2 All	Model 3 All	Model 4 International
$FUND_{ijt-3}$	0.091 ***	0.010	0.333 ***	0.334 ***
	0.005	0.007	0.009	0.010
International $FUND_{ijt-3}$		0.148 ***		
		0.009		
$COPUB_{ijt-3}$	0.267 ***	0.256 ***	0.275 ***	0.247 ***
	0.004	0.004	0.004	0.004
$FUND_{ijt-3}COPUB_{ijt-3}$			-0.062 ***	-0.066 ***
			0.002	0.003
Control Variables				
PUB_i	0.553 ***	0.548 ***	0.536 ***	0.583 ***
	0.005	0.005	0.005	0.005
PUB_j	0.563 ***	0.559 ***	0.543 ***	0.586 ***
	0.005	0.005	0.005	0.006
$DISTANCE_{ij}$	-0.214 ***	-0.217 ***	-0.219 ***	-0.248 ***
	0.007	0.007	0.007	0.008
$COUNTRY_{ij}$	-1.551 ***	-1.606 ***	-1.550 ***	
	0.021	0.022	0.021	
$LANGUAGE_{ij}$	-0.444 ***	-0.452 ***	-0.464 ***	-0.491 ***
	0.018	0.018	0.019	0.020
CONSTANT	-9.056 ***	-8.892 ***	-8.627 ***	-10.87 ***
	0.079	0.079	0.080	0.100
LOG-LIKELIHOOD	-295897	-295751	-295436	-239631
N	160655	160655	160655	148395

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$. All regressions are estimated with robust standard errors.

Table 4.9: *Model 2 explaining the number of co-publications after inter-regional acquisition of FP-funding for ICT*

	Model 1 All	Model 2 All	Model 3 All	Model 4 International
$FUND_{ijt-3}$	0.091 ***	0.008	0.277 ***	0.267 ***
	0.005	0.008	0.009	0.009
International $FUND_{ijt-3}$		0.124 ***		
		0.009		
$COPUB_{ijt-3}$	0.246 ***	0.242 ***	0.266 ***	0.253 ***
	0.005	0.005	0.005	0.005
$FUND_{ijt-3}COPUB_{ijt-3}$			-0.060 ***	-0.069 ***
			0.002	0.003
Control Variables				
PUB_i	0.552 ***	0.547 ***	0.531 ***	0.580 ***
	0.005	0.005	0.005	0.006
PUB_j	0.554 ***	0.550 ***	0.532 ***	0.579 ***
	0.005	0.005	0.005	0.006
$DISTANCE_{ij}$	-0.214 ***	-0.219 ***	-0.222 ***	-0.232 ***
	0.008	0.008	0.008	0.009
$COUNTRY_{ij}$	-1.334 ***	-1.373 ***	-1.310 ***	
	0.024	0.024	0.023	
$LANGUAGE_{ij}$	-0.417 ***	-0.411 ***	-0.419 ***	-0.430 ***
	0.020	0.020	0.020	0.021
CONSTANT	-8.283 ***	-8.143 ***	-7.837 ***	-9.984 ***
	0.079	0.079	0.080	0.101
LOG-LIKELIHOOD	-257451	-257362	-257108	-212128
N	160655	160655	160655	148395

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$. All regressions are estimated with robust standard errors.

Contrary to our expectation, the analysis presented in this paper provides little empirical evidence to support this claim. Based on a regionalised dataset of joint FP participations and joint co-publication activities, we studied whether the acquisition and effect of FP funding is disproportionally concentrated in the leading research regions. We find that core regional pairs that co-publish frequently do not receive a disproportionate amount of funding from the FPs. Our analysis also shows that the more a regional pair co-published before, the less the additional effect of FP funding is on their subsequent co-publication activities.

In its most basic form, the presented analysis contains a convenient truth. FP funding has a substantial effect on structuring the European Research Area (ERA), particularly by promoting international scientific collaboration networks which are still relatively uncommon in comparison to national collaboration networks. This suggests that participation in the FPs indeed reduces fragmentation of research activities across Europe.

In doing so, the FPs do not compromise the cohesion objective of the European Union. Our findings suggest that FP funding is rather equally distributed across regions given their past scientific performance and that the impact of funding on subsequent publication output is highest for peripheral regions. The results suggest that FPs turn out to be more effective in establishing ties between poorly connected regions than in further strengthening existing ties between core regions. When doing the latter, FP funding is likely to substitute for other funding sources, which decreases the intended 'behavioural additionality' the FP projects aim to provide, since the impact of FP funding is the lowest for core regions.

Putting these findings into historical perspective, whereas in FP3 and FP4 the lagging regions acquired disproportionate funding relative to their R&D capacities (Sharp 1998), we showed that in FP6 this relative favourable treatment has ended. One can interpret this as a move of the FPs towards scientific excellence over the successive funding rounds. However, a more skeptical reading of our research findings holds that the excellence objective of the European Commission is still more rhetorical than practical in nature. This rhetoric may legitimise the RTD policies of the European Commission among the national governments of the scientific powerhouses in Europe (e.g. Germany, United Kingdom, France, The Netherlands). Yet, we found that researchers located in these countries do not rely disproportional on FP funding and seem to substitute acquired funding for alternative funding sources, possibly including those of national governments and industry. This implies that if the European

Commission indeed wants to take the policy rationale of excellence serious there is a need for a further adjustment of the FPs towards excellence funding. Specific measures in this direction include increasing the attractiveness of grants for more productive scientists engaged in cutting-edge research, decreasing the size, paperwork and inflexibility of the FP projects, and a focus away from applied research towards projects aimed at enhancing fundamental understanding (see Arnold et al. 2009).

Alternatively, the EC can reallocate funding from the FPs to the recently established European Research Council (ERC). Given its explicit focus on excellence funding and fundamental research, it might be expected that the ERC will be more effective in selecting excellent proposals and funding internationally competitive science. Such reallocation may also facilitate the development of a clearer vision on the potential contribution of the FPs to the cohesion objective. In contrast to the evidence that cohesion policy has had little influence on the economic development of Europe's peripheral regions (see Farole et al. 2011), our investigation of the FPs presented here suggests that there are visible and positive effects of the FPs on peripheral regions. If one considers these collaboration networks effective conduits for knowledge transmission and training, peripheral regions can gain from FP funding, especially when this funding is in line with the industrial R&D specialisations of these regions (see Foray et al. 2009). However, in this case research funding needs to become more systematic as it takes long periods to build up sustainable channels of high-quality and effective research collaboration.

Admittedly, our study provides a partial window on the state and dynamics of the European Research Area. We limited ourselves in this study to sub-national regions, whereas mechanisms of FP participation merit further study at a micro level (see Autant-Bernard et al. 2007). In addition, our research design does not allow for studying the dynamics of entire research consortia and we only focused on dyads instead of entire project networks (see Maggioni and Uberti 2011). Finally, our main indicator of collaboration being co-authored research publications between organisations is biased towards impact in the scientific domain. Our conclusions therefore hold especially for science and science-based technologies, and should be interpreted with caution when extrapolating our results to other contexts.

APPENDIX C

In model 1 we are interested to investigate how the acquisition of FP funding is affected by existing scientific collaboration networks. We model a stochastic dependent variable Y_{ij} that is realised by the inter-regional FP participation y_{ij} between two regions i and j (i, j = 1, ..., n). Since we deal with observations between discrete spatial units we adopt a spatial interaction modeling perspective that employs three types of functions explaining the variation of inter-regional interaction: (i) the origin function O_i which characterises the origin i of interaction, (ii) the destination function D_j which describes the destination j of interaction, and (iii) the separation function S_{ij} which measures the spatial separation or distance between an origin region i and a destination region j. Due to the true integer, non-negative nature of our dependent variable, we adopt a Poisson spatial interaction model (see, for instance, Scherngell and Barber 2009 for further details). Our empirical model to be estimated is given by

$$f(Y_{ij} \mid y_{ij}) = V_{ij}^{y_{ij}} \exp(-V_{ij}) \big/ y_{ij}! \qquad i, j = 1, \ldots, n \qquad \text{(C.1)}$$

with

$$V_{ij} = O_i D_j S_{ij} + \varepsilon_{ij} \qquad i, j = 1, \ldots, n \qquad \text{(C.2)}$$

and

$$O_i = o_i^{\alpha_1} \qquad i, j = 1, \ldots, n \qquad \text{(C.3)}$$

$$D_j = d_j^{\alpha_2} \qquad i, j = 1, \ldots, n \qquad \text{(C.4)}$$

$$S_{ij} = \exp\left[\sum_{k=1}^{K} \beta_k \, s_{ij}^{(k)}\right] \qquad i, j = 1, \ldots, n \qquad \text{(C.5)}$$

where o_i and d_j denote some appropriate origin and destination variables, respectively, and $S_{ij}^{(k)}$ are k = 1, ..., K separation measures. ε_{ij} with $E[\varepsilon_{ij} \mid y_{ij}] = 0$ is a random term that varies across all (i, j)-region pairs, α_1, α_2 and β_k are parameters to be estimated, and can be interpreted as elasticities of y_{ij} with respect to the origin variable o_i, the destination variable d_j and the separation variables $S_{ij}^{(k)}$.

Parameter estimation is achieved via Maximum Likelihood estimation procedures (see Long and Freese 2001).[49]

In our study, o_i and d_j are measured in terms of the total number of FP participation of region *i* and region *j*, respectively. With respect to our research question, our separation variable of central interest $s_{ij}^{(1)}$ is the number of co-publications between region *i* and region *j*. Further, we add some control variables: $s_{ij}^{(2)}$ accounts for effects of previous FP participation as measured by the number of times the (*i*, *j*)-region pair previously participated in thematically related FP5 projects, while $s_{ij}^{(3)}$ is the number of times the (*i*, *j*)-region pair previously participated in thematically unrelated FP5 projects. $s_{ij}^{(4)}$ denotes the geographical distance between two regions *i* and *j* as measured in terms of the great circle distance, while $s_{ij}^{(5)}$ controls for language area effects and takes a value of zero if two regions *i* and *j* are located in the same language area, and one otherwise. All variables, except dummies, are log normalised.

[49] Note that the Poisson model assumes equidispersion, that is: $V_{ij} = Var[\, y_{ij} \mid O_i, Di, S_i \,] = E[y_{ij} \mid O_i, Di, S_i]$. We check whether this assumption is correct by allowing for overdispersion using a Negative Binomal specification (see Long and Freese 2001). However, the respective dispersion parameter is insignificant indicating that the standard Poisson specification as given by Equation D.1 is to be preferred.

APPENDIX D

In model 2 we seek to estimate the effect of various exogenous factors on the co-publication activity between two regions i and j ($i, j = 1, ..., n$) at time t ($t = 1, \ldots, T$). Again we rely on a spatial interaction modeling perspective incorporating origin and destination specific measures, and variables accounting for the separation between two regions regions i and j. In contrast to model 1, we consider the time dimension inherent in the data and employ a panel perspective.

Let us denote Y_{ijt} as a stochastic dependent variable that is realised by the observed co-publication activity y_{ijt} between region i and j in time period t. Then, our basic model is given by

$$Y_{ijt} \mid y_{ijt} = V_{ijt} + \varepsilon_{ijt} \qquad i, j = 1, ..., n; \quad t = 1, ..., T \qquad \text{(D.1)}$$

where V_{ijt} is a function that captures the stochastic relationship to other random variables sampled from a specified probability distribution dependent upon some mean, say μ_{ijt}. ε_{ijt} is a disturbance term with the property $E[\varepsilon_{ij} \mid y_{ij}] = 0$.

$$V_{ijt} = O_{it}\ D_{jt}\ S_{ijt} \qquad i, j = 1, ..., n; \quad t = 1, ..., T \qquad \text{(D.2)}$$

and

$$O_{it} = o_{it}^{\alpha_{1t}} \qquad i, j = 1, ..., n; \quad t = 1, ..., T \qquad \text{(D.3)}$$

$$D_{jt} = d_{jt}^{\alpha_{2t}} \qquad i, j = 1, ..., n; \quad t = 1, ..., T \qquad \text{(D.4)}$$

$$S_{ijt} = \exp\left[\sum_{k=1}^{K} \beta_{kt}\ s_{ijt}^{(k)}\right] \qquad i, j = 1, ..., n; \quad t = 1, ..., T \qquad \text{(D.5)}$$

where o_{it} and d_{jt} are the origin and destination variables, $S_{ij}^{(k)}$ is a multivariate measure of spatial separation that varies across all origin-destination pairs with K separation measures. α_{1t}, α_{2t} and β_{kt} ($k = 1, ..., K$) are parameters to be estimated.

As in model 1, we assume the stochastic dependent variable to follow a Poisson distribution so that

$$Y_{ijt} \mid y_{ijt} = \exp(V_{ijt} + \varepsilon_{ijt} + \gamma_{ij}) \qquad i, j = 1, ..., n; \quad t = 1, ..., T \qquad \text{(D.6)}$$

where γ_{ij} denotes the unobservable individual specific effect, also referred to as the one-way error component model (see Baltagi 2008). As the cross-sectional dimension in our case corresponds to regional pairs, γ_{ij} is the random term that is time-invariant but varies across all (*i*, *j*)-region pairs. We assume the γ_{ij} to be correlated across our time periods for the same (*i*, *j*)-region pair, i.e. we follow a random effects specification, and integrate out the random effect γ_{ij} of the joint probability $\prod_{t=1}^{T} \Pr\left(y_{ij1}, ..., y_{ijT}\right)$ by obtaining:

$$\Pr\left(y_{ij1}, ..., y_{ijT}\right) = \int \Pr\left(y_{ij1}, ..., y_{ijT}, \ \gamma_{ij}\right) d\gamma_{ij} = \int \Pr\left(y_{ij1}, ..., y_{ijT} \mid \gamma_{ij}\right) g(\gamma_{ij}) d\gamma_{ij}. \quad \text{(D.7)}$$

As shown, for instance, by Baltagi (2008), this is the same approach used in models for event counts to condition the heterogeneity out of the Poisson model to produce the Negative Binomial model. As given by Equation D.6 we take $\Pr(\gamma_{ijt} \mid \gamma_{ij})$ to be Poisson with mean $\mu_{ijt} = \exp(V_{ijt} + \varepsilon_{ijt} + \gamma_{ij})$ and $\exp(\gamma_{ij})$ is distributed Gamma; then our *random effects negative binomial model* to be estimated is given by:

$$\Pr\left(y_{ij1}, ..., y_{ijT}\right) = \frac{\left(\prod_{t=1}^{T} \mu_{ijt}^{\ y_{ijt}}\right) \Gamma\left(\theta + \sum_{t=1}^{T} y_{ijt}\right)}{\left(\Gamma(\theta) \prod_{t=1}^{T} y_{ijt}!\right)\left[\left(\sum_{t=1}^{T} \mu_{ijt}\right)^{\sum_{t=1}^{T} y_{ijt}}\right]} Q_i \left(1 - Q_i\right)^{\sum_{t=1}^{T} y_{ijt}} \quad \text{(D.8)}$$

with

$$Q_i = \frac{\theta}{\theta + \sum_{t=1}^{T} \mu_{ijt}} \quad \text{(D.9)}$$

where $\Gamma(.)$ denotes the Gamma distribution and θ its variance. Parameter estimation is achieved via Maximum Likelihood estimation procedures (see Cameron and Trivedi 1998).

In this model o_{it} and d_{jt} are measured in terms of the total number of publications of region *i* and region *j* in time period *t*, respectively. In our separation function we include three separation variables that are of central interest in the context of our research question: $s_{ijt}^{(1)}$ is the previous number of joint projects between region *i* and region *j* at time *t*, $s_{ijt}^{(2)}$ is the number of previous joint publications between region *i* and region *j* at time *t*, $s_{ijt}^{(3)}$ is the interaction term between $s_{ijt}^{(1)}$

and $s_{ijt}^{(2)}$. Then we add some control variables, that are $s_{ijt}^{(4)}$ denoting the geographical distance between two regions i and j in time period t as measured in terms of the great circle distance, and $s_{ijt}^{(5)}$ controlling for language area effects taking a value of zero if two regions i and j in time period t are located in the same language area, and one otherwise. Main effects and interaction terms are centered on their mean value and all variables, except dummies, are log-normalised.

