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Networks of knowledge: The distributed nature of medical innovation

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Innovation in medicine is a complex process that unfolds unevenly in time and space. It is characterised by radical uncertainty and emerges from innovation systems that can hardly be comprehended within geographical, technological or institutional boundaries. These systems are instead highly distributed across countries, competences and organisations. This paper explores the nature, rate and direction of the growth and transformation of medical knowledge in two specific areas of research, interventional cardiology and glaucoma. We analyse two large datasets of bibliometric information extracted from ISI and adopt an empirical network approach to try to uncover the fine structure of the relevant micro-innovation systems and the mechanisms through which these evolve along trajectories of change shaped by the search for solutions to interdependent problems.

Introduction

In the area of innovation research a large body of literature exists on national innovation systems.[1] In this theoretical framework, geo-political boundaries are used to

[1] Classic references are, among others, FREEMAN (1995); NELSON (1993); LUNDVALL (1993); and EDQUIST (1997).

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define the ecology of organisations and regulatory settings where invention, innovation and diffusion of new products, processes and services take place. This approach is especially relevant in countering the limitations of those accounts of macro-economic processes of growth that overlook the role played by institutions, and by the connections between them, in transforming the economic and social landscape. It has also proved invaluable in its emphasis on the structural conditions that nurture the creation and communication of knowledge as a major source of competitive advantages for economies, industries and firms. The regional variants of the system approach to innovation (for example, COOK et al., 1997) address the problem of variety within national borders; sectoral ones (MALERBA, 2005) depart from geopolitical boundaries and define the unit of analysis by associating organisations that are interdependent across nations or regions and operate in the same product market; technology-based approaches (for example CARLSSON, 1995) privilege instead the composition of competences underpinning innovation across sectors.

A different framework is suggested in COOMBS et al. (2003) and METCALFE & TETHER (2003), where the authors highlight the need to focus on innovation *processes* and to investigate the way these are dynamically *distributed* across organisations as economic systems evolve. This is very close to the approach used in this contribution to analyse invention and innovation systems in medicine. Building on previous efforts (METCALFE et al., 2005), as well as on the fundamental contributions of BLUME (1992, 1995), GELIJNS & ROSENBERG (1995, 1999), in this paper we explore the evolution of medical knowledge in the areas of cardiology and ophthalmology. We do so by following over relatively long time periods the search for treatments for specific pathologies and by decomposing along the relevant *sequences* of innovations that have emerged over time, the distributed nature of knowledge, and the associated division of labour, across *epistemic*, *geographical* and *organisational* domains.

We take an *empirical network approach* to the study of medical innovation and try to uncover the fine structure of the innovation system and the mechanisms through which it changes from within, together with the knowledge it embeds. A network perspective, as POWELL & GRODAL (2005) argue in a recent survey, provides an ideal tool for the analysis of distributed processes of knowledge creation and diffusion spanning across boundaries and linking universities, government and industry both locally and globally. It has already been applied successfully to the study of innovation (see MURRAY, 2002; and OWEN-SMITH & POWELL, 2003 for recent contributions) and has a strong tradition in the field of bibliometrics (see for example, BHATTACHARYA et al., 2003; and LEYDESDORFF & MEYER, 2004).[2]

[2] Since the purpose of this paper is markedly empirical, it is beyond its scope to provide extensive discussions on networks or network tools for bibliometric analysis. For the first, we refer the reader to FREEMAN (1991) and POWELL & GRODAL (2005) and for the second to BARABASI (2002).

In this paper, we use techniques of network analysis to conduct a comparative study of two medical problems, one – relatively solved – in the field of cardiology, and one – relatively unsolved – in the field of ophthalmology. The first is *coronary artery disease*, which causes severe disability and more death than any other disease, including cancer, in affluent societies. The medical conditions associated with it are angina, ischaemia, unstable angina, myocardial infarction, arrhythmias, heart failure and sudden death. The now dominant surgical treatment for coronary artery disease is *percutaneous transluminal coronary angioplasty* (PTCA), heralded as one of the greatest achievements of modern medical research.[3] The second problem we explore is *glaucoma*. This is a disease of the eye, where progressive damage to the optic nerve leads to loss of vision. Global prevalence of the disease is estimated at 50-70 million persons and total blindness caused by Glaucoma at 7-8 million (GLAUCOMA FOUNDATION, 2003). The onset of glaucoma is slow and painless and the lack of obvious symptoms during the early stages has led to glaucoma being referred to as the 'silent thief of sight'. Currently there is no universally accepted definition of glaucoma and damage caused by the disease can be arrested, but not reversed. In contrast to treatment alternatives available for coronary artery disease, glaucoma remains very much a problem that has resisted scientific solution

The paper is organised as follows. In the next section we present the data used and illustrate our methodological approach. We then profile the clinical conditions of coronary artery disease and glaucoma and the nature of progress in clinical research in the two areas. We explore in some detail the epistemic, geographic and organisational dimensions of the division of labour in interventional cardiology and glaucoma research. We conclude with a brief discussion of the limitations of the work and of the paths we consider for further investigation.