5

The geographical constitution of leadership in globalised clinical trials

5.1 Introduction

Collaboration and globalisation are defining characteristics of contemporary scientific knowledge production, with the randomised clinical trial being a textbook-like example. The conduct of clinical trials necessitates the collaborative involvement of many researchers with roles ranging from designing protocols and enrolling human subjects for data collection to analysing data and preparing manuscripts for publication (Flanagin et al. 2002). Standardisation and harmonisation of these research practices - as envisaged in the ICH-GCP guideline – has made the travelling of clinical data between geographically dispersed research sites less complicated (Petryna 2009). This has facilitated the emergence of 'global' clinical trials with increasing involvement of researchers from nontraditional research locations, especially in Central and Eastern Europe, Latin America and Asia (Karlberg 2008; Thiers et al. 2008).

However, as clinical trials become ever more global, worries have been voiced over the division of roles and responsibilities in those projects. Critics argue that global clinical trials are primarily conducted for the benefit of a small group of leading scientists and companies located in the major pharmaceutical markets. Investigators from nontraditional research locations are only hired in these projects to bring in their patients as 'experimental subjects', without having significant roles in defining research questions, analysing the data or drafting manuscripts for publications (Petryna 2009; Glickmann et al. 2009).

These concerns might be particularly warranted in large scale multi-center clinical trials that require the appointment of trial management and evaluation teams such as Executive Committees, Steering Committees, Data Safety

Monitoring Boards and Outcome Adjudication Committees. These bodies take overall responsibility for the integrity of the study and the knowledge production process and they also have the authority to construct knowledge claims for publications.

The constitution of these management teams often takes place in consultation between the sponsor and the first appointed principal investigator. Membership can in principle be completely decoupled from more operational tasks executed at clinical sites. Scientific leadership might therefore be driven by other considerations than providing an actual reflection of the clinical knowledge that is available 'on the ground'. High quality clinical trials necessitate the involvement of researchers who have knowledge about the patient characteristics and about geographical specificities that may drive clinical trial design, drug response and study endpoints. Such differences are for instance found in the research questions that are relevant in particular locations, the efficacy and safety of a drug (different dose response relations and side-effect profiles) and the societal environment that affects the behavior of patients and doctors. In order to enhance the scientific and ethical integrity of clinical trials, trial management should thus reflect the geographical diversity of the studied patient populations.

Since there is however no data available on the interaction between participation in trials and appointment in trial management, we set out to quantify the extent of this phenomenon by conducting a bibliometric analysis. In doing so we focus on the extent to which authors on the primary publication – as an indicator of leadership - are located in the countries where clinical researchers are involved with human subjects at clinical sites.

5.2 METHODS

DATA COLLECTION

Our cohort of articles encompasses original research on clinical trials that can be linked to protocols registered at www.clinicaltrials.gov. To establish the link between protocols and publications, we searched MEDLINE via PUBMED to find all publications that list a national clinical trial identifier (NCTID) in the title, abstract or as a secondary source ID. In order to obtain a sample that only contains original clinical trial research, the publication search was limited by study type ("*clinical trial*" and "*human*") and excluded publications with the following study types or MeSH terms: "*editorials*", "*letters*", "*in vitro*", "*animal*",

"*review*", "*meta-analysis*". We also excluded publications if they made reference to more than one clinical trial identifier.

The publication sample was matched with information from the protocols, after retrieving and parsing the entire XML version of www.clinicaltrials.gov in January 2011. We only included completed or terminated trials that set out to test either a drug or a biological. In addition, we only focused on trials that had either a start date after June, 2005 or a completion date after September, 2005, after which trial registration was mandated by the International Committee of Medical Journal Editors before onset (De Angelis et al. 2004).

As our prime interest was in the sponsors and clinical research sites that are involved in the conduct of the clinical trials, we focused on the data listed in the lead sponsor field and in the study location field. Because information in the study location field was not always accurately reported, we had to exclude 391 protocols. The final search linked 1,450 protocols to 1,687 publications (Figure 5.1).

143 of the 1,450 protocols were referenced in at least two clinical trial publications. As we were interested in the primary publication following clinical trial conduct, we retrieved the citation impact scores of all publications from Scopus Elsevier and determined for each protocol which publication received the highest number of citations. We assumed here that the publication that received the highest number of citations could be considered the primary outcome publication. In case two publications received an equal amount of citations, we took the earliest publication. In addition, we removed an additional 5 publications and registrations because they listed only a group-authorship in the byline of the article.

For all 1,445 protocols, we extracted the information in the lead sponsor field and in the study location fields of www.clinicaltrials.gov. Using this information we listed the name of the organisation that is the lead sponsor of the clinical trial (n=1,445 lead sponsors) and all countries that are mentioned in the study location field for each protocol, after removing duplicate occurrences of a country on a protocol (n=4,908 countries).

For the 1,445 publications, all author names were extracted from both PUBMED and Scopus Elsevier and the number of authors listed on each publication was compared. In 82 publications there was disagreement between PUBMED and Scopus Elsevier on the number of authors. This disagreement was resolved by manually checking the full-text of the article.

We subsequently retrieved the organisation and country of origin of all authors that are listed on the publications. We downloaded this information from Scopus Elsevier, which systematically keeps track of address information of authors. For 226 publications organisation or address information of at least one of the authors was missing. In these cases we retrieved the data from the full-text of the article. We were successful in doing this for all but four authors. After retrieving address information, we listed the name, organisation and country of all authors per publication (n=14,303 author-addresses).

Matching procedure

Protocols and publications were combined in 1,445 protocol-publication pairs. For all protocol-publication pairs we determined whether the study location countries were mentioned on the publications, by matching the country information in the author-addresses with the table that listed enrollment countries. In doing so, we obtained a new table that depicted for every enrollment country in a trial (n=4,908) whether an author from that enrollment country was listed on a subsequent publication.

We also manually determined whether the organisation name of the lead sponsor was mentioned as an author-address on the publication. In doing so, we made a match between the name of the organisation on the protocol and the names of the organisations on the publication. Next to exact name matches we also included the relevant sub-organisations of all organisations. These relevant sub-organisations included hospitals with exactly the same name as the university (and vice versa) and alternative spellings and names of the same organisation.

Robustness Checks

To ensure that our data is of high quality we conducted three manual checks on the 180 publications in our sample that were published in the Journal of the American Medical Association or in the New England Journal of Medicine. We first assessed which data of the conducted clinical trial was described in the publication after reading the protocol, the abstracts and if necessary the full text of the publications. Of the 180 publications, all but one publication reported on the primary endpoint of the clinical trial. The single non primary outcome publication described the result of a secondary endpoint.

We subsequently tested our assumption that authorships on primary outcome publications are granted to members of trial management teams. Of 180

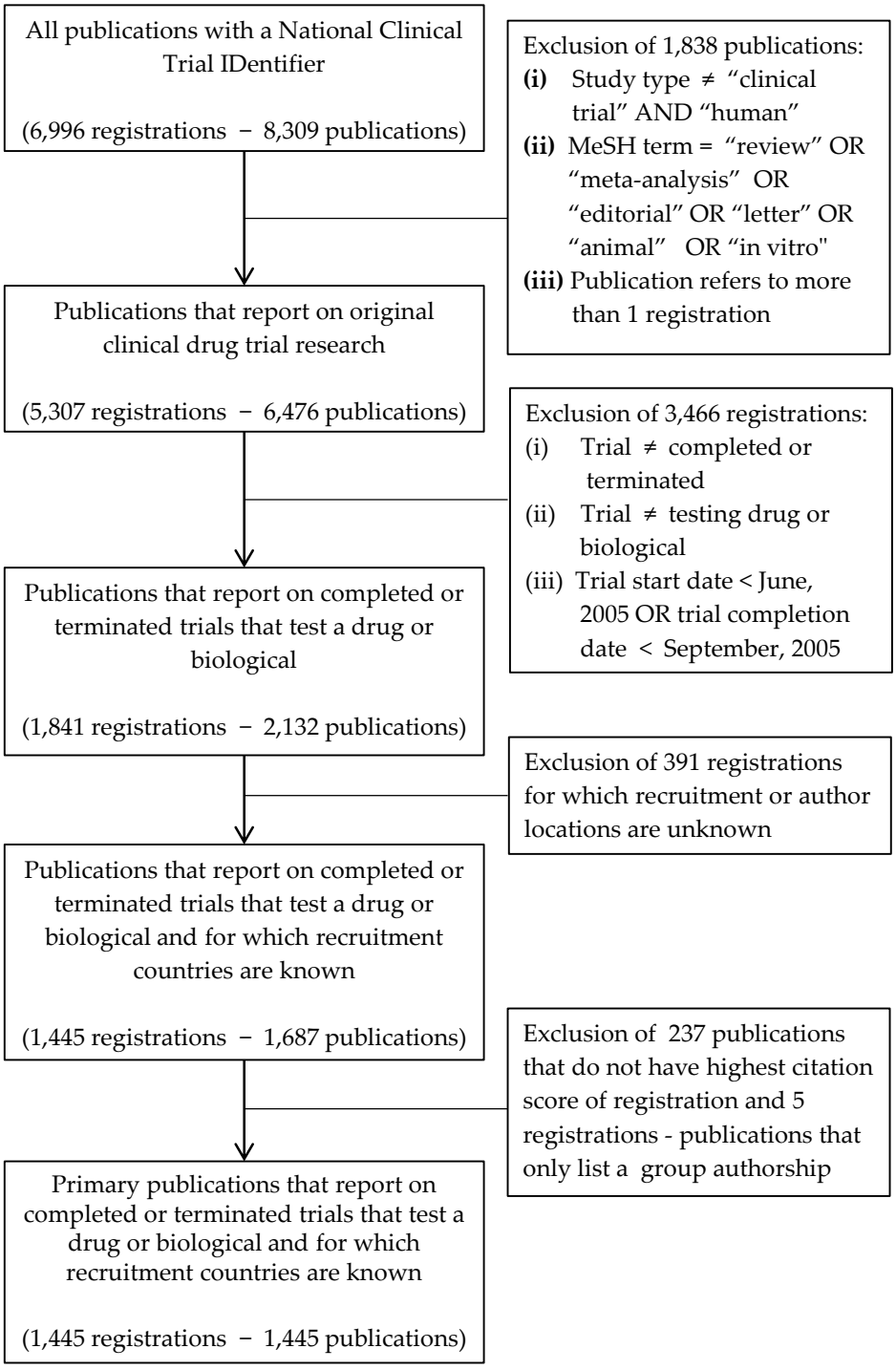

Figure 5.1: *Inclusion flow-chart of sample*

Table 5.1: *Number of authors and publication rates of sponsors and countries*

	Total	1	2	3	*p*-value
Number of Protocol-Publications	1445	650	130	665	-
Number of authors	14298	6367	1509	6422	
Mean	9.89	9.8	11.61	9.66	< 0.001
Publication rates of countries					
Number of countries on protocol	4908	3945	156	807	
Mean	3.40	6.07	1.20	1.21	
Number of countries on publication	3285	2092	178	1015	
Mean	2.27	3.22	1.37	1.53	< 0.001
Countries on protocol and on publication	2469	1572	141	756	
% of total number of countries	50.3%	39.9%	90.4%	93.7%	< 0.001
Publication rates of sponsors					
Publications that list sponsor	1161	543	52	566	
% of total number of publications	80.1%	83.2%	40.0%	84.9%	< 0.001
Sponsor related authors on publications[a]	5099	1717	187	3195	
Mean	4.39	3.16	3.6	5.64	< 0.001

Notes. 1 = industry funding; 2 = government funding; 3 = other not-for-profit funding.

p-values are reported for one-way anova tests or pearson chi-square tests.

[a] Reported mean value only for those publications that list a sponsor related author

publications, 66 publications provided the names of the management team members who were installed in an executive committee or steering committee. 76.7% of all authors were members of a trial management team or were affiliated with the sponsor. This percentage was 82.9% when only focusing on industry funded publications.

Third, we checked the quality of the study location data by comparing them with the provided information on enrollment countries in the acknowledgement sections of publications. Of the 1347 countries in which patient enrollment took place according to www.clinicaltrials.gov, we only found 26 study locations (1.9%) that were not mentioned in the trial publication.

Analysis

Our main analytical question was whether sponsors and researchers from enrollment countries became authors on subsequent publications as an indicator of clinical trial management team membership. We therefore first conducted an

analysis of the overall rates to which study locations are represented on publications, broken down by sponsor type. Secondly, we analysed country distributions of publication rates, which are defined as the proportion of enrollment efforts that result in a publication. Obviously, the maximum publication rate is 100 percent, which would indicate that every time a patient from a particular country is recruited in a clinical trial, the country also is represented by an author on a publication. Thirdly and for reasons explained below, we focused specifically on industry funded trials and assessed publication rates per country after excluding industry sponsor related authors from the author-addresses on publications.

5.3 Results

Publication rates by funding type

The 1,445 protocol-publication pairs listed 4,908 countries in the study location field. 2,469 (50.3%) of these enrollment countries also appeared with an author-address on a subsequent publication (Table 5.1). This means that almost 50 percent of all study location countries were not represented by authors on a subsequent publication. The extent to which patient enrollment resulted in subsequent authorship on publications was significantly different between funding sources ($p<0.001$). For government and not-for-profit funded clinical trials, enrollment countries were well represented with publication rates that surpassed 90 percent. In contrast, representation of enrollment countries for industry funded trials was 37.8 percent. Differences between funding sources were also statistically significant when focusing on a subset of 'smaller' clinical trials that recruited in less than five countries ($p<0.001$, not shown).

Turning to the presence of sponsors on subsequent publications, in more than 80 percent of all publications the sponsor became an author on a subsequent publication (Table 5.1). This percentage was particular high for industry funded clinical trials (83.2%) and other not-for-profit funded clinical trials (84.9%), in comparison to government funded clinical trials (40.0%). Other not-for-profit organisations listed on average most sponsor related authors on their funded publications (average=5.7), whereas the averages were similar for industry funded (average=3.2) and government funded clinical trials (average=3.6).

Figure 5.2: *Publication rates per country for all country-protocols (n=4,908)*

Country distributions

The extent to which patient enrollment resulted in subsequent authorship on publications was unevenly distributed between countries (Figure 5.2). As low publication rates predominantly occurred in industry funded research we report country-specific results for this subset of protocol-publication pairs in Table 5.2. The United States had by far the highest publication rate (98.3%) followed by Japan (72.0%), Germany (68.0%) and United Kingdom (64.8%). Although enrollment activities are nowadays substantial in nontraditional research locations (Thiers et al. 2008), these countries showed relatively low publication rates judged from for instance the publication rates of Poland (27.3%), Mexico (14.1%), Czech Republic (23.3%) and Argentina (24.1%).

A reason behind the high publication rates of traditional research locations might be that pharmaceutical companies are more often located in those countries. This might have biased our results towards countries that host many pharmaceutical companies, because those companies were also often represented as authors on

Table 5.2: *Publication rates for industry-funded trials per country, including and excluding sponsors*

Country	Number of protocols	Publication rates		Difference
		Including sponsor	Excluding sponsor	
United States	399	98.2%	92.7%	-5.5%
Germany	194	68.0%	66.0%	-2.1%
Canada	171	59.6%	58.5%	-1.2%
France	165	57.6%	56.4%	-1.2%
Spain	146	39.0%	39.0%	0.0%
United Kingdom	142	64.8%	60.6%	-4.2%
Italy	127	42.5%	41.7%	-0.8%
Belgium	119	36.1%	34.5%	-1.7%
Netherlands	115	40.9%	40.0%	-0.9%
Australia	110	36.4%	35.5%	-0.9%
Poland	110	27.3%	27.3%	0.0%
Sweden	97	41.2%	37.1%	-4.1%
Mexico	92	14.1%	14.1%	0.0%
Denmark	91	47.3%	42.9%	-4.4%
Czech Republic	90	23.3%	23.3%	0.0%
Argentina	87	24.1%	24.1%	0.0%
Russia	85	22.4%	22.4%	0.0%
Brazil	84	28.6%	28.6%	0.0%
South Africa	80	22.5%	22.5%	0.0%
Hungary	71	15.5%	15.5%	0.0%
Austria	69	20.3%	20.3%	0.0%
Finland	69	23.2%	23.2%	0.0%
Switzerland	69	36.2%	26.1%	-10.1%
Norway	65	16.9%	16.9%	0.0%
Greece	58	12.1%	12.1%	0.0%
China	57	47.4%	47.4%	0.0%
South Korea	54	24.1%	24.1%	0.0%
India	53	30.2%	30.2%	0.0%
Israel	49	16.3%	16.3%	0.0%
Romania	49	16.3%	16.3%	0.0%
Taiwan	47	27.7%	27.7%	0.0%
Puerto Rico	46	17.4%	17.4%	0.0%
Portugal	45	11.1%	11.1%	0.0%
Turkey	43	18.6%	18.6%	0.0%
Slovakia	42	14.3%	14.3%	0.0%
Chile	40	2.5%	2.5%	0.0%

publications. We therefore controlled for this in the second set of columns in Table 5.2, where we assessed whether a researcher from an enrollment country became author, after removing all sponsor-related authors from the publications. Indeed, this rendered a decrease in the overall publication rates of countries, which was particularly pronounced for the United States, United Kingdom, Germany, Sweden, Denmark and Switzerland. Hence, those countries relatively often only listed sponsor related author-addresses on publications. However, despite a decrease in publication rates the general observation remained the same. Publication rates of traditional research locations and of countries with many pharmaceutical companies had very high publication rates in comparison to nontraditional research locations.

5.4 Discussion

This study showed that although clinical trial activities are now executed across the globe, scientific leadership in these trials is disproportionally concentrated in traditional research locations. This spatial decoupling of patient enrollment and clinical trial management is most pronounced in industry funded research. Although we did not empirically investigate its reasons, we provide three explanations and their implications below.

First, the constitution of trial management teams is determined by the social structure in which the activities of sponsors and principal investigators are embedded (Granovetter 1985). Collaborations with researchers who hold central positions in scientific networks are likely to boost the quality, credibility and dissemination of clinical trial results. It follows that researchers with well-established reputations and affiliations to renowned medical institutes are more likely to become part of management teams than clinical investigators from nontraditional research locations. Over time, these social network structures will be strengthened by the development of trust based relations that facilitate repetition of existing social ties (Rivera et al. 2010). Given these social network dynamics, the observed geography of scientific leadership becomes performative, as the key roles of researchers in traditional research locations are 'confirmed' over and over again at the expense of the roles of researchers in nontraditional research locations.

Second, the structure of clinical trial management might be driven by the efficiency of coordination among team members. Despite recent advances in information and communication technologies, face-to-face interaction remains important to carry out the complex tasks associated with scientific research

(Collins 1985; Olsen and Olsen 2000). In selecting clinical trial leaders, pharmaceutical companies might thus have a preference for researchers that are located in close geographical vicinity as proximity facilitates the arrangement of face-to-face meetings and decreases coordination costs.

Third, from an organisational perspective relations between clinical investigators in nontraditional research locations and clinical trial management teams might be mediated by a Contract Research Organisation (CRO). Pharmaceutical companies increasingly outsource the operational aspects of clinical trials to CROs who negotiate contracts with clinical sites and monitor data production (Azoulay 2004; Fisher 2009). The use of CROs creates a relatively distant relation between the management team that initiates and designs the trial and the clinical investigators at study sites. Hence, in outsourced clinical trials the role of clinical investigators in other tasks than patient enrollment is frequently modest.

All three arguments point towards distant connections between the researchers that enroll patients and those who produce clinical knowledge for publications. This has implications for the integrity of individual clinical trials and the clinical research enterprise as a whole. With regard to the integrity of individual clinical trials an important implication concerns the increased diversity of patients and their habits in global clinical trials. It is well known that responses to treatment differs considerably between patients according to local diets, drug adherence, body sizes, genetic makeup and the local health care delivery system (Petryna 2009; Glickmann et al. 2009). Proper interpretation of data therefore necessitates close interactions between those researchers that are in immediate contact with patients and researchers that design trials and interpret clinical trial results. The transfer of context specific knowledge may therefore be best served by increased leadership for researchers from nontraditional research locations. They can create awareness about local specificities and will stimulate debate about the extent to which the findings of clinical trials are generalisable to varying populations across the globe.

Another implication relates to the quality of data that follows from globalised clinical trial conduct. Although it is difficult to make definitive statements here, physicians and researchers from nontraditional countries are often trained in different contexts and are generally less experienced in conducting clinical trials. In addition, they may have a lower incentive to be accurate in data collection when they are not involved in the final knowledge production process or when they do not have access to the data they collected (Davidoff et al. 2001; Gøtzche et al. 2006; Abbas 2007). Rigorous training of local researchers and increased engagement at leadership level can improve data quality because researchers are

made accountable for the final scientific evidence that is produced. Indeed these measures should be taken in addition to strict independent monitoring and regulatory oversight of clinical sites, which is under increasing pressure as indicated by the observation that the FDA inspected only 0.7% of all foreign clinical trial sites in 2008 (Office of the Inspector General 2010).

Equal inclusion of researchers in clinical trial management is also an important step to steer clinical trial conduct in a direction where it serves the health needs of communities across the globe. The globalisation of clinical trials has raised many ethical concerns including the provision of treatments to patients after the study has ended, obtaining informed consent from illiterate patients, the ethical standards of care that should be provided to control groups and the availability of test products on local markets. It seems in the best interest of patients that researchers from nontraditional research locations have a clear voice in these issues when clinical trials are designed, conducted and when their results are interpreted. This will raise more awareness of the promises and pitfalls of realising inclusive evidence-based medicine that is to the benefit of patients and researchers across the globe.

6

Persistence bias in the publication of evidence by pharmaceutical companies

6.1 Introduction

The changing relation between science and the marketplace has raised new questions about the nature of knowledge production (Gibbons et al. 1994; Nelson 2004; Shapin 2008). Although firms are active producers of scientific knowledge, they do not necessarily conform to the norms held by the academic community (Dasgupta and David 1994; Vallas and Kleinman 2008). Numerous scholars have therefore expressed concerns over strategic publication behavior of firms in which they disclose research findings that support their market strategies and suppress negative findings (Lexchin et al. 2003; Sismondo 2008). This behavior seems above all significant in close-to-the-market settings where appropriation of the underlying technology has already taken place and scientific signals are primarily intended to inform regulators and to support the diffusion of the new technology.

Biomedicine is a prime example in this context. Historically, this is one of the fields where the role of industry in the production and publication of scientific research has been extensive (Swann 1988; Furman and MacGarvie 2007). Despite this established position, the academic community and the public have raised concerns over the scientific integrity of research conducted by pharmaceutical companies (see, for instance, Angell 2004; Smith 2006). This situation can be best understood by making reference to the hegemonic status of evidence-based medicine which is an attempt to directly ground clinical decision making in the available scientific evidence on medical therapies (Timmermans and Berg 2003). An important condition for the functioning of this system is that firms produce evidence by conducting clinical trials on the safety and efficacy of their

innovations and that they disclose this evidence as to inform regulators and practitioners. However, for a long time firms have been forced to contribute to evidence making (in order to gain market approval for their innovations), but not to evidence disclosure *per se*. This has provided them with the opportunity to conceal the outcomes of research that failed to detect a hypothesised effect because the dissemination of such evidence can hamper the successful introduction of a new drug on the market. This phenomenon is known as publication bias and holds that scientific publication takes place based on the direction or strength of the observed effects of a study (Rosenthal 1979; Dickersin 1990, Lexchin et al. 2003; Bekelman et al. 2003; Dwan et al. 2008).[50]

To remedy the situation the Food and Drug Administration (FDA 2007) and the International Committee of Medical Journal Editors (De Angelis et al. 2004) have recently mandated both registration of clinical research in a public database before study onset and publication of research results after study completion. These institutional reforms provide us with a unique opportunity to unravel the publication decision of firms by studying their considerations to disclose their research findings either in scientific publications or in web-based repositories. We will argue that the decision to submit research results to scientific journals rather than publishing these results on the web remains a strategic choice because scientific articles, unlike web reports, provide certification by experts that the research is scientifically sound, methodologically rigorous and thus credible (Merton and Zuckerman 1973; Crane 1976). Our results suggest that even under conditions of complete information disclosure, firms still have an interest to carefully construct and mobilise scientific publications resulting in a persistent bias in the scientific publication of evidence.

We make our contribution in the context of research on diabetes mellitus which is one of the fastest growing diseases in the world. At a global scale the number of adult diabetics has doubled within the past three decades and one in four US adults now suffers from diabetes (Daneai et al. 2011). The promising market prospects have attracted large investments from pharmaceutical companies and many insulins and compounds are currently in the development stage. In this study, we focus on a very homogenous group of research projects that all test

[50] Recent examples are controversies surrounding the diabetes drug Avandia (Bloomgarden 2007), the nonsteroidal anti-inflammatory drug Vioxx (Horton 2004) and SSRI anti-depressants agents (Turner et al. 2008). Note also that the phenomenon of study publication bias is not restricted to medicine and has also been detected in other fields including animal experiments (Sena et al. 2010), ecology (Murtaugh 2002), sociology (Gerber and Mahotra 2008) and economics (Stanley 2005).

whether the experimental therapy is effective in controlling blood glucose values, which is the prime marker for all current diabetes research (Tattersall 2009). This implies that the clinical trials in our sample all answer the same research question and only differ in terms of research design (e.g. control group, size), the therapy being tested, project organisation and the results of the study. The homogeneity of our sample allows us to address many issues that are considered important in evidence-based medicine, including definitions of scientific quality and clinical relevance.

The remainder of this paper is organised as follows. In section 2 we provide a theoretical framework to understand the decision of firms to publish their results in scientific journals against the background of evidence-based medicine. Section 3 introduces the data and methods. We then proceed in section 4 with the empirical analysis which consists of a comparison between publication practices in industry funded research and publicly funded research, followed by the main analysis in which we explain the decision of industry to publish in scientific journals as compared to web-based repositories. Section 5 concludes.

6.2 Theory Development

In the contemporary context of corporate drug testing, firms are mandated to publish the evidence that results from the conduct of clinical trials. In doing so, they now face the choice of publishing clinical trial evidence either in scientific literature or in web-based repositories. Publication of evidence in scientific journals fulfils a specific function in this context. Both the specific 'inscription practices' used in scientific publications and critical peer-evaluation of the outcomes before, during, and after publication contribute to the establishment of credibility in the truth value of the results (Collins 1985; Latour 1987; Shapin 1995b). Scientific publications are subject to review by peers who certify that the conducted evidence has been obtained by methods that are scientifically sound (Merton and Zuckerman 1973; Crane 1976). Reviewers and overseeing editors also make sure that clinical trial results are reported in a standardised way and that all relevant information to interpret the results and replicate the study design becomes available. Peer-review thus facilitates both consistent interpretation of clinical trial evidence by readers and readily made comparison of treatment effects of different therapies communicated in different publications (Polidoro and Theeke 2011).

Web-reports do as of yet not have these components and it is also not likely that they will become more authoritative sources in the near future. The published

data in web-reports is not reported in standardised formats *per se* and there is no quality control on the evidence. Although penalties for non-compliance to mandatory disclosure are high (up to $10,000 per day), it is unlikely that strict quality control of the content will be performed in the near future as this would be time-consuming and therefore too costly (Wager 2008). The absence of independent scrutiny and peer review implies that quality-control is only ensured by firms themselves which is likely to hinder the construction of credibility in the results of web-reports, as compared to scientific publications.[51]

Given the differences between scientific publications and web-reports, we expect the persistence of bias in publication practices where firms continue to strategically certify research findings in scientific literature following their commercial interests. Firms consider scientific publications not merely as objects that signal information, but as devices that need to be carefully constructed and mobilised to anticipate on impact on practitioners and regulators (Gøtzche, et al. 2007; Sismondo 2009). In the search for impact, firms need to conform to the epistemologies of the academic community and its associated norms (DiMaggio and Powell 1983). In case of clinical trial research these norms are defined within the context of evidence-based medicine. Our main argument thus holds that firms make scientific publishing simultaneously dependent upon their commercial interests and the quality standards defined within evidence-based medicine.

The rise of evidence-based medicine can be best understood against the background of the increased use of randomised clinical trials as a means to legitimate medical treatments on the market. Strict regulatory oversight of corporate drug testing became mandated in the sixties but its use for producing evidence did not eradicate geographical variations in medical practice. Over the years, new treatment options also emerged and this rendered medical decision making increasingly complex for practitioners (Timmermans and Berg 2003; Elstein 2004). Proponents of evidence-based medicine provided a solution by de-emphasising *"intuition, un-systematic clinical experience and pathophysiologic rationale as sufficient grounds for clinical decision making"* (Evidence Based Working Group 1992, p. 2420) and advocating instead "*the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual*

[51] Now web-reporting is becoming a standard practice, more practical questions are also warranted including how to cite this evidence in scientific literature and how and when to acknowledge study teams and writing groups for their contributions (see Wager 2006).

patients" (Sacket et al.1996 p. 71). Following this definition, evidence-based medicine is an attempt to strengthen the link between scientific research and clinical decision making, by explicitly formulating standards on what is considered best evidence (Timmermans and Berg 2003).[52] Firms consider these standards when pursuing scientific publication of their studies, because this is a necessary condition for having impact. Two elements that shape definitions of 'best evidence' are of particular importance in this respect.

First, the idea of best evidence has become closely related to the design characteristics of research. Evidence-based medicine relies on hierarchical grading systems of research quality and results derived from randomised clinical trials are consistently ranked on top of this hierarchy (Atkins et al. 2004; Glasziou et al. 2008). The assumption underlying hierarchical quality ratings is that the evidence obtained from medical studies provides regulators and practitioners with varying degrees of certainty about the true effects of medical treatments (see Montori and Guyatt 2008). Quality ratings standardise this certainty by providing a probability that the estimates of a treatment effect will be falsified or adjusted in future studies (Balshem et al. 2011). The uncertainty about possible changes in effect estimates is reduced when studies with superior research designs are performed as these studies are more likely to approximate the unknown true effect of a treatment. [53] Due to this expression of mechanical objectivity (Porter 1995), it is rather the research design that is important for the quality of the study than the outcome of the study as such. In its most apparent form this has led to a situation where prestigious journals issue a provisional commitment to publish research findings purely on the base of research designs (Horton 1997; McNamee et al. 2007).

The nature of graded quality standards and its direct association with experimental designs provides firms with explicit guidance to conform to the norms of the academic community. Although the conduct of clinical trials is

[52] Indeed, evidence-based medicine has also been criticised for many reasons (see, for instance, Goldenberg 2005, Lambert 2006), including for being too positivist and empiricist (Hjorland 2011) and for its limited impact on changing physicians actual decisions (Timmermans and Berg 2003; Armstrong and Ogden 2006; Greenhalgh et al. 2008).

[53] This view on uncertainty cannot deal with unknown unknowns which are bound to be present in a knowledge activity where the full spectrum of a treatments' effect is inherently uncertain (Knight 1921). However, it is believed that large enough clinical trials will eventually signal such effects after which regulatory agencies mandate additional studies or gather advisory committees to assess its relevance.

costly[54], investments in high-quality research designs are instrumental in mitigating the risks of critical peer evaluation by academic experts both before, during and after publication. The possibility of actual replication is very low in clinical research, yet firms are still anxious to publish knowledge of low quality standards as it is more likely that in these cases the estimates are subject to change in future studies.