Data and methodology

After reviewing the relevant medical literature with the aid of expert advice from staff of the Medical School of the University of Manchester,[4] we explore the composition and development over time of the problem sequences associated with treatments for coronary artery disease and glaucoma. The expected result is to provide valuable insights into the evolution of the epistemic dimension of medical research through time and across clinical fields. Secondly, we map the structure of the core networks of practitioners over a period of about thirty years, explore the distribution of

[3] A recent survey of general internists actively involved in patient care by FUCHS & SOX (2001) ranked coronary angioplasty 3rd (only behind MRI and CT scanning and ACE inhibitors) of the 30 most important medical innovations over the last 25 years.

[4] We are especially grateful to Dr. Luigi Venetucci, Prof. A.M. Heagerty and Prof. D. Hansen.

medical knowledge within and across innovation systems and uncover the organisational structures that underpin the growth of this knowledge.

For this purpose, we constructed two bibliographic datasets with records extracted from the Thomson Scientific (Institute for Scientific Information; ISI) data resources. The first is a bibliographic database of papers published in the area of interventional cardiology between 1979 and 2003. It contains basic details and bibliographic citations for 11,240 publications that were identified by keyword pairs crosschecked and validated by practitioners consulted in preliminary phases of research. The second dataset contains bibliographic information related to papers published in relation to glaucoma, which served as the main keyword. It consists of 12,654 papers published between 1970 and 2003. We note two interesting feature of the data. First, as is clear from Figure 1 there has been a logistic growth of publications in the two fields of focus.

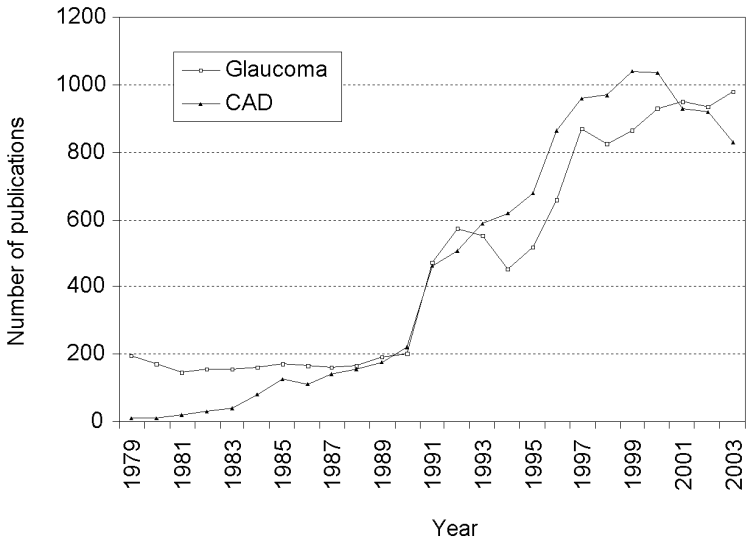

Figure 1. Growth of glaucoma and CAD Articles 1979–2003

The number of publications has increased remarkably in the last twenty-five years with especially fast rates of growth around 1990 and 1995 for both research areas. Rates of growth are also associated with rates of transformation, as the composition of paper cohorts has also changed considerably (we shall see this in some detail later). To explore the nature and scope of change and the interrelations between research efforts through time we use some of the information contained in the two datasets to construct a series of graphs that map, at different levels of aggregation, the epistemic,

geographical and organisational dimensions of the development of scientific knowledge in the areas of interventional cardiology and glaucoma.

We deploy techniques for structuring and visualising large networks. The tool of choice for this paper is Pajek, a special piece of software developed by mathematicians from the University of Ljubljana. The software can implement various algorithms to find and extract clusters from networks to enable analysis of the relationships among them. The network maps we created for illustrating our arguments used the Kamada-Kawai spring embedding algorithm which is based on the minimisation of the total energy of the system (BATAGELJ & MRVAR, 2003).

Epistemic division of labour

In this section of the paper, we briefly summarise the process of emergence of different streams of research in interventional cardiology and glaucoma[5] and then move to longitudinal network analyses of the bibliographic data we have gathered and structured.

Coronary artery disease

Coronary artery disease (CAD) results from a process called atherosclerosis through which plaque forms on the inner layer of the coronary artery and impedes the flow of blood to the heart. No symptoms are felt by the patient while deposits start to accumulate in the vessels, but as the disease progresses the patient experiences chest pains of varying degree as well as shortness of breath. If untreated, the eventual outcome of the process may be a heart attack.[6] The discovery of beta blockers and calcium channel blockers, in the 1960s and 1970s respectively, greatly contributed to alleviate the condition. However, although they provided relief for some of the most debilitating symptoms, they were not a remedy for their underlying cause. The development of coronary artery bypass surgery was a path-breaking contribution as it provided a mechanical solution to restore normal blood flow. Bypass surgery is a highly invasive surgical procedure through which blockages of coronary vessels are circumvented by using blood vessels harvested from other parts of the body (legs or chest walls). It is a long and complex procedure[7] and in spite of fierce disputes about its effectiveness in relation to the high risks it involved, it diffused rapidly during the 1970s.

[5] Detailed case studies are to be found in MINA et al. (2005) and CONSOLI et al. (2005), respectively.
[6] It only becomes painfully evident when the vessel is approximately 70% occluded (blocked). At this level of closure, the oxygen-enriched blood that the heart receives is only adequate when the body is at rest.
[7] It requires general anaesthesia, the use of a heart-lung machine to substitute for heart lung functioning during surgery and a lengthy post surgery recuperation period.

An alternative to purely pharmacological treatments and to bypass surgery emerged in the late 1970s and was to revolutionise the whole discipline of cardiology. Its champion was an angiologist from the University of Zurich named Andreas Gruentzig. Building upon established methods used for cardiac catherisation and transluminal angioplasty he developed a balloon tipped catheter of very minute proportions to dilate the constricted coronary artery. This new technique of percutaneous transluminal coronary angioplasty (PTCA) was successfully applied to animal models in 1976 and in 1977 succeeded on a human patient. The technique spread quickly thereafter particularly in the US and contributed to the establishment of interventional cardiology as a distinct medical speciality.

A vast number of improvements in devices and practice soon followed. These included the invention by Simpson in the early 1980s of the steerable balloon catheter, which allowed much greater ease in reaching the diseased vessels. But as new solutions were found, new problems emerged. The solution to the catheter problem and Greuntzig's balloon device to compress the plaque opened up new territory for it was soon found that the plaque often reformed after surgery (a condition called restenosis) with the consequence of dramatically reducing the efficacy of the treatment and raising its real cost. The solution to this new problem was the invention of the stent, an expandable metal device that is left in situ after the occlusion is eliminated to support the blood vessel wall and prevent the formation of new deposit. Interestingly, not even the stent provides a final solution because restenosis can occur on the inside of the stent. As a consequence, a number of drugs, devices and procedures are now being developed to prevent in-stent restenosis and further improve the already invaluable benefits of PTCA.

Glaucoma

While coronary artery disease has found (in PTCA) an effective, minimally invasive and increasingly popular treatment option, the same cannot be said for glaucoma, which to date has unclear causes and few treatments of limited success. Glaucoma is a chronic disease of the optic nerve whose main symptom is the progressive restriction of the field of vision. This initially involves loss of peripheral vision and is associated with an excavation of the optic nerve that can be detected by internal inspection of the eye. Although specialised textbooks abound of theories, there is neither agreement nor strong evidence of the cause inducing the degeneration of the optic nerve and leading to the loss of sight.

Up until the early 1950s the dominant paradigm in the study of glaucoma considered abnormal intra-ocular pressure (IOP) as the origin of the disease. As a consequence, research efforts were directed to understanding the reasons underlying the increase in IOP. In this frame of analysis, two types of glaucoma were identified and classified on

the basis of the relative openness or closeness of the angle of the eye comprised between the pupil and the iris. From the 1950s the association of glaucoma and IOP started to be looked at with scepticism and a variety of alternative hypotheses started to develop. IOP is now simply considered as one among many potential causes of the disease and glaucoma is generally interpreted as a complex optic neuropathy.

As the fundamental understanding of the disease changed over time, so did the technologies developed for therapeutic and diagnostic use. When IOP was the focus of clinical research, this was the privileged target for surgery and pharmaceuticals. The same can be said for diagnostic devices. Among them, tonometers were used to assess IOP, perimetry tools to measure reductions in visual field, ophthalmoscopic and gonioscopic devices to inspect the structural features of the optic nerve. While useful to some extent, none of these technologies has emerged as an ultimately satisfactory solution and although numerous innovations, among which computers and lasers, have found useful application in the field of glaucoma, much of the most recent state-of-the-art treatments still target IOP reduction. Naturally, if this is not the only cause of the disease, only a minority of patients can really benefit from this kind of treatment and the chances to reverse glaucomatous damage across the spectrum of potential causes remain very limited and the scope for investigation broader than ever.

The evolution of research paths

In the evolution of scientific and technological knowledge, trajectories often emerge in the form of sequences of innovative ideas (METCALFE et al., 2005). These involve coherent directions of change and signal the cumulativeness of research activities whose results build on previous knowledge. Furthermore, they involve specific configurations (for example, technical designs) embodying ways of combining knowledge which become formal of informal standards (UTTERBACK, 1994) in the search for solutions to problems. The emergence of trajectories (DOSI, 1988) implies that evolution of knowledge is not random. At the same time the direction of progress can very rarely be seen *ex ante*, which means that there can be little determinism in the process through which trajectories of change take form. Research paradigms emerge through complex processes and out of the highly dispersed activities of practitioners who, however connected through the institutional ties of the relevant communities, have different experiences, competences and visions. If it were not so, no novelty could ever be introduced into the system because every agent would either have identical thinking or converge to the same frame of thought and sooner or later the innovative potential of the existing search space would become sterile.