One of the main factors affecting the quality of studies in this respect is the size of the clinical trials and its associated statistical power to detect treatment effects. Ideally, clinical trials should be large enough to detect reliable effects of the intervention on the primary outcome measure, and it is not uncommon that studies fail to do so simply because they are too small (Moher et al. 1994; Halpern et al. 2002). Larger studies have the benefit that - next to an analysis of the primary outcome measure - relevant secondary questions can be answered and subgroup analyses can be conducted to test whether the effects of a treatment differ between patient groups. Moreover, larger studies are more likely to detect adverse events of treatments, especially if those adverse events are rare.

In addition to sheer number of patients, size also refers to the study locations where the clinical trial is conducted. It can be expected that the effects of an intervention will differ between population groups with varying genetic and cultural backgrounds. Clinical trials that are conducted in many countries can factor out these 'contaminating' effects by controlling for differences between study locations. Hence, the authority of clinical trial results tends to increase when clinical trials are conducted in multiple countries.

A second element that is key to the idea of 'best evidence' in evidence-based medicine relates to the clinical relevance of the research. Evidence-based medicine emphasises critical appraisal of the scientific literature by clinical decision makers in order to match available evidence with the needs and values of individual patients (Evidence-based medicine Working Group 1992). This implies that clinical trials explicitly designed to assist health care decision makers are considered to be of higher quality than clinical trials that are merely designed to understand the effectiveness of an intervention. This prioritises clinical trials that resemble in their experimental set-up practical choices facing patients and practitioners such as head-to-head comparisons between multiple therapies and

[54] The exact costs of conducting clinical trials is an area of contestation itself with estimates ranging from $802 million at the high end (DiMasi et al. 2003) to well under $100 million at the low end (Angell 2004).

testing particular treatments against viable alternative clinical strategies (Tunis et al. 2003; Angell 2004). In contrast, comparisons between an experimental therapy and a placebo do not provide practitioners with knowledge on the trade-offs between alternative treatment options.

In sum, evidence-based medicine defines quality of evidence largely on the base of research designs and its value for clinical decision making. Clinical trials that score high on these elements are therefore more likely to have impact within evidence-based medicine. Firms anticipate on impact and devote resources to scientific publishing when the perceived quality of their clinical trials is high as expressed both in the statistical power of the project and the clinical relevance of the research design. Our first hypothesis thus holds:

HYPOTHESIS 1: *The likelihood that clinical trials conducted by pharmaceutical companies are scientifically published increases with the quality of the evidence according to evidence-based medicine standards.*

An associated outcome of the rise of evidence-based medicine is that clinical decision making on therapies and associated pharmaceutical sales have become directly dependent upon signals in the scientific literature (Azoulay 2002). The rise of evidence-based medicine has thus created an incentive for firms to carefully construct and mobilise scientific publications in order to strengthen their market position (Sismondo 2009). In contrast to publishing in basic research, this incentive is further facilitated by the fact that appropriation of the underlying technology has already taken place during corporate drug testing which makes scooping risks associated with scientific publication a relatively minor concern (Nelson 1959; Arrow 1962; Dasgupta and David 1994).

It follows that firms select clinical trial results to create a consistent drug profile in the literature (Henry 2009; Sismondo 2009). The publication bias literature has in this context confirmed over and over again that publications funded by companies are disproportionally more often favorable to the tested therapy (Bekelman et al. 2003; Lexchin et al. 2003; Dwan et al. 2008; Sismondo 2008). Importantly, this empirical result is neither driven by a lower quality of industry funded research designs which is at least perceived to be similar if not higher (Djulbegovic et al. 1999; Clifford et al. 2002) nor by higher rejection rates of either industry funded trials or trials with negative results (Olson et al. 2002; Lee et al. 2006).

Even experiments with therapies that are ultimately assessed as being safe and efficacious can render negative results due to incorrect clinical trial design or

simply by chance. Negative findings may interfere with the approval process and are less likely to result in scientific and clinical impact because these results cast doubt on the efficacy and safety of the experimental therapy and may contradict other findings that are already published. Thus, research that fails to detect a hypothesised effect of a firms' technology can seriously lower the chances of commercial success of the drug. Hence, firms are expected to publish these results in a web report rather than submit it to scientific journals, despite the fact that the research design is sophisticated enough to warrant publication. Our second hypothesis holds:

HYPOTHESIS 2: *The likelihood that clinical trials conducted by pharmaceutical companies are scientifically published increases when the evidence is favourable to the compound that is being tested.*

One can argue that evidence-based medicine has augmented the fear of negative impact as clinical decision making responds directly to scientific signals in the literature. It is ironic, however, that this incentive runs counter to evidence-based medicine which crucially relies on the public availability of all evidence, irrespective of the actors involved or the direction or strength of the observed effects (Scargle 2000; Guyatt et al. 2011). Evidence from multiple clinical trials accumulates in meta-analysis, systematic reviews and clinical guidelines which have become reputable sources to disseminate proven diagnostic and therapeutic knowledge among peers and practitioners (Timmermans and Berg 2003). Publication bias is especially problematic in light of this accumulated evidence which can be severely distorted due to the absence of negative findings. In its most extreme manifestations it is the 5% of studies with positive findings simply due to statistical fluctuations that are published, whereas the 95% with negative findings remains hidden in 'file drawers' (Rosenthal 1979; Scargle 2000). We argue that the institutional reforms that mandate disclosure have opened the 'file drawers' but have not changed scientific publication behaviour per se.

6.3 DATA AND METHODS

SAMPLE DEFINITION

The starting point for the empirical analysis in this paper is registrations of clinical trials on diabetes mellitus in the public database www.clinicaltrials.gov. This internet based registry managed by the US National Library of Medicine was established in response to the enactment of Section 113 of the 1997 FDA Modernisation Act that called for the establishment of a public resource for

information on ongoing clinical studies that target serious or life threatening diseases, including diabetes mellitus. In 2004, the editors of the most prestigious medical journals (i.e. the International Committee of Medical Journal Editors) acted upon this law by announcing that they would only consider for publication manuscripts that were properly registered in this database (de Angelis et al. 2004). As a result, registration of clinical trials soared between May and October, 2005 (Zarin et al. 2005), in the years afterwards (Zarin and Tse 2008), and www.clinicaltrials.gov now contains information on more than 100,000 clinical studies (Zarin et al. 2011).

The representatives of all major pharmaceutical companies changed their policy accordingly by announcing that "*the pharmaceutical industry has committed to registering information about all new and ongoing clinical trials*" (PhRMA 2004). In the same press release PhrMa also announced that they established a web-based clinical trial result database (www.clinicaltrialstudyresults.org) and several large companies (e.g. Elli Lilly, GlaxoSmithKline, Merck) immediately committed to this initiative by disclosing the research results of all clinical trials going back to 2000. Section 801 of the FDA Amendment Act 2007 further mandated the disclosure of research results (FDA 2007), although web-reporting of research results had already become common practice before the act was implemented.

The registered clinical trials provide us with information about research projects well before the research results are disclosed in scientific publications or web reports. We limit ourselves to studies for which registration has become mandated before onset in order to avoid the selection problem that research projects simply may be registered because the researchers want to publish the results in scientific journals. To further prevent selection bias due to the possible exemption of individual clinical trials from mandatory disclosure we only focus in the main analysis on research projects that are disclosed in scientific publications or on the web. In this way, we avoid the well-known file drawer problem which holds that the results of studies that are not published in the scientific literature cannot be known (Rosenthal 1979; Scargle 2000). It follows that we do not have to rely on surrogate measures such as funnel plots or meta-regression analysis (Sutton et al. 2000; Stanley 2005) to study publication bias.

Construction of our sample closely follows the registration specifications enforced by the ICMJE and the FDA which resulted in the inclusion of 329

research projects. In short, we consider completed or terminated[55] clinical trials that were specifically designed to test whether a drug or insulin intervention is effective in controlling blood glucose values as a primary endpoint. This implies that our sample is very homogenous and that the research projects only differ according to the therapy being tested, the research design (e.g. control group, size) and project organisation. All tested experimental treatments in the sample are in later stage development (i.e. Phase II or Phase III) or already on the market. Details of inclusion criteria pertaining to the relevant fields in www.clinicaltrials.gov are found in Figure 6.1.

Important in this study is that we equal industry funding with the production and intentional publication of evidence by pharmaceutical companies. This is a realistic assumption given the focus on an efficacy endpoint and the observation that most of the therapies in our sample are in the development stage. Certain tasks and responsibilities in these clinical trials may be outsourced to academic centers, contract research organisations or for profit clinics but this does not shield pharmaceutical firms from responsibility for the scientific integrity of the study (Azoulay 2003). The active involvement of pharmaceutical companies in the production and publication of evidence is also indicated by the observation that all registrations are posted and maintained by firms. In addition, the web-reports in our sample are almost always published on the websites of pharmaceutical firms (Merck being an exception as they post all their results on www.clinicaltrials.gov), whereas all but four scientific publications have at least one author from a pharmaceutical company. Exclusion of these four cases did not change the reported results.

ASSESSMENT OF REGISTRATIONS AND PUBLICATIONS

An extensive data collection effort was made (i) to code the research design characteristics of the 329 research projects, (ii) to link the registrations to subsequent publication in the scientific literature or on the web and (iii) to assess the results of the clinical trial as being positive or negative. In all these three steps most data was independently collected and coded by the two authors, after which differences were resolved by consensus. We provide a short description of this effort below and refer to Appendix E for a more elaborate description and an overview of all collected variables.

[55] Terminated clinical trials are defined as projects for which the recruitment or enrollment of patients halted prematurely but definitive (National Institutes of Health 2008).

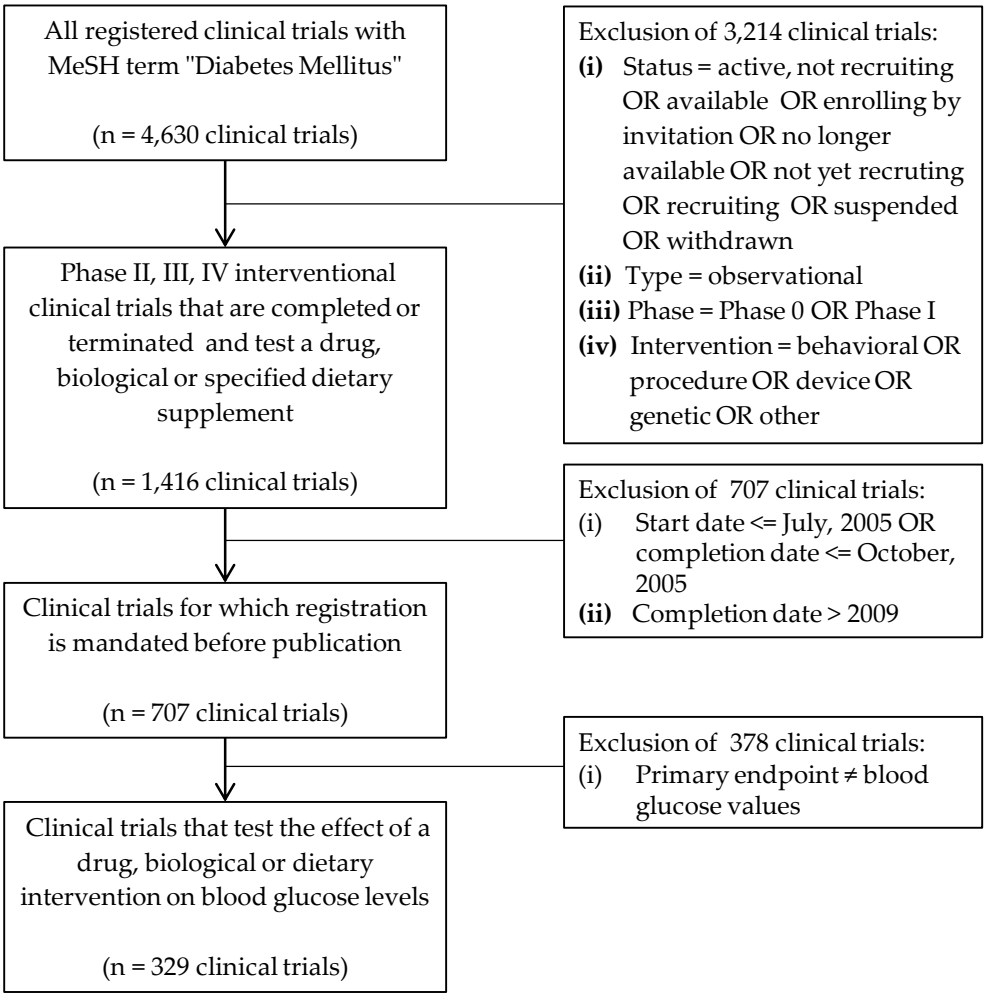

Figure 6.1: *Inclusion flow-chart of sample*

In a first step, research design characteristics of the clinical trial were extracted from the registrations and classified. Among these characteristics are the name of the sponsor, the sponsor-type (i.e. industry or public), the name of the treatment that is being tested (i.e. the experimental arm), the type of diabetes that the experimental therapy targets and the nature of the control group (i.e. active, placebo, uncontrolled etc.). The status and history of all experimental therapies was tracked down to determine whether and when the therapy was approved on the market.

In a second step, a search protocol was used to determine the publication status of the 329 clinical trials by categorising them as belonging to one of three mutual exclusive categories: scientific publication, web report or no disclosure. We only considered original reports of clinical trials that provide information on the results of the primary endpoint of the project as defined in the registration (i.e. blood glucose values). The search protocol was elaborate and included searches of the medical literature (PubMed and Embase), publications indexed in a citation database (Scopus) and manuscripts and citations in clinical trial result databases (www.clinicalstudyresults.org, www.clinicaltrials.gov and firm databases). Abstracts and full texts of all potential matches where manually screened in order to prevent both false positives to be included and false negatives to be excluded. Our final match of disclosed research projects is 74.4% which is comparable to, or even somewhat higher than, previous efforts (Lee et al. 2008; Ross et al. 2009; Bourgeois et al. 2010).

In a third step, we determined for all publications whether the reported results were favourable or unfavourable to the experimental therapy being tested. Results were considered favourable if they were statistically significant (judged from p-values or confidence intervals) and confirmed the hypothesis on the primary endpoint as stated in the registration or publication. The assessment of manuscripts was classified as unclear in case no significance analysis was performed on the primary endpoint of the study.

DEPENDENT VARIABLE

Our research is concerned with the factors that explain the scientific publication of research projects. To understand these factors we first analyse differences in publication practices between publicly funded and industry funded clinical trials. In doing so, we implicitly evaluate the effects of the new disclosure policies and follow the traditional publication bias literature that has analysed differences in the results of scientific publications according to funding sources.

However, we also show that traditional publication bias analysis cannot distinguish between the reasons why pharmaceutical companies produce and the reasons why they publish more positive evidence (which both turns out to be the case in our sample). We consider this distinction between production and publication pertinent and this draws attention in the empirical strategy to the construction of a very precise control group.

Without trivialising the importance of publication bias, there are many reasons why companies obtain more often positive results in clinical trials compared to

non-industry funded trials. Given the high costs of clinical development they only advance innovations in clinical trials that are technologically promising and they reconsider their decision every time evidence from a clinical trial becomes available (DiMasi et al. 2003). Part of observed publication bias between industry funded and publicly funded research might therefore be driven by a selection process where only those clinical trials are conducted that have a high likelihood of obtaining positive results. The same reasoning also applies to the termination of clinical trials which is more likely when firms are involved than other actors (Lexchin 2005).

From an empirical perspective this necessitates a within-group comparison of industry funded trials that all focus on the same research question. By employing this strategy we rule out many alternative explanations that are bound to be present in the publication process. Our main dependent variable is therefore the choice of pharmaceutical companies to publish their research findings in scientific publications as compared to reporting in web-based repositories.

INDEPENDENT VARIABLES

RESULT VARIABLES. To test the influence of clinical trial outcomes on the likelihood that the study is published in a scientific journal, we created a dummy variable that is set to 1 if the hypothesis on the primary outcome of the study is confirmed (i.e. positive outcome) and to 0 if the hypothesis is rejected (i.e. negative outcome). In order to prevent that our assessment was influenced by selective presentation of research results in the publications such as a change of hypothesis from superiority to non-inferiority to obtain positive results (Boutron et al. 2010), we also test a model in which all outcomes are assessed on the base of a superiority hypothesis, irrespective of the actual stated hypothesis.

RESEARCH DESIGN VARIABLES. The influence of quality standards in evidence-based medicine on scientific publishing is captured by including variables on the statistical power of clinical trials and the clinical relevance of the evidence. With respect to the statistical power we include as a variable both the number of patients and whether patients from multiple countries are enrolled in the clinical trial. With respect to the clinical relevance of the evidence, we focus on the control group in the clinical trial that is used to compare the relative safety and efficacy of the experimental arm. We create a dummy variable which is set to one, in case a clinical trial makes a head-to-head comparison with another therapy or compares alternative clinical strategies for administrating the same or similar therapies (e.g. difference in the times of administration, different titration schemes). These control groups reflect actual clinical decision choices facing

patients and practitioners. The reference group in this case becomes placebo-controlled studies and therapies that are tested as an add-on to existing treatments.

CONTROLS. We control for several potential sources of heterogeneity across observations that may influence both the design and outcome of research projects and their subsequent reporting in scientific publications or on the web. More specifically, the interest in this paper is in understanding the type of evidence that firms disclose in scientific publications and as such we want to control for other factors that influence their publication strategies. In order to do so we start by excluding all 23 disclosed but terminated clinical trials in our sample which are always disclosed in web-reports and often do not provide enough information to make an assessment of their results.

We take into account in all models the possibility that publication decisions are driven by unobserved heterogeneity at the level of the firm and at the level of a therapy's development programme. At the level of the firm, disclosure decisions may be influenced by explicit policies or the presence of (internal or external) staff that have a taste for science (see Sauermann and Stephan 2011). We capture this effect by including firm-level dummies.

At the level of development programmes, unobserved characteristics of a therapy may drive our results as some experimental therapies may be intrinsically better which influences both the likelihood that positive results are obtained and the willingness to highlight these results in the scientific literature. Disclosure policies may also be decided on the therapy level instead of the firm-level. To account for these potential factors we include a set of dummies for the therapies that are being tested in multiple clinical trials.

We also consider the possible effect of time-lags on scientific publishing by including dummies for completion years of the clinical trial. Although all clinical trials are completed before 2009 and disclosure of most research results is mandated within 12 months after completion date, firms might have a strategy of disclosing initially on the web after which the evidence appears in scientific publications.

In addition to these variables we control for an additional set of factors that may influence the decision to disclose scientifically. *First*, firms often conduct clinically relevant studies after their therapies are already approved on the market (i.e. Phase IV), although not necessarily so. To make sure that publication is driven by clinical relevance and not by the market conditions of the therapy we include a

dummy set to one for all experimental arms that are already on the market when the clinical trial is completed. *Second,* we include a dummy variable set to one if a clinical trial targets diabetes, type 2 and to zero otherwise, because market prospects and associated publishing may differ between diabetes types. *Third*, we control for the duration of the study by including the number of weeks the experimental treatment is administered to patients as the costs of clinical trials tend to increase with the length of the study. *Fourth,* we control for the observation that studies mainly conducted in major pharmaceutical markets are considered more convincing to regulators and better resemble the actual situations in which practitioners work. To test this we include the percentage of recruitment in traditional research countries in North America (i.e. United States and Canada), Western Europe (i.e. EU15+Switzerland+Norway), Japan, Australia and New Zealand.

Model estimation

We estimate the probability that the evidence of a research projects becomes disclosed in a scientific publication. This implies that our dependent variable either takes on a value of one in case the evidence from a research project is scientifically published, or zero in case the evidence of a research project is published on the web. Because of the binary categorical nature of this variable we estimate logistic regression models and report the coefficients of the independent variables which are equal to the log-odds ratios (Long and Freese 2001). We estimate our model using robust standard errors, as decisions on several components of the research design of a clinical trial may not be completely independent.

6.4 Results

Funding source comparison

Table 6.1 presents the results of a comparison in publication practices between industry funded trials and publicly funded trials. Publication rates between industry (75.3%) and publicly funded trials (71.2%) are similar (p=0.498) suggesting that institutional reforms indeed have eradicated disclosure differences between funding sources. Publicly sponsored trials are almost by default published in scientific journals, whereas firms choose to publish clinical trial reports either in scientific journals or on the web. It follows that industry funded trials are significantly less likely to be published in scientific journals (p<0.001). The results also strongly confirm that scientific publishing of industry

funded trials still depends on the observed outcomes of clinical trials. The percentage of positive results observed in all clinical trial reports is already higher in industry sponsored research (72.7% versus 59.6%), but these differences are augmented when focusing only on publications in the scientific literature (87.6% versus 58.7%).

Although our narrowly defined sample only includes trials that are designed to test the effect of an experimental treatment on controlling blood glucose values, we observe striking differences in the nature of the tested therapies between industry and publicly funded trials. The fast growing market of diabetes, type 2 attracts many resources from industry whereas diabetes, type 1 is especially being studied in publicly funded clinical research. Publicly funded research also tends to be more explorative and often studies new causal associations of therapies that are not explicitly designed to control blood glucose values. As a final note, Table 6.1 shows that industry funded studies are more often terminated, probably because the financial risks associated with those trials are larger.

Table 6.1: *Differences in disclosure and treatment according to funding source*

	Industry funded (n=263)		**Publicly funded (n=66)**		***p*-value**
Disclosure type					
All	198	75.29%	47	71.21%	0.498
Scientific	121	46.01%	46	69.70%	0.001
Positive outcomes					
All	154	77.78%	30	63.83%	0.047
Scientific	111	91.74%	29	63.04%	0.000
Terminated	34	12.93%	2	3.03%	0.021
Experimental therapy					
Diabetes treatment	253	96.20%	35	53.03%	
Non-diabetes treatment	8	3.04%	12	18.18%	
Foods and supplements	2	0.76%	19	28.79%	0.000‡
Diabetes Type					
Diabetes Mellitus	7	2.66%	14	21.21%	
Only Type 1†	26	9.89%	12	18.18%	
Only Type 2†	230	87.45%	40	60.61%	0.000‡

Notes. *p*-values are based on two-tailed proportional t-tests; † A clinical trial can test both on patients with diabetes type 1 and type 2; ‡ Chi-square test

We conclude from these results that publication bias according to funding source persists in the scientific literature despite institutional reform. Yet, we also show that the tested treatments are significantly different between funding sources rendering simple comparisons between industry funded and publicly funded clinical trials problematic, even when focusing on a single primary endpoint. To control for these factors, we study the decision of industry to disclose their research results either in web-reports or in scientific publications in the next section.

Design comparisons

A concern of our analysis is that industry funded trials are simply less interesting to publish in scientific journals and have higher rejection rates when considered for publication. We test this proposition in Table 6.2 by comparing the research designs of industry funded clinical trials that are published on the web with publicly funded research projects that are published in the scientific literature. We focus specifically on the quality of the studies according to evidence-based medicine standards that can be derived from the statistical power of studies as indicated by project size and the clinical relevance of the research as captured by the control groups used.

Table 6.2: *Differences in research design according to funding source*

	Public Scientific (n=46)		**Industry Scientific (n=121)**		***p*-value**	**Industry funded Web (n=77)**		***p*-value**
Project Size								
# Patients†	72.35	76.53	540.83	632.1	0.000	279.19	226.46	0.000
International	2	4.35%	87	71.90%	0.000	32	41.56%	0.000
Design								
Active	18	39.13%	52	42.98%		33	42.86%	
Placebo	17	36.96%	50	41.32%		21	27.27%	
Uncontrolled	4	8.70%	2	1.65%		12	15.58%	
Alternative	6	13.04%	9	7.44%		6	7.79%	
Other	1	2.17%	8	6.61%	0.123	5	6.49%	0.415

Notes. Data represents number (percentage) and associated two-tailed proportional t-tests compated with publicly funded; † mean (standard deviation) and associated two-tailed mean sample t-test .

Table 6.3: *Correlation matrix*

	1	2	3	4	5	6	7	8	9
1 Scientific publication	1.00								
2 Positive result	0.33	1.00							
3 # Patients	0.36	0.17	1.00						
4 International	0.38	0.07	0.43	1.00					
5 Clinical Relevance	0.10	-0.11	0.04	-0.10	1.00				
6 Diabetes Type	-0.04	0.02	0.14	-0.02	-0.30	1.00			
7 Trial duration	0.00	-0.14	0.37	0.23	0.17	-0.06	1.00		
8 Therapy on Market	-0.22	-0.13	-0.22	-0.26	0.28	-0.15	0.08	1.00	
9 % Traditional locations	-0.02	0.08	-0.19	-0.35	0.13	-0.13	-0.11	0.02	1.00

The results indicate that – according to evidence-based medicine standards – web-disclosed industry funded studies are of statistical similar or higher quality as publicly funded clinical trials that are published in the scientific literature. More specifically, industry funded trials are larger in size and the strength of their control treatments does not differ between funding sources. The former outcome probably reflect the financial resources and infrastructure of pharmaceutical companies which are able to finance much larger research projects than public science.

These empirical observations demonstrate that web reports of industry funded clinical trials are of high enough quality to warrant publication in the scientific literature. The regulatory nature of corporate drug testing ensures that the late-stage clinical trials in our sample (i.e. Phase 2 and Phase 3) conform to basic evidence-based medicine standards. In addition, there are ample initiatives within the academic community to create specific outlets for publishing 'deviant' results and for publishing as many results as possible (due to open-access which is not limited by space-constraints). This means that scientific publishing of clinical trial results by firms can be considered a deliberate choice by firms rather than an outcome of the peer-review process. [56]

[56] For instance, there are now journals that publish studies only based on technical standards and not on the base of relevance or impact (e.g. PloS One), and there are journals that publish only studies with negative results (e.g. Journal of Negative Results in Biomedicine).

MAIN ANALYSIS

Table 6.3 reports the correlation matrix for the included variables. Table 6.4 presents the estimates of the logistic regression on the likelihood of scientific publication. All models include firm-level dummies, therapy-level dummies and publication year dummies. Model 4-5 also include additional control variables. Estimation of the model with firm-level dummies results in the exclusion of 12 clinical trials from one firm (Eli Lilly) which are all published in the scientific literature. In addition, therapy-dummies render the exclusion of 8 additional clinical trials on the compound Alogliptin (developed by Takeda) which are also always scientifically published. This implies that our sample for estimation consists of 157 clinical trials.

Hypothesis 1 predicts that scientific publication by pharmaceutical companies depends on the explicit quality standards of evidence-based medicine. Consistent with this prediction, we observe a positive and significant coefficient for the project size of clinical trials as captured by the number of patients and by a dummy that indicates whether the trial enrolls patients from multiple countries. In Model 3, the number of patients is only significant at the 10% level ($p = 0.090$) which is probably due to the correlation between the two project size variables ($r = 0.431$). We also find a positive coefficient for clinical trials with clinically relevant study designs. These results are simultaneously significant whilst controlling for a number of possible alternative explanations.

Hypothesis 2 states that firms are more likely to report evidence in scientific publications when they obtain positive results. Model 2-5 confirm this hypothesis by showing positive and highly significant ($p < 0.007$) coefficients for this variable. The results hold independent of the introduction of a number of additional control variables in Model 4 and a uniform definition of positive results based on a superiority hypothesis in Model 5.

Several control variables show some influence on the decision of firms to highlight evidence in scientific publications. Particularly noteworthy in this case is the proportion of traditional research countries in the clinical trial. The coefficient of this variable is positive and significant ($p < 0.05$) in Model 5. In addition, tests on the joint significance of the included dummy variables at the firm level and therapy level are significant ($p < 0.016$) in all models.

Table 6.4: Determinants of likelihood of scientific publishing

	Model 1	Model 2	Model 3	Model 4	Model 5
Results					
Positive		2.298 ***	2.604 ***	2.005 ***	2.404 ***
		0.734	0.693	0.743	0.795
					superiority
Research Design					
# Patients	0.585 **		0.535 *	0.702 **	0.863 **
	0.285		0.316	0.333	0.347
International	2.141 ***		2.279 ***	2.587 ***	3.196 ***
	0.583		0.650	0.726	0.828
Clinical Relevance	2.069 ***		2.120 ***	2.173 **	3.601 ***
	0.741		0.005	0.864	0.988
Control Variables					
Diabetes Type				-0.063	-0.753
				0.935	0.956
Trial duration				-0.499	-0.834 *
				0.362	0.435
Therapy on Market				-0.765	-1.541 *
				0.711	0.810
% Traditional locations				0.996 *	1.300 **
				0.587	0.655
Constant	-4.049 **	-1.557	-6.296 ***	-5.954 **	-5.632 **
	1.770	1.119	2.117	2.453	2.306
Therapy Dummies	YES	YES	YES	YES	YES
Firm Dummies	YES	YES	YES	YES	YES
Year Dummies	YES	YES	YES	YES	YES
Log Likelihood	-55.58	-67.25	-50.35	-48.94	-46.09
N	157	157	157	157	157

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$. All regressions are estimated with robust standard errors.

6.5 Discussion

Firms' leeway in marketing their products is often limited by legislative and normative standards. This raises the issue to what extent firms can still pursue their market interest when they have to conform to institutional norms. We address this issue by focusing on pharmaceutical companies who in order to convince regulators and practitioners of the relevance of their drugs need to produce evidence on the safety and efficacy of their innovations. The publication bias literature has shown that pharmaceutical companies are prone to highlight only positive evidence, but recent regulatory reforms have mandated pharmaceutical companies to report the evidence of almost all the studies they perform. The key question then becomes how firms strategically operate within a context of complete information disclosure.

We address this issue by first comparing the reporting of evidence between industry funded and publicly funded diabetes trials. Our initial results indicate that pharmaceutical companies do indeed not report less evidence than other researchers in the new institutional context. However, although firms can no longer conceal evidence, they now make a deliberate choice to report their evidence either in scientific publications or in web-based repositories. This stands in stark contrast to the research of non-industry sponsored projects which by default is published in scientific journals.

These initial empirical outcomes call for an understanding of the decision by pharmaceutical companies to highlight their evidence in the scientific domain. We argue that publications in scientific journals consist of a continuous scrutiny of the evidence before, during and after publication which increases the truth value of the evidence and establishes trust in the results. Companies are aware of this function of science and therefore carefully select the evidence they wish to certify. In order to anticipate on impact, firms also need to conform to particular standards that are deemed relevant by the academic community. In case of clinical research these standards are defined by the emphasis of evidence-based medicine on the quality of research designs. We therefore hypothesise that the decision of firms to publish in scientific journals is simultaneously dependent on the direction of the obtained evidence and the quality of research designs.

Our main analysis confirms our argument and rules out alternative explanations at the level of the firm, development programme and clinical trial. Publication bias thus persists as positive findings are more likely to be published in scientific publications, whereas negative findings are more often filed in web-repositories.

In addition, we also a find a bias of scientific publications towards studies that are of higher quality according to evidence-based medicine standards.

We conclude from these observations that pharmaceutical firms still find a way to strategically highlight particular pieces of evidence in scientific journals despite the recent institutional reforms. This implies that concerns about publication based on the nature of evidence have shifted rather than disappeared. The results in this paper thus signal a problem of persistent publication bias of a more fundamental nature which is not easily solved by regulatory reform alone.