In the evolution of medical knowledge, phases of consolidation of past results coexist with exploration of new search spaces. Mapping the development of clinical research should therefore uncover dynamics of convergence and divergence between

streams of investigation; areas of intense density and areas where contributions are scarce; and single or multiple trajectories that follow one another or coexist in the same time period. Techniques of longitudinal network analysis allow us to do precisely this. Figure 2 shows developments in research in interventional cardiology over the past three decades.

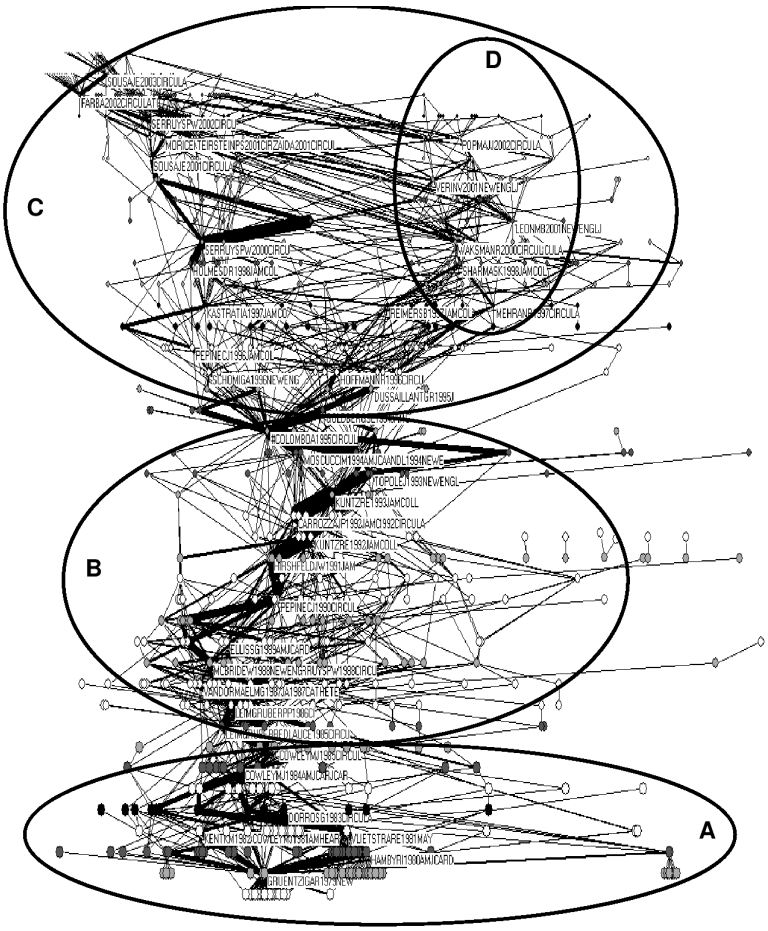

Figure 2. Network evolution of medical knowledge for PTCA

The map is obtained from paper citations and displays from bottom to top key papers that are connected through citations from 1979 to 2003. To construct it we used a variation of the Main Path Algorithm, described in BATAGELJ (2002), which enables a parsimonious longitudinal examination of citation networks and illustrates branches of

developments that the medical community itself selects out as especially important by quoting the relevant contributions. Among all possible "chains" of citations from the most recent records to the oldest, the algorithm computes the paths that are most frequently encountered.[8] The resulting visualisation permits an appreciation of, at each time period and across time periods, diverging and converging streams of developments, that is to say the trails pursued by the medical community in the search for solutions to the problem of coronary artery disease.

Inspection of the map reveals that nodes broadly contained in cluster A are strongly connected to the original breakthrough of Gruentzig and clearly illustrate a phase of intense exploration of the search space opened up by the first appearance of coronary angioplasty. Analysis of a number of these papers reveals that these are concerned with the efficacy of PTCA and the conditions under which the procedure could work. Among them, special mention should be made of the study by COWLEY et al. (1985) which was produced under the sponsorship of the National Heart Lung and Blood Institute and provided early evidence on the effective use of balloon angioplasty procedures in medical centres across the US and in other countries.

Between 1986 and 1995 (cluster B) papers reported various developments of the technique and began to focus on the unexpected problem of restenosis[9] (for example, PEPINE et al., 1990). During the latter part of the 1980s the application of stent as a promising solution gathered momentum and it is in relation to this specific device that we can explain the visible convergence of the epistemic network between areas B and C to mark a new step change in the progress of clinical research. Until the mid 1990s, results from clinical trials where stents were used failed to meet the expectations that were raised because of the great variability in the outcomes of surgery. The watershed in the evolution of the network (studies by FISCHMAN et al., 1994 and COLOMBO et al., 1995) coincided with the emergence of persuasive evidence of the advantages of stenting compared to 'simple' balloon angioplasty and to the finding that the success rate of the procedure heavily depended on the placement of the stent graft.