To better understand this issue we suggest to focus the attention on the science system itself which allows for differential media exposure of individual research findings. Evidence on the meaning of a particular research object (such as the effectiveness of a drug) is preferably reviewed in light of the whole body of evidence of a research object (and related objects). Current publication practices however only make sure that a single piece of evidence is certified on its own merit. It follows that pharmaceutical firms can 'buy' certainty by conducting a number of clinical trials that attain to the highest quality standards while only highlighting the one which has the most favourable evidence components. In addition, firms can decide to publish multiple pieces of evidence at the same time if they want to draw attention to a new therapy.[57] Yet, the submission of an individual piece of trial evidence does not give an overview of the whole body of evidence which hinders an integrated evaluation of the qualities of a therapy and prevents reflection on the internal validity of entire development programmes.

This suggestion stands in contrast to earlier studies on publication bias which merely question the scientific integrity of pharmaceutical firms, but do not acknowledge the limits of the science system and evidence-based medicine in dealing with the problem. We show that the organisation of science has not prevented pharmaceutical companies from responding timely and in their own interest to recent regulatory reforms that mandate ever more transparency on their behalf. It seems therefore especially important to build institutions that enforce scientific integrity irrespective of firms' intentions, rather than spending much effort on mandating any further change in the behavior of pharmaceutical companies.

[57] For instance, we observe in our sample that when the diabetes drug Sitagliptin was under review by the FDA, Merck submitted at the same day three papers on the same drug to prestigious scientific journals which were all accepted for publications a couple of months before the final decision on market approval was made.

APPENDIX E

In this appendix we describe in detail the three steps involved in classifying registrations, linking those registrations to disclosed manuscripts and assessing the outcomes of the disclosed manuscripts.

ASSESSING REGISTRATIONS AND CLASSIFYING DRUGS

We extracted the 329 research projects from the XML version of www.clinicaltrials.gov on October 21, 2010. Each registration contains information on the lead sponsor of the study and research design characteristics of the clinical trial. However, information about the latter is not consistently indexed in pre-defined fields. In order to obtain consistent research design information across all trials we manually assessed clinical trial registrations on the following dimensions:

- Type of diabetes: Diabetes Type 1, Diabetes Type 2, Diabetes Gestational
- Name of experimental arm: The experimental arm is defined as a single drug that is being tested on efficacy against a comparator treatment. The experimental drug is most often explicitly mentioned as such in the registration, although in a small number of cases we determined the experimental arm based on a match between the producers of the therapy and the sponsor of the clinical trial. In 5 publicly funded clinical trials the experimental arm could not be determined because more than one drug was being tested and no explicit hypothesis was stated about the drug that should have favorable effects *vis a vis* control groups.
- Control group (see also Table 6.5): In controlled experiments such as clinical trials, the effect of the experimental arm is compared with a control group keeping other baseline characteristics of patients (e.g. age, sex, weight) as identical as possible. We classified the control group as one of five types: (i) no intervention control (ii) placebo control (iii) active control (iv) dose control or (iv) alternative control. In case a clinical trial has more than one comparator arm we turn to the stated hypothesis to determine the main comparator (see below). All encountered examples are mentioned in Table 6.5.

We searched the FDA catalogue of approved drug products (www.accessdata.fda.gov/scripts/cder/drugsatfda) to determine whether the experimental arm was approved on the market. For all approved drugs we collected the approval year.

***Table 6.5** : Definition of control group*

Active control
Drug A *versus* Drug B
Drug A+B *versus* Drug C
Drug A+B *versus* Drug B+C
Drug A *versus* Drug B+C
Drug A_1+B *versus* Drug A_2
Drug A *versus* Drug B
Drug A+B *versus* Drug C

Placebo Control
Drug A *versus* Placebo
Drug A+B *versus* Placebo

No therapy control
Drug A *versus* no therapy
Drug A+B *versus* Drug A

Dose control
Drug A_1 *versus* Drug A_2
Drug A_1 *versus* Drug A_2 *vs* Drug A_n
Drug A_1+B *versus* Drug A_2+B
Drug A_1+B_1 *versus* Drug A_2+B_2

Alternative control
Drug A *versus* Drug B, difference in:
time of administration,
type of administration,
titration schemes,
group-analysis

A search protocol was used to determine whether the results of the 329 clinical trials were disclosed. Publications were defined as original manuscripts of clinical trial results that reported on the primary endpoint of the project as defined in the registration (i.e. blood glucose values). The search protocol to identify such disclosed manuscripts consisted of five steps that were independently executed by both authors. After each step, the authors compared the results of their search and any differences in findings were resolved by reading (again) abstract and full text of the publication. We searched for disclosed manuscripts for each clinical trial registration until we found a scientific publication. In a last step we complemented the set of all scientific publications with web reports for those clinical trial projects that were not scientifically disclosed. Part of the procedure is an adjustment of recent work in the medical literature (Ross et al. 2009; Bourgeois et al. 2011).

The five steps in the search process were as follows:

1. Examination of abstract and if necessary full text of scientific publications that are listed in the publication field of www.clinicaltrials.gov. This field is used to list citations of trial results or other relevant 'background' research as provided by the researchers.

2. Search of the medical literature (PubMed and Embase) using the national clinical trial identifier (NCTID) which is the unique identifier of each clinical trial registration. Many journals that follow ICMJE requirements (including the ICMJE member journals) publish this identifier in the abstract or acknowledgement of the scientific publication. The number is also indexed in PubMed as 'secondary ID' and in Embase as 'clinical trial numbers' and these fields can be searched as such.
3. Internet search (Google) using other clinical trial identification numbers mentioned in the field 'other study ID numbers' in www.clincialtrials.gov. Firms assign their own identification number to a particular project and clinical trials may also be indexed in other registries with relevant citations. Note that this search already resulted in a set of web reports that were only included in step 5. In this step we only screened those reports to assess whether they contained references to scientific publications.
4. Free search of the medical literature (PubMed and Embase) and of a citation database (Scopus) using various search combinations of the name of the experimental arm, name of the comparator arm, name of the sponsor, name of the principal investigator (if mentioned), diabetes type, treatment period, recruitment countries and approximate patient enrolment. It turned out that in this free search not yet found scientific publications were easily identified. We therefore decided to stop searching for a scientific publication of a project if a relevant publication was not found within ten minutes.
5. Search of web reports by screening the web repositories maintained by all pharmaceutical companies that sponsor clinical trials in our sample. In addition, we also searched the result pages maintained in www.clinicaltrials.gov and an online register, www.ClinicalStudyResults.org, which is consistently fed by some firms. As a final search action, we again screened all web reports for any additional references to the scientific literature which had remained unnoticed until that point, but we did not find any additional scientific publications.

All searches were updated and finalised as of June 1, 2011.

Outcome assessment of publications

We determined for all published manuscripts (web and scientific) whether the reported results were favourable or unfavourable to the experimental drugs being tested. In doing so we compared the effect of the experimental arm to the main control group that was mentioned in a stated hypothesis in the registration or publication. Before we made an assessment of the result of the publication, we stated the hypothesis of the clinical trial as either superiority or non-inferiority of

the experimental arm to the control group. In a small number of cases no explicit hypothesis was stated in registration or publication. We solved this issue by taking superiority as our default hypothesis for all control groups except for active comparisons for which we stated a non-inferiority hypothesis.

The outcome assessment was made on the base of significant statistical differences in primary endpoint between the experimental arm and the control group. Results were considered favourable if the experimental arm demonstrated significant greater improvement in primary endpoint (in case of superiority hypothesis) or statistically similar improvement in primary endpoint (in case of non-inferiority hypothesis). Statistical significance was judged based on *p*-values or confidence intervals. If significance levels were not reported the outcome assessment remained unclear.

In case of active control groups we also made assessments that were not based on the stated hypothesis in the registration or publication but on both a non-inferiority hypothesis and a superiority hypothesis. This was done for consistency reasons and in order to prevent that our assessment was influenced by selective presentation of research results in the publications such as a change of hypothesis from superiority to non-inferiority to highlight that the experimental treatment was beneficial despite non significant differences in primary endpoint (Boutron et al. 2010).

Next to an assessment of research results in the publications, we also noted for all publications the exact number of patients that were enrolled in the study and the countries were patients were recruited. Although these data elements are also available in www.clinicaltrials.gov they are sometimes missing or classified as 'anticipated numbers' (Sekeres et al. 2009; Ross et al. 2009).

7

On error in scientific publications and its detection: the case of pharmaceutical clinical trials

7.1 Introduction

Writing manuscripts for publication is a fundamental component of scientific research and the number of journals, papers and authors is still on the rise (Wuchty et al. 2007). The last decade has witnessed however a steady increase in the number of mistakes that accompany publications which cannot be explained by an increase in the production of error alone (van Noorden 2011). Any study on publication errors should therefore focus on elements that can explain both the production of error and its detection. In order to do so we draw attention to the concepts of coordination and prestige as co-constituting the occurrence of a mistake in the scientific literature.

Perhaps because of its unglamorous nature, the occurrence of errors in publications has received little attention up to now (see for exceptions: Loepprich 1973; Hubbard 2010; Molckovsky et al. 2011). Most errors in publications are honest ones that are not big enough to cause a stir in the academic community and not significant enough to alter the main conclusions that can be drawn from the publication. Most of the time, they also do not lead to the retraction of the publication from the literature which often follows from scientific misconduct or fraudulent practices (Lacetera and Zirulia 2011; Furman et al. 2012) Rather, most errors in publications follow either from inaccurate and inconsistent reporting of research findings or from deviations of publishing norms. Such mistakes include amongst others the misreport of measurement units, the transposition of numbers between two columns in a table and mistakes in the name or order of authors on a publication.

We argue however that the correction of even such 'minor' mistakes in the literature signals valuable information about peer control in the research process, and more in general about the ability of the academic community to self-correct. We hypothesise that lack of internal peer control impacts upon the production of mistakes, whereas external peer-control is the traditional safeguard for its detection. It follows that in this study error in publications refer to the combined act of producing, publishing, noticing and acknowledging a mistake. That is, for error to be present authors need to publicly acknowledge it which is done when a written account of the mistake and its correction appear in the scientific literature as an erratum.

We make our contribution in the context of clinical trial research which is an important case for the study of error in scientific publications for at least three reasons. *First*, the rise of 'evidence-based medicine' as an organising principle of this field has led to a situation where practitioners' decisions are directly grounded in the available scientific evidence on therapies (Evidence Based Working Group 1992; Timmermans and Berg 2003; Montori and Guyatt 2008). This adds relevance to the errors we study as dissemination of incorrect research findings may have direct repercussions for patient care (through for instance incorrect drug dosing or survival information). *Second*, the standardisation of many aspects of research practice including uniform guidelines for the submission of manuscripts for publication (e.g. ICMJE, CONSORT) has accompanied the rise of evidence-based medicine. This standardisation facilitates the development of common reference frames against which inconsistencies and deviations can be more easily detected. *Third*, as research practices become increasingly standardised in this field, we witness major changes in clinical trials' organisational structure, characterised by both commercialisation and globalisation tendencies (Angell 2004; Mirowski and van Horn 2005; Petryna 2009). This situation adds logistical complexity to clinical trial research and justifies inquiry in the importance of modes of coordination as a possible determinant of error in publications.

The main goal of our empirical analysis is to explain the number and nature of error in scientific publications both from the prestige of research findings and from the coordination modes of the writing process. In doing so, we use detailed protocol information on the funding sources, research designs and study locations of approximately 5,000 clinical trials. We link these research projects to scientific publications that report on their outcomes and follow these publications over time to observe whether a scientific erratum or retraction is issued. All corrections are classified based on the number of independent mistakes in the publication and whether they report on error related to the content of a

publication (e.g. error in analysis, patient data etc.) or errors due to deviations from particular publishing norms (e.g. error in authorship, acknowledgements etc.).

In the next section we develop a theory on error in scientific publications and discuss its components in relation to our case of clinical trial research. We subsequently describe our empirical setting and modeling strategy in section 3, turn to our research findings in section 4 and conclude in section 5.

7.2 THEORY DEVELOPMENT

Scientific institutions have long been praised for their remarkable ability to expose error through self-correcting mechanisms (Peirce 1878, Merton 1973). The gate keeping peer-review system provides a first check to prevent the publication of erroneous findings, while 'organised skepticism' among the academic community corrects such findings in case they accidentally slip through the peer-review process and enter the domain of certified knowledge (Merton 1973). Replication of experiments is key to post-publication appraisal, as peers independently confirm or reject the obtained scientific results by reproducing the original experimental settings (Collins 1985). Governments have long acted upon this idea by enforcing a 'social contract of science' in which scientists themselves regulate the conduct of their peers "*in an effective, democratic and self-correcting mode*" (Guston 2000, p. 144).

However, following an increase in the published cases of misconduct, skeptics have started to question the self-correcting ability of science. Moreover, the narratives of individual cases of wrongdoing have been substantiated by studies that question the effectiveness of scientific institutions that are designed to ensure the integrity of the research enterprise. In doing so, they cast doubt upon the ability of science to correct mistakes on at least three grounds.

First, although the peer-review system still holds it original function to certify research results (Merton and Zuckerman 1973; Crane 1976), its efficacy as a gatekeeper of scientific standards has been described as being based on faith rather than facts (Jefferson et al. 2002; Smith 2006). Given limited time and resources of researchers and the voluntarily nature of peer-review, there are high opportunity costs involved when researchers engage in a thorough peer-review process, and these opportunity costs are likely to decrease their efforts. Consequently, evaluations of reviewers have been described as diverging, inconsistent or outright contradictory (Weingart 2005). Smith (2006) provides an

extreme example of the extent to which the opinions of reviewers on the same paper can differ:

"Reviewer A: 'I found this paper an extremely muddled paper with a large number of deficits'
Reviewer B: 'It is written in a clear style and would be understood by any reader'"

It has also been proven difficult to improve the quality of peer evaluation. In a series of experiments initiated by the prestigious British Medical Journal, it was shown for instance that blinding reviewers to the identity of authors, training of reviewers, and opening up the communication of the peer-review process had little effect on the quality of reviews as measured by validated quality instruments (Smith 2006).

Second, the critical post-publication appraisal of papers is at least impartial as indicated by the observation that more than a quarter of all papers are never cited and a considerable number probably never read (Garfield 1998). Important for post-publication scrutinising is that scientific publications are written in such a way that they contain essential information to 'virtually witness' complex experimental scenes and to replicate the experimental settings at a distance (Shapin 1984; Collins 1985). Yet, the winner-takes-all nature of scientific institutions decreases the incentive to actually engage in replication, '*because there is no social value-added when the same discovery is made a second, third or fourth time*' (Dasgupta and David 1994, p. 499). Moreover, Collins (1985) has gone so far as to argue that independent confirmation of experimental results can never be attained when the desired result is not known beforehand. In these situations, either the skills of the researchers or the correctness of the experimental set-up can always be questioned which ultimately necessitates the introduction of external arguments (e.g. reputation, trust) to reach a consensus on the value of a particular outcome within the academic community (Frenken 2010).[58]

Third, the philosophy of science has drawn attention to the tendency of science to incorporate anomalous research findings up to the point that the accumulated set of research findings becomes so ambiguous that science itself reaches a crisis. In these cases scientists simply start asking different questions, instead of correcting prior art (Kuhn 1962). It follows that conceptual frameworks and terminologies become incommensurable between research programmes which hinders the

[58] In addition, actual replication of clinical trials is low due to the high costs associated with those studies.

objective functioning of a self-correcting mode. The ability to correct peers in this context is also limited by the ever increasing fragmentation and specialisation of scientific knowledge (Price 1963; Jones 2009).

It follows from these three arguments that the correction of the scientific literature can never be perfect. Inquiry in the logic of error in scientific publication should therefore start from the assumption that some mistakes are more likely to be detected than others, and - equally important - that many mistakes will probably never be noticed. By acknowledging this we come to the somewhat counterintuitive hypothesis that the likelihood of error in scientific publications increases with the prestige of the research.

A large part of the prestige of research findings in publications is only established after the research has been published, as it is in the post-publication stage that findings are used in successive research activities and practical decision making (Gilbert 1976; Latour 1987). As the prestige of research findings increase, so does the relevance of scientific mistakes that possibly accompany them. This implies that both scrutinisers and producers become increasingly aware of the detection of mistakes once the published findings gain in importance. From the perspective of scrutinisers this can only be done insofar as inconsistencies are visible from the surface. However, the incentives for authors to correct mistakes also increase in more prestigious research because scientists' reputations become linked to the research findings and reputation damage becomes a more pertinent issue when mistakes are not acknowledged but are still detected via other channels.[59]

Editors of journals may actively steer this process of error detection. The relation between error detection and prestige implies that efforts to organise impact around particular publications facilitates critical post-publication scrutinising of the results at the same time. Such scrutinising can be initiated by inviting experts to comment on papers or by opening forums were findings are publicly discussed. In addition, a growing group of scientific journals also mandates from authors to explicate the conditions under which research results have been obtained in order to enhance transparency and ensure the scientific integrity of research findings. Some of these institutions provide the necessary yardsticks to scrutinise publications on error by including, for instance, original information

[59] This expectation is different from the implications derived from the model on scientific misconduct of Lacetera and Zirulia (2011). They argue that reputable researchers are less likely to be caught when committing fraud, although they acknowledge that the scrutinising process potentially influences their findings (p. 584).

from protocols or datasets. Other regulations mandate insight in the research settings under which the findings have been produced. This potentially creates awareness among readers of particular conditions that may have jeopardised the 'disinterestedness' of authors, such as conflicts of interests and funding sources that have a commercial interests in the findings.

The efforts of journal editors to mandate an increasing amount of information about the research process itself also feeds back upon the prestige of papers that are published under these conditions. More specifically, publications that reveal a wealth of information about the conditions under which the research findings have been produced, become subject to an increased likelihood of error exposure. Authors, readers and editors anticipate on this likelihood which renders the potential of error exposure a constituent part of the prestige of the publication. In sum, the likelihood of error increases with the prestige of publications which can be actively steered by editors. Moreover, prestige of publications also follows from anticipatory behavior of authors and readers based on the potential of error exposure.

HYPOTHESIS 1: *The likelihood of error in scientific publications increases with the prestige of a scientific publication.*

A necessary condition for the detection of error in publications, is its production in the first place which depends on the coordination modes of the writing process. Big Science nowadays requires the collaborative participation of many researchers (Price 1963; Gibbons et al. 1994; Ziman 2000). Tasks which are commonly associated with a single or small group of researchers (e.g. designing protocols, collecting data, analysing data, writing manuscripts) are distributed over an increasing number of individuals and locations (CHAPTER 3; Wuchty et al. 2007). A major challenge for the organisation of distributed research projects is the integration of these different tasks in order to reduce their outcomes to tables, diagrams and text which can be effectively communicated to a scientific audience (Latour 1990). Coordination mechanisms are necessary to facilitate this reduction process especially when distances between authors need to be bridged and researchers are assembled in loosely coupled teams with limited shared past or anticipated future. Such coordination mechanisms come at a price. Consequently, it has been shown that distributed research projects have less coordination activities which has negative implications for the outcomes of these projects (Hinds and Bailey 2003; Cummings and Kiesler 2007).

A major solution to the problem of coordination is provided by the organisation of physical co-presence which facilitates the creation of mutual understanding

and a shared language that cannot be easily expressed in words or visualisations alone (CHAPTER 1; Collins 2001; Amin and Roberts 2008). In doing so, moments of co-presence strengthen proximities between researchers (e.g. cognitive, social, organisational) and as such provide a means to overcome coordination problems (Boschma 2005). Although they can be organised on a temporary base (Torre 2008), organised proximity is subject to higher coordination costs than co-location of authors on a more permanent base. Moreover, technology mediation can as of yet not fully substitute for the physical co-presence of individuals at the same location (Olsen and Olsen 2000). Geographically dispersed teams are therefore more likely to experience conflict, free-riding, lack of monitoring and diverging interests (Hinds and Bailey 2003). Consequently, we hypothesise that error in scientific publications is more often produced in geographically dispersed teams.

The organisation of clinical trials forms a significant case to study whether the likelihood of error increases with the geographical distribution of writing processes. Traditionally clinical trial activity has been mainly located in the U.S., Europe and Japan. However, triggered by the international standardisation of clinical practice (e.g. ICH-GCP guideline), more and more patients are currently enrolled in nontraditional research locations in Central and Eastern Europe, Latin America and Asia (Thiers et al. 2008; Petryna 2009). This globalisation process of clinical research raises new questions with respect to the division of labour in research projects, the ethical standards-of-care for patients across the globe and effective oversight of research activities at distributed clinical sites (CHAPTER 5; Petryna 2009).

With respect to the writing of publications, it can be questioned whether clinical research has become standardised enough to facilitate a straightforward reduction process from the complex reality of data collection in the clinic to a uniform manuscript for publication. The complexity of this process is likely to increase when differences between research cultures and patient populations need to be bridged, and effective peer-control cannot be easily executed. The preferred mode of coordination relies in this case on the exchange of knowledge through face-to-face interactions and personal mobility, rather than on a simple transfer of codified protocols alone. This implies that in geographically dispersed clinical trials errors are more likely to be produced.

HYPOTHESIS 2: *The likelihood of error in scientific publications increases with the geographical distance between authors.*

Lack of institutional proximity defined as the extent to which researchers operate under the same incentive structure imposes greater coordination costs and

creates potential conflict of interest between researchers (Ponds et al. 2007). Open science is based on the pursuit of priority and as such encourages rapid disclosure of research findings in scientific journals (Merton 1973; Stephan 1996). This disclosure is meant to be unconditional and independent of the conditions under which the research has been produced. In contrast, firms rely on secrecy and protective mechanisms such as patents to ensure returns to their investment and they are selective in publishing research findings when they have a commercial interest in the results (Dasgupta and David 1994). These differences in incentive structures give rise to complex arrangements when universities and firms collaborate which makes conflicts over publication practices more likely.

The prevalence of collaboration between university researchers and firms makes coordination of conflicting interest and the alignment of incentive structures a central concern in clinical trial research. Clinical trials are often funded by pharmaceutical companies to test the safety and efficacy of their compounds in order to gain market approval. The publication of this evidence in scientific journals is an important means for firms to provide certainty about the effects of a therapy and to communicate the qualities of approved compounds to regulators and the medical community (CHAPTER 6; Polidoro and Theeke 2011). Firms rely on university researchers to legitimise their research findings in the scientific literature, but in doing so they also try to stay in control of the outcomes of the writing process (Gøtzche, et al. 2007; Sismondo 2009). This conflicting interest has resulted in publication practices that are heavily criticised from within the academic community, including the restriction of data-access and the right to publish (Lexchin et al. 2003; Sismondo 2008), the use of ghost- and guest authors (Gøtzche, et al. 2007) and the selective publication of particular findings in commercial supplements (Angell 2004). Given these tensions over scientific norms, we expect that industry funded research is more likely to result in error in scientific publications. Moreover, given that especially conflicts over the norms of science are prevalent in these collaborations, we particularly expect that industry funded research is likely to err with regard to the provision of information on the settings of the research (e.g. authorship norms, disclosure of interest).

HYPOTHESIS 3A: *The likelihood of error in scientific publications increases when the research is industry funded.*

HYPOTHESIS 3B: *Industry funded research is especially likely to result in errors regarding the norms of scientific publishing.*

7.3 DATA AND METHODS

DATA

The starting point of the empirical analysis are protocols of pharmaceutical clinical trials extracted from www.clinicaltrials.gov which is a publicly accessible register of clinical trials managed by the US National Library of Medicine. The registration of clinical trials in this database is now mandated by national law in various countries and is also a requirement before clinical trial outcomes are considered for publication in peer-reviewed journals that follow the recommendations of the International Committee of Journal Editors (ICMJE) (deAngelis et al. 2004). Currently, the database contains more than 100,000 clinical trials and provides detailed information on the project size, funding sources, research design, enrolment locations and diseases targeted of ongoing and completed clinical trials (Zarin and Tse 2008; Zarin et al. 2011).

We extract information on a subset of protocols for which we were able to establish a link with an outcome publication that reports on clinical trial results in the period 2005-2010. In order to do so, we search Medline via PubMed for protocol registration numbers that are indexed as 'secondary source IDs'. We only focus on studies that have indexed clinical trial registration numbers which biases our sample towards journals that follow - to varying degrees - the uniform requirements of the ICMJE. The ICMJE recommends minimum standards to journals for many aspects of the research and writing process, including authorship norms and the correction of mistakes (ICMJE 2010).

In order to obtain a sample that only reports on original pharmaceutical clinical trials we limit the search by publication focus ("*clinical trial*" and "*human*"), publication type (no "*letters*" or "*comments*") and by only considering publications with drug-related terms ("*drug*" or "*drugs*" or "*pharmaceutical*" or "*placebo*" or "*dosage*" or "*dose*"). We also exclude publications that make reference to more than one clinical trial.

For all matched publications we download bibliometric information both from PubMed and Scopus Elsevier. The former indexes the publication of a scientific errata, detailed journal and authorship information (including group-authorships) and also uses a fixed terminology to characterise the scientific focus of the study (MeSH terms). The latter systematically keeps track of the address information of authors and of the citation rates of individual publications and entire journals. To ensure accuracy of the author information we compare the number of authors listed in PubMed with Scopus Elsevier and retrieve data from

the full-text of articles in case of any inconsistencies. For a small set of articles we were not able to retrieve address-information and we remove those cases from our sample. Our final sample consists of 4,777 protocol-publications.

We follow our sample of protocol-publications over time to determine whether an erratum or retraction is issued on any aspect of the publication. In case an errata is written or the paper is retracted, we extract the full-text of both the original article and of the correction. By reading all corrections, we count the number of independent mistakes that are present in a single correction. This implies that multiple occurrences of the same mistake throughout the manuscript are counted as one error. Such mistakes include for instance mistakes in the units of measurement that occur in multiple places and incorrect reporting of numbers that are repeated throughout the text.

We also classify all individual corrections as either describing mistakes in the description of the research content of the publication which we call content errors, or describing mistakes in the description of the conditions under which the publication has been produced which we call context errors. More specifically, content errors describe errors on patient characteristics (e.g. inclusion criteria, baseline values), interventions (e.g. drug-action, dosage), reported results (e.g. survival rates, adverse events) or the interpretation of prior art (e.g. referencing). Context errors are mistakes in the description of author-affiliation information, acknowledgements (e.g. contributors, conflict-of-interest statements), or other organisational settings of the clinical trials (e.g. enrolment locations). Other minor corrections such as typos, layout errors and missing online links are not counted as errors as they are also likely to follow from mistakes by the publisher. The errata information was finally updated at November 1, 2011.

Dependent variable

Our hypotheses test the likelihood of error in scientific publications. We therefore create an observation for each protocol-publication pair in the sample and construct a dependent variable that takes on a value of one in case an erratum is issued on the publication, and zero otherwise. Next to this general analysis we also study the number and nature of mistakes and therefore consider several alternative dependent variables. First, to consider the quantity of an erratum we take as a dependent variable the number of independent mistakes that are corrected in an erratum. Second, differences in the type of mistakes are captured by two alternative binary dependent variables: (1) a content-error dependent variables that take on a value of one in case an erratum describes a mistake in the

content of the research and zero otherwise, (2) norm-error dependent variable that takes on a value of one in case an erratum is issued on a mistake in the description of the contextual conditions under which the publication has been produced, and zero otherwise.

INDEPENDENT VARIABLE

PRESTIGE (HYPOTHESIS 1). To test the influence of prestige on the likelihood that an errata is issued we take into account three variables. The first prestige variable is the Source Normalised Impact per Paper (SNIP) which is computed for every journal that is listed in Scopus dabase. In contrast to the well-known Impact Factor available in the Web of Science, SNIP corrects for differences between the 'citation potential' of journals. These differences follow from the observation that scientific publications in some journals have longer reference lists and differ in the amount of citations to other publications in the same journal (Moed 2010). The use of SNIP instead of the Impact Factors is thus a necessary control in our sample as citation potential is likely to differ between therapeutic fields (e.g. diabetes, oncology). The measure we employ is the natural logarithm of the SNIP of a journal in the year prior to publication although we also consider a fixed SNIP value for the year 2005 which yields similar results.

A second factor relating to the prestige of a publication is a dummy variable that captures whether commentaries on the research findings are published along the original scientific publication. This measure signals that the research findings are deemed relevant by the editors of scientific journals and that critical post-publication scrutinising of the results by experts in the field is warranted. These comments can be considered an early indication of citation count of the scientific publication.

Third, we include in the model a dummy variable that takes on a value of one for all core member journals of the International Committee of Medical Journal Editors (ICMJE) and zero otherwise. The ICMJE is a group of general medical journals that create and enforce uniform requirements for manuscripts which cover a wide range of research and writing practices, including authorship guidelines and standardised procedures for the correction of error. Although all journals in our sample follow the ICMJE requirement to varying degrees (as they list clinical trial numbers in their publications), the standards are developed by the editors of a smaller group of core journals and communicated through their own outlets. The ICMJE only assures enforcement in these journals and they fulfill as such an exemplary role within the medical community (ICMJE 2010).

COORDINATION (HYPOTHESIS 2 AND 3). The impact of coordination on error in scientific publications is taken into account by including the natural logarithm of the average geographical distance between researchers on a scientific publication. In order to do so we follow Leydesdorff and Persson (2010) and extract geographical information from the publications by aggregating the organisational addresses of all authors to the level of cities. We subsequently determine the geographical coordinates of all cities in our sample. Using these geographical coordinates we compute the average kilometric distance between any pair of authors on a publication with a minimum of zero in case all authors are located in the same city. More specifically, we sum the kilometric distance between all author-pairs on a publication and divide this by the total number of author-pairs. Given n authors, the number of author-pairs can be computed by $(n^2-n/2)$. We also test our models using the maximum kilometric distance in a research project. The obtained results are similar.

Our second measure of coordination characterises the institutional conditions under which the clinical trial is conducted. We extract information on the lead sponsor of the clinical trial and determine whether the clinical trial is sponsored by a firm, government or other not-for-profit organisation. The models include dummy-variables for industry funded and government funded trials, leaving not-for-profit funded trials as a reference group.

CONTROLS

ADDITIONAL COORDINATION CONTROLS In addition to the formulated hypotheses on the funding sources of clinical trials and their geographical organisation, we also include a number of possible alternative explanations related to the coordination of research projects which may independently influence the likelihood that a publication contains an error. One such factor pertains to the cognitive and logistical complexity of clinical trials which increases with the size of the clinical trial, because more resources are needed to reduce the collected data of large clinical trials to scientific publications. In order to capture this effect we include the natural logarithm of the number of patients that are enrolled in each clinical trial as a variable in our model. Furthermore, in clinical trial research, logistical complexity also increases as a function of the number of locations where patients are recruited. This potential effect is captured by a variable denoting the natural logarithm of the number of recruitment countries in each clinical trial.

Publications written by more authors are also more likely to involve higher coordination costs and we therefore include the natural logarithm of the number

of authors on a publication as a control variable. Moreover, authors may be only represented on a publication as part of a research group, while the actual writing is done by a smaller writing committee. In these projects, there are simply too many researchers to be involved in the writing process, and knowledge needs to be transferred from non-authors to authors in order to assure an effective writing process. To control for this factor we include a dummy variable that takes on a value of one in case the authorship byline includes a group-authorship and zero otherwise.

OTHER CONTROLS. To account for the possibility that erratum issuance is mainly determined by editorial policies at the journal level we include a measure that captures the percentage of pharmaceutical clinical trial articles per journal that result in an erratum. In order to obtain this number we extracted all pharmaceutical clinical trials in the period 1990-2010 (n=291,132) from PubMed and divide the number of errata per journal by the total number of publications per journal for the three years prior to publications in our sample. We use this measure as a robustness check in a second set of models and exclude in these models the two other prestige variables on the journal level (e.g. SNIP and ICMJE).