Subsequently, new scope for exploration opened up to new contributions (papers in cluster C) whose aim became not only to improve upon the use of stents but also to deal with the problem of the plaque reforming inside the stent (in-stent restenosis). This very problem also triggered the emergence of parallel trajectories of research. Among the various solutions that were explored in the last period we consider are stents coated with drugs that are locally delivered to the point of the lesion, pharmacological therapies that precede or follow stenting, and radiation therapies (cluster D).

While the angioplasty network developed rather consistently along a highly coherent path, the citation network of glaucoma, which is fully comparable in size, displays far less unity and the patterns of convergence are partial and untidy.

[8] For details on the use of the algorithm, see RAMLOGAN & TAMPUBOLON (2004).
[9] Restenosis is the re-narrowing of the artery after treatment.

As shown in Figure 3, when the paradigm of IOP started to be challenged towards the end of the 1950s, papers cluster distinctively in groups A, B and C. Around the 1980s, a partial convergence appears to take place in cluster D, after which clusters E and F branch out to occupy the extreme areas of the diagram after the mid-1990s. The early years were a highly exploratory period as indicated by the horizontal deviations from core streams. These correspond to the growth of complementary fields of analysis, whose building blocks are the much-cited treatises by POSNER & SCHLOSSMAN (1948) on the clinical course of glaucoma, and by CHANDLER (1952) and BARKAN (1954) on pupillary block and angle-closure glaucoma.

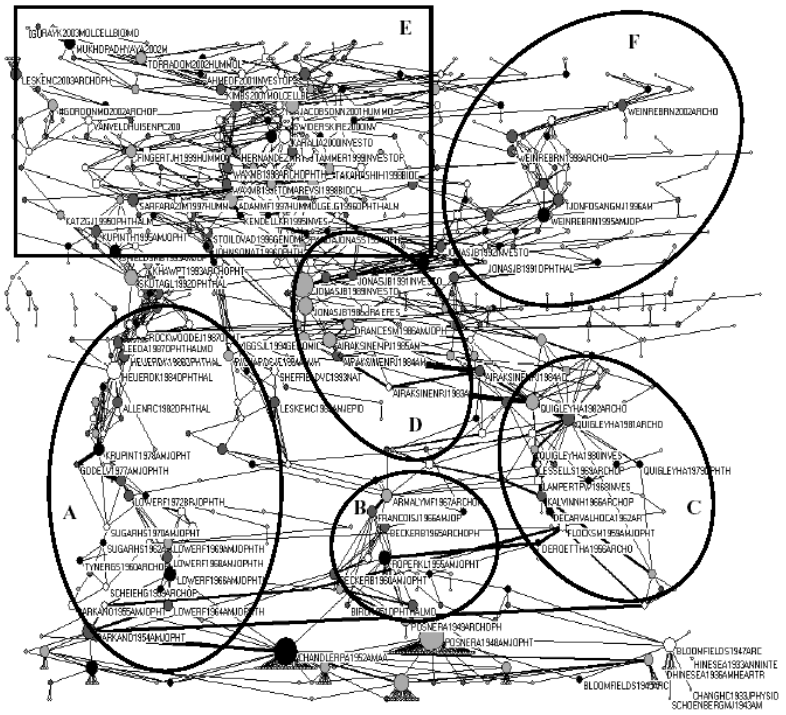

Figure 3. Network evolution of medical knowledge for glaucoma

Cluster A (roughly 1954–1987) contains papers mainly focused on Primary angle-closure glaucoma.[10] Papers in cluster B (roughly 1949–1967), investigated hereditary forms of glaucoma. The connected cluster C (roughly 1956–1982) targets the refinement of the concept of Open-Angle glaucoma and the process of aqueous outflow

[10] The most recent ones in this group (i.e. after KRUPIN et al., 1978) analyze various results obtained with the technique of filtration surgery.

through experimental glaucoma. The important works by Quigley (see QUIGLEY et at., 1981; and QUIGLEY, 1982) on the mechanisms underlying optic nerve damage also figure prominently in this cluster and it is through his contributions that this cluster connects with cluster D (roughly 1983–1991), where the system temporarily appears to converge. Here we find turning points in the growth of medical knowledge on glaucoma, such as the contributions of Airaksinen (see AIRAKSINEN & HEIJL, 1983), Drance (see DRANCE et al., 1986) and Jonas (see JONAS et al., 1988), which are considered the foundations of modern ophthalmology. These works to some extent unified the dispersed hypotheses previously formulated on the damage of the optic nerve by discovering the retinal nerve fibre layer and the association between its changes and the progression of glaucoma.

From this point onwards, divergent streams of research can be identified to show how modern ophthalmology has further evolved across disciplinary boundaries. Cluster F (top far right) contains a number of technology-related papers that deal with the repetitive scanning of the optic nerve head, notably by means of Scanning Laser Polarimetry. Cluster E (top left), instead contains studies on a number of developments following the discovery of the Trabecular (meshwork) Induced Glucocorticoid Response protein (TIGR) gene in 1993. Interestingly, in this cluster journals chiefly concerned with ophthalmology coexist with publications in the area of genetics and molecular biology, signalling a drastic shift not only from the study of IOP, but also from analysis of the structure of the optic nerve.