Furthermore, correction is subject to time-lags and in our sample mistakes are - on average - only corrected after 3.6 months. This implies that at the time of analysis not all mistakes in clinical trial publications may have been detected yet. In order to control for this we include dummies for publication years. These dummies control at the same time for changes in the self-correcting ability of science over time. Finally, the occurrence of mistakes may be field-specific and as such partly driven by the disease that is being targeted in the study. In order to control for this factor we include a set of dummies for the ten most occurring diseases in our sample.

MODEL

We estimate the probability that a research project results in an error as measured by the presence of a scientific erratum or retraction. This implies that our dependent variable either takes on a value of *one* in case an erratum or correction is issued on the publication, or zero otherwise. Because of the binary categorical nature of this variable we estimate logistic regression models and report the coefficients of the independent variables which are equal to the log-odds ratios (Long and Freese 2001).

In addition to the question which research projects eventually result in an erratum, we are also interested in the quantity of the correction as measured by the number of independent mistakes in an erratum. This second dependent variable is a non-negative count variable that follows a quasi-poisson distribution and contains an excessive number of zeroes. Consequently, we use a zero-inflated negative binomial model (Burger and Van Oort 2007) in which we include the errata probability per journal in the zero-inflated part of the regression, and all other independent variables in the negative binomial part. The choice of the model is both confirmed by the over dispersion parameter and the Vuong statistic.

7.4 RESULTS

The increased prevalence of error correction in clinical trial research for the period 1990-2010 is shown in Figure 7.1. The total number of issued errata increases from 1.0% of all publications in 1990 to 1.9% of all publications in 2010, with a peak of 2.1% in 2007. This percentage is strikingly lower than the number of errata issued in ICMJE core journals which increases from 4.3% in 1990 to 9.7% in 2010 with a peak of 14.5% in 2005.

Table 7.1 reports descriptive statistics and the correlation matrix for the included variables. In our sample, 5.7% of all publications result in an erratum which is almost three times higher than the average percentage of issued errata in all Medline indexed clinical trial publications.[60] Because the publications in our sample result from registered clinical trials and list a clinical trial registration number in their acknowledgements, the difference is probably due to the observation that the journals in our sample follow to varying degrees the uniform requirements of the ICMJE which only accept publications of registered trials and also recommend standard ways to correct mistakes in publications.

Turning to the regression results, hypothesis 1 predicts that the likelihood of error increases with the prestige of scientific publications. Consistent with this prediction, we observe in Model 1 a positive and significant coefficient of all three variables that capture prestige in our model ($p < 0.01$). More specifically,

[60] Only 3 (0.06%) of these publications are not formal errata but are retracted from the literature. Estimating the models with or without these three retractions does not influence the results except for the effect of geographical distance in Model 6 which becomes significant ($p < 0.05$).

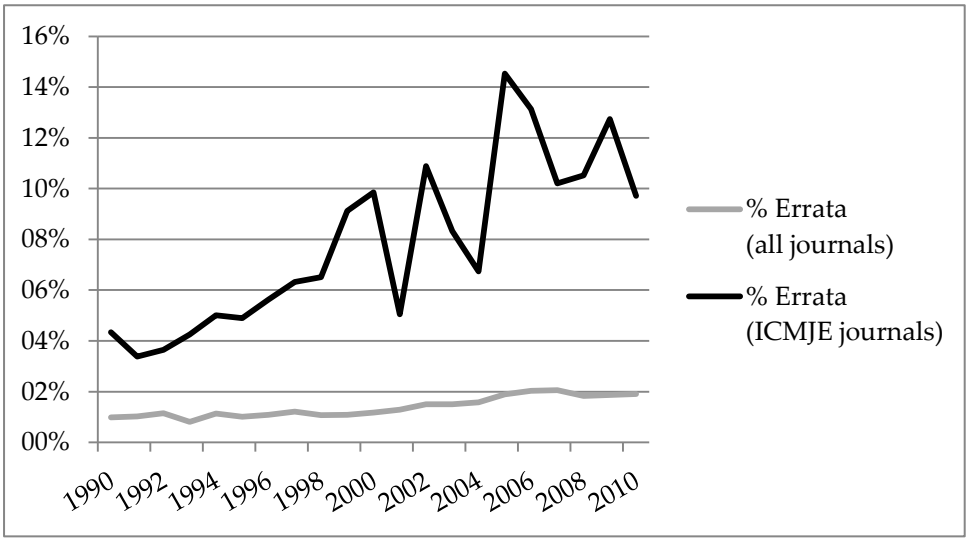

Figure 7.1: *Number of published errata on clinical trial research in PubMed-indexed journals*

scientific publications are more likely to contain error when they receive attention by means of comments and when they are published in journals that have either a higher Source Normalised Impact or are core-members of the ICMJE. After controlling for a number of alternative explanations in Model 4 these effects become less pronounced but particularly the effects of ICMJE and commenting ($p < 0.05$) remain positive and significant on the likelihood of error. The positive effect of commenting on error is also significant in case of content errors (Model 7), whereas comments have no effect on the correction of norm-related errors (Model 6), suggesting that they merely fulfill a function in scrutinising the content of publications.

Hypothesis 2 states that the likelihood of error in scientific publications increases with the geographical distance between authors. We test this hypothesis in Model 2-5 and show that larger geographical distances between authors significantly increase the likelihood of error ($p < 0.05$) in all models. Model 5 indicates that the hypothesised relation between geographical distance and the number of independent mistakes is only positively significant at the 10 percent level.

Hypothesis 3 predicts a positive relation between error in scientific publications and industry funded research. In Model 2-5 positive and significant results are obtained for this variable, while the coefficient of government funding does not

Table 7.1: *Descriptive statistics and correlation matrix*

	Mean	SD	Min	Max	1	2	3	4	5	6	7	8	9	10	11	12
1 Errata	0.057	0.231	0	1	1.00											
2 SNIP (ln)	1.228	0.550	0	2.46	0.16	1.00										
3 ICMJE member	0.174	0.379	0	1	0.18	0.69	1.00									
4 Comment	0.237	0.425	0	1	0.14	0.47	0.49	1.00								
5 Errata Propability	0.046	0.057	0	1	0.19	0.61	0.69	0.47	1.00							
6 Average distance (ln)	5.594	3.088	0	9.35	0.10	0.19	0.18	0.16	0.18	1.00						
7 Industry Funding	0.390	0.488	0	1	0.08	0.03	0.04	0.06	0.05	0.41	1.00					
8 Government Funding	0.147	0.355	0	1	-0.01	0.10	0.04	0.02	0.03	0.02	-0.33	1.00				
9 # Patients (ln)	5.570	1.757	0	12.24	0.12	0.26	0.29	0.20	0.25	0.34	0.20	0.10	1.00			
10 # Enrolment Countries (ln)	0.602	1.027	0	3.97	0.11	0.25	0.23	0.21	0.22	0.40	0.47	-0.14	0.47	1.00		
11 # Authors (ln)	2.175	0.526	0	4.52	0.10	0.34	0.28	0.25	0.26	0.32	-0.01	0.11	0.21	0.21	1.00	
12 Group Author	0.268	0.443	0	1	0.12	0.30	0.29	0.23	0.26	0.28	0.14	0.10	0.38	0.36	0.28	1.00

show any significance in these models. We also predicted in Hypothesis 3B that industry funded research disproportionally produces errors that can be considered deviations from the norms of scientific publishing. We test this hypothesis in Model 6-7 and show indeed that industry funding has a significant influence on the likelihood of norm-related errors ($p < 0.05$), but not on the likelihood of content-related errors. In addition, we also show that geographical distance between authors follows the reverse pattern. The likelihood of error in publications significantly increases with the geographical distance between authors in case of content-related errors ($p < 0.05$), but not in case of norm-related errors.

Several control variables show positive and significant results in Model 2-5. The number of patients and the number of authors show a significant and positive influence on the likelihood of error in model 2-5 although in one of the models this effect is only significant at the 10 percent level. Group authorship becomes positively significant in all models with the exception of Model 6 that explains the number of independent mistakes in a publication. The number of enrollment countries does not show any significance in the models, possibly due to the high correlation with alternative coordination variables.

We also show in Model 6-7 that the likelihood of norm error depends on the number of authors, whereas the likelihood of content error depends on the number of patients. This results may well signal that conflicting norms are more likely to occur in larger teams eventually leading to error in the information in the byline of publications. In contrast, the likelihood of content-errors is merely dependent on the complexity of the clinical trial which correlates with the size of the study.

7.5 Discussion

In this paper we provide a systematic attempt to explain the increasing prevalence of error in scientific publications which is a little studied topic up to now. We theorise about the production of error as a coordination failure in the writing process where knowledge present at distributed sites needs to be reduced to text that can be effectively communicated to a scientific audience. Error production increases with the distance between authors in this process, as distributed writing hinders effective peer-control and the creation of mutual understanding. It also increases with the production of scientific knowledge by 'external' partners such as firms as these actors are less familiar with the norms of scientific publishing.

Table 7.2: Determinants of likelihood of error in publications

	Model 1 Logit All	Model 2 Logit All	Model 3 Logit All	Model 4 Logit All
Prestige				
SNIP (ln)	0.466 *** 0.164		0.328 * 0.170	
ICMJE	0.729 *** 0.210		0.536 ** 0.221	
Comment	0.563 *** 0.167		0.433 ** 0.173	0.452 ** 0.182
Errata Probability				5.670 *** 1.566
Coordination				
Average Distance (ln)		0.077 ** 0.032	0.069 ** 0.032	0.065 ** 0.032
Industry-funded		0.405 *** 0.157	0.448 *** 0.160	0.451 *** 0.162
Government-funded		-0.072 0.216	-0.092 0.218	-0.024 0.217
Coordination (control)				
# Patients (ln)		0.152 *** 0.043	0.120 *** 0.043	0.131 *** 0.044
# Enrollment Countries (ln)		-0.027 0.072	-0.079 0.075	-0.074 0.075
# Authors (ln)		0.554 *** 0.148	0.265 * 0.158	0.332 ** 0.157
Group Author		0.503 *** 0.150	0.320 ** 0.155	0.356 ** 0.156
Constant		-6.009 *** 0.425	-5.693 *** 0.454	-5.676 *** 0.430
Disease Dummies	YES	YES	YES	YES
Year Dummies	YES	YES	YES	YES
LOG-LIKELIHOOD	-955.25	-955.16	-928.75	-924.42
N	4777	4777	4777	4777

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$. All regressions are estimated with robust standard errors.

Table 7.2: Determinants of likelihood of error in publications (continued)

	Model 5 ZINB All	Model 6 Logit Norm Error	Model 7 Logit Content Error
Prestige			
Comment	0.452 ***	0.281	0.527 **
	0.171	0.255	0.219
Errata Probability	-16.784 ***	3.836 ***	5.778 ***
	3.763	1.380	1.665
	In inflated part		
Coordination			
Average Distance (ln)	0.055 *	0.071	0.085 **
	0.031	0.059	0.037
Industry-funded	0.356 **	0.680 **	0.260
	0.167	0.283	0.190
Government-funded	-0.020	0.121	-0.119
	0.253	0.359	0.259
Coordination (control)			
# Patients (ln)	0.122 ***	0.036	0.174 ***
	0.042	0.070	0.051
# Enrollment Countries (ln)	0.020	-0.024	-0.113
	0.074	0.120	0.090
# Authors (ln)	0.262 *	0.753 ***	0.149
	0.137	0.232	0.187
Group Author	0.223	0.451 *	0.351 *
	0.159	0.245	0.183
Constant	-4.056 ***	-7.053 ***	-6.071 ***
	0.472	0.704	0.494
Disease Dummies	YES	YES	YES
Year Dummies	YES	YES	YES
LOG-LIKELIHOOD	-1154.2	-434.03	-689.13
N	4777	4777	4777

Notes. *** $p < 0.01$; ** $p < 0.05$; * $p < 0.1$. All regressions are estimated with robust standard errors.

However, the production of error is only part of the story, as for error to be present it needs to be detected and publicly acknowledged by the authors. We argue that this process of error detection is more likely to occur in prestigious science where institutions to self-correct are more responsive and where it can even be argued that in a feedback loop the potential of error exposure has become a constituent part of prestige itself.

Our empirical findings are consistent with these arguments. Using detailed information on the protocols, publications and published corrections of a large set of clinical trials, we reveal that the likelihood that a publications will be corrected depends on the expected impact of publications, on the type of funding and on the geographical distance between researchers. We also show that content-related errors are associated with larger geographical distances between researchers, norm deviating errors are more likely in case of industry-funded research projects. These effects occur simultaneously whilst controlling for many other characteristics of the research and writing process.

The findings suggest that the ability of science to self-correct is imperfect. The observation that correction is biased towards prestigious research seems counterintuitive as this research is generally considered to be of a higher quality and subject to rigorous peer-review. We infer from this finding that many more mistakes are present in the scientific literature which will never be corrected. Based on this finding one is inclined to cast doubt on the accuracy of scientific publications in general, although it can also be argued that efforts to correct mistakes are effectively allocated when they focus on prestigious research, as those publications are more likely to steer further scientific inquiry and to influence practical decision making.

Our findings further suggest that the increasingly distributed nature of scientific research poses new challenges with respect to the accuracy of scientific publications. New commercial and global contexts have been cited as contributors to the quality, impact and practical application of research findings (Gibbons et al. 1994; Hessels 2011). Our results do not argue with this finding, but point at least to a potential side-effect of distributed research. More specifically, as in distributed research projects traditional mechanisms to ensure internal peer-control erode, increased responsibility is put on institutions to correct mistakes in scientific publications.

One institution that has an effect on the correction of errors in this respect is the enforcement of explicit requirements of journals. Authors need to follow these guidelines in order to publish their results in scientific journals. The ICMJE is a

straightforward example as their uniform requirements for manuscripts increasingly mandate that authors provide insight in the conditions under which the research was produced. Such information may provide the necessary yardsticks to judge publications on error and to subsequently correct such mistakes. They may however also augment the occurrence of error, as unintended deviations from the particular publishing norms of the ICMJE become mistakes in itself which previously could not have been made. Our results indicate that this process is indeed occurring and that it disproportionally affect firms as relative 'outsiders' to the scientific system, judged from their higher likelihood of producing this type of norm-deviating errors.

A final important issue is to what extent the study of error presented in this paper is specific to the empirical setting we examined. We have argued that clinical trial research is remarkably standardised and that obtained research findings bear direct implications for regulatory agencies and patient care. High levels of standardisation and accountability facilitate unequivocal judgments about error and increase the relevance of its detection. An analysis of error across disciplines could therefore take such differences in standardisation and accountability as a starting point in order to analyse whether these factors indeed contribute to error detection and to the ability of scientific institutions to ensure the accuracy and consistency of publications.

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Jarno Hoekman contributed to all chapters and sections of this dissertation.

CURRICULUM VITAE

Jarno Hoekman was born on 4 November 1983 in Zwolle, The Netherlands. He studied Human Geography and Planning at Utrecht University and graduated cum laude in 2007. During his studies he worked as a junior researcher at the Netherlands Institute for Spatial Research (now: Netherlands Environmental Assessment Agency) where he was involved in a research project on European innovation policy. After graduation, Jarno started his PhD project which was carried out at both the School of Innovation Sciences, Eindhoven University of Technology and the Department of Economic Geography, Utrecht University. In the Spring of 2011, Jarno spent several months as a visiting scholar at the Science Policy Research Unit (SPRU) in Brighton, United Kingdom.

The research that Jarno Hoekman conducted has been presented at various international conferences as well as at national and European government agencies. He published in *Journal of Economic Geography*, *Research Policy*, *Journal of Informetrics*, *Technological Forecasting and Social Change*, *Economics of Innovation and New Technology*, *The Annals of Regional Science,* and *Journal of Economic and Social Geography (TESG)*. At present, he holds a position as a post-doc researcher at the Department of Clinical Pharmacology, University Medical Center Groningen.