Comparison between Figure 2 and Figure 3 reveals more streamlined patterns of research in interventional cardiology than in glaucoma. While this may signal that a robust trajectory has emerged in the first, in the second research efforts are more scattered, and although coherent patterns can be identified over time, exploration of the search space appears to take very different streams. The objection could be advanced that this is due to the different time periods considered for CAD (30 years) and for glaucoma (50 years), which are justified by the emergence at different times of comparably radical breakthroughs (the invention of coronary angioplasty and the challenge to the IOP paradigm respectively). In fact, as the algorithm underpinning the graphs computes the longitudinal connectivity of the network, consideration of longer time periods may favour the elimination of variety because the selective mechanism of citations progressively weeds out paths that have produced relatively less good results in the long run. This seems to be precisely the case. The map we can obtain using the last 30 years of data on glaucoma reveals equally fuzzy structures.

A second problem that could distort the comparison could derive from the strategy used to retrieve the publications records, which relied on the specifically chosen keywords. Ultimately, the search strategies conformed to textbook knowledge and expert advice. Moreover, the paths illustrated in Figures 2 and 3 are remarkably fitting ‘quantitative’ complements of virtually all the qualitative accounts of long-run progress in coronary disease and glaucoma contained in the relevant medical literatures. Finally, there is a chance that the entropy of the network structures may depend on the way in

which titles, abstracts and references are compiled in the relative scientific domain. However, we found no such difference in the practices adopted in CAD and glaucoma research.

A difference can instead be found in the patterns of co-authorships in the two networks. It has been widely recognized that progress in science and indeed innovation, is characterized by extensive and increasing degree of collaboration. WALSH & BAYMA (1996) for example pointed out that the paper which announced the discovery of the quark listed 398 authors from 34 institutions across 5 countries. Multiple-authorship is also a characteristic feature of the medical domain. Figure 4 shows the distribution of authorship per paper in our databases.

Single authorships account for 6 and 16 percent in Interventional Cardiology and Glaucoma respectively. However, whereas 85 percent of the papers in Glaucoma were authored by no more than 5 persons, in the case of cardiology the respective figure was just 46 percent. Larger teams co-author in interventional cardiology and this may to some extent reflect differences between fields that may be due to such factors as research cultures and incentives.[11]

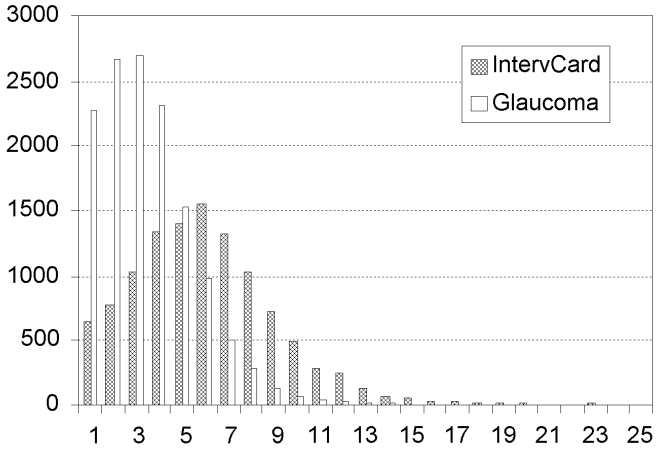

Figure 4. Distribution of co-authorships in interventional cardiology and glaucoma, 1968–2003

[11] Various explanations of the phenomenon in the literature have been classified by WAGNER & LEYDESDORFF (2004) according to environmental factors within which science operates, for example, the differences in incentives/funding available within and across countries; and to the connections within and around science, particularly the increasing capacity to conduct science globally and the increasing connectedness of scientists within and across countries for reasons related to transdisciplinarity and the accessibility of internet related technologies. Wagner and Leydesdorff further suggest that these explanations cannot be supported by a review of the data and instead propose that the growth of international co-authorships can be attributed to self organising phenomenon based on preferential attachment, an issue which has been explored in various papers, see NEWMAN (2000) and with respect to interventional cardiology in RAMLOGAN & TAMPUBOLON (2004).

International division of labour

Our concern in this and the following section is to further examine the issue of the distributedness of innovative efforts in medicine and to do so with regard to the geographic and institutional structure of the glaucoma and interventional cardiology networks that emerged over the last few decades. We focus in particular on the collaborative dimensions that underlie what progress has been made in these two medical areas. This serves to illustrate the nature of the division of labour which transcends very clearly the boundaries of national systems. As we have observed in our data some of the most important clinical trials are distinctly international in scope and the reasons for this and consequences cannot be fully appreciated if one were to proceed from a national system perspective. This is not to deny but rather to complement understanding of intra national connections between firms and local knowledge bases.

As our data reveal, dealing with these major health problems which afflict mankind is a burden shared, albeit unevenly, by the international community. We extracted addresses[12] from the bibliometric records and coded the data by locality, either US state (because of the preponderance of research and publishing activity across the US) or country to derive the respective network maps for the two medical areas shown in Figures 5 and 6.[13] The data show more states/countries interacting in the case of glaucoma research than in interventional cardiology. Some 157 units were identified in the former compared to 116 in cardiology. We isolated those nodes which related to single authored papers or multiple authored papers from the same country/US state and constructed the respective networks to give a visual appreciation of the distribution of collaborative research activities across countries over the period. The interventional cardiology map therefore relates to 106 nodes (countries/US states) while the glaucoma map accounts for 137 nodes.[14]

It is apparent from even a casual glance at these maps, that a lot of collaborative publication (and by inference research activity) takes place within the US, indeed, 47 states are represented in the glaucoma network while all 50 states are present in cardiology research. It also appears from the maps that there is a greater quantity of collaborative publication among cardiology researchers than is the case for glaucoma. Indeed this is confirmed by the network density of the two maps. This statistic measures the proportion of links which exist between all members in a network relative to potential links if all nodes connected with each other. The interventional cardiology network has a density of 30 percent, approximately three times higher than that of glaucoma.

[12] Just over one thousand records in the glaucoma database which relate mainly to the pre-1970 period did not contain author addresses.
[13] Nodes were further classified by shape, triangle for US states, squares for European countries, white circles for countries from Australasia and dark circles for others.
[14] All maps were energised by the Kamada-Kawai algorithm in Pajek.

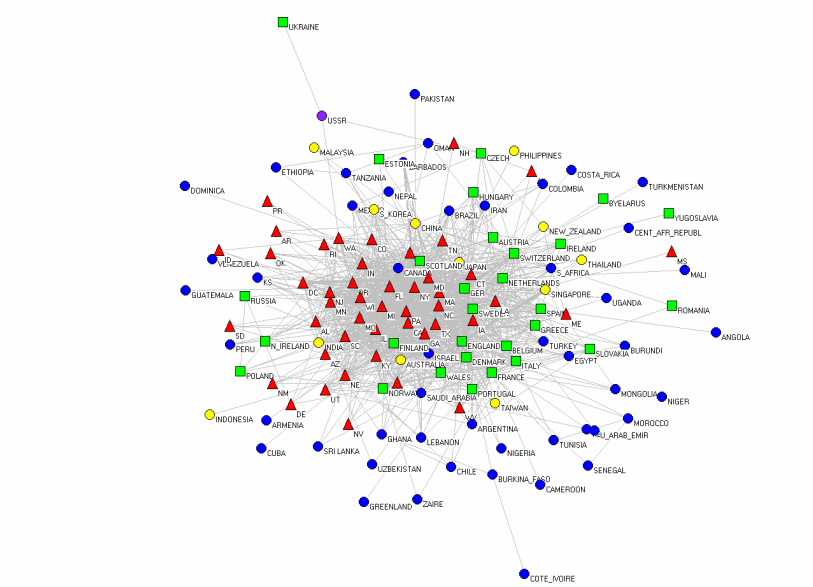

Figure 5. The galucoma country network

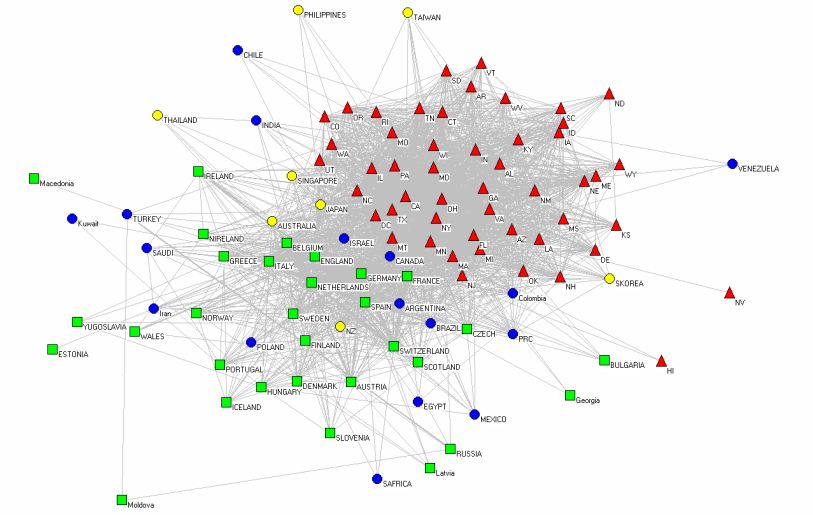

Figure 6. The interventional cardiology country network

The diagrams show a distinctive patterning in the clustering of nodes. Countries from the periphery tend to be linked with those in the denser part of the network and by and large these are Third World countries and those from Eastern Europe. There generally seems to be a partitioning between the American states and European countries which is particularly clear in the interventional cardiology network. Some important innovators such as Singapore, Japan, and Israel as well as large emerging economies such as Brazil and India occupy the frontier between the North American and European coalitions (with Canada almost equally distant from New York and France). No such ordered pattern is found in the Glaucoma network.

One of the obvious questions that could be posed when viewing these rather complicated networks is who are the most important actors? There are various measures used in the literature to examine this question and in this context we use a normalised degree centrality statistic.[15] This is the degree centrality of each node expressed as a proportion of the maximum degree – that is the number of other nodes in the network (DE NOOY et al., 2005, p. 128). Table 1 shows the centrality rankings for the top twenty nodes for the two networks. As is intuitively obvious from the diagrams the American presence is particularly weighty occupying 14 of the top 20 positions in Glaucoma and 15 in the case of Interventional Cardiology. England, Germany, Canada and France are common to both networks although their rankings are different while Finland and Japan only appear in the Glaucoma top twenty and the Netherlands in the Cardiology top twenty.

In graphing a map for the whole period we delete the inter-temporal dynamics and risk providing an overly static picture of the evolution of the international collaborations. In an attempt to understand even in a limited way how the network has evolved, we have partitioned the data and constructed networks for earlier periods using 1989 as a cut-off period. The data allowed us to construct a network for Glaucoma between 1968 (the earliest recorded address) and 1989 and for Interventional Cardiology between 1979 and 1989. We then recomputed the centrality scores for the respective lists in third and sixth columns of Table 1 and established the rankings again based on the centrality measure. Researchers from Kentucky, Japan, Mississippi and England seemed to have made the most progress in terms of cross-country collaborations in Glaucoma.[16] Texas was the star performer in Interventional Cardiology, climbing 26 positions to share the number one rank with California and France.

[15] A number of measures for centrality are available in the social network literature (see also the discussion of their limitations in BORGATTI, 2005). For the purpose of this exercise the normalised degree centrality seems sufficient.

[16] In order to explain the movement in the ranking of individual countries/states a different but complementary framework of analysis, and data on the rates of internal incentives to collaborate, is needed.

Table 1. States centrality

Glaucoma			Interventive cardiology		
	Centrality ranking			Centrality ranking	
	1968–1989	1968–2003		1978–1989	1978–2003
CA	2	1	FRANCE	18	1
NY	1	2	CA	2	1
ENGLAND	18	3	TX	27	1
MD	4	4	CANADA	8	2
MA	2	5	GERMANY	15	2
PA	4	6	NY	13	2
GER	18	7	OH	18	2
TX	8	8	MA	1	3
FL	9	9	PA	3	3
CANADA	6	10	FL	0	3
MI	27	11	MN	6	4
IL	7	11	DC	10	5
FRNACE	20	12	NC	17	6
MO	9	12	MD	3	7
NC	11	13	ENGLAND	0	7
FINLAND	20	13	MI	16	8
JAPAN	37	14	GA	8	9
KY	40	14	NJ	n.a.	10
WI	13	14	NETHERLAND	18	11
OR	24	15	WI	6	12

0 = isolate
n.a. = not in the network in time period

New Jersey, which had no publication between 1979 and 1989 achieved a ranking of 10 by 2003 while England moved from a zero score (no cross country collaborations) in the earlier period to reach number 7.

Organisational division of labour

In the previous section we explored the international dimension of the division of labour in clinical research in the fields of glaucoma and interventional cardiology. In this section we focus on the institutional distributedness of the networks and provide evidence of the range of complementary competences that underpin progress in medical science. BLUME (1995) and GELIJNS & ROSENBERG (1995) have previously characterised the innovation process in medical devices in terms of the interaction between multiple disciplines and multiple agencies with close relations emerging between firms, clinicians and academic scientists. We have been able to locate in our

two networks universities, hospitals, independent research institutes, foundations, government departments and firms.

Hospitals comprise a fundamental component in medical innovation systems because they are the loci of clinical practice. It is only through practice that new treatments reveal their latent potential as well as their drawbacks and that serendipitous observations are made that may hold the key to the formulation of new ideas for treatments. Among them, research hospitals (and research foundations or research institutes where clinical services are also delivered) are especially important institutions. On the one hand, they tend to be teaching institutions and to form integral parts of academic institutions. They are therefore prime mechanisms for the intergenerational diffusion of knowledge, whose tacit components are often predominant in the field of medicine. On the other, research hospitals provide the organisational links between basic science, mostly produced in universities, with experimental phases of research where firms are involved as partners in the development of prototypes (be they drugs or devices) or as suppliers of products that must be tested in clinical trials in order to receive market approval from regulatory authorities. In this case, firms often act as sponsors for the trials.[17]

In Table 2 we classified by type of institution all the addresses extracted from the databases to show the percentage institutional composition of the networks.[18]

Table 2. Organisational distributedness

	Interventive cardiology		Glaucoma	
Type	No of addresses	%	No of addresses	%
University and University Hospitals	17115	55.0	18443	67.0
General Hospitals	8269	26.6	4934	17.9
Firms	2560	8.2	842	3.1
Foundations/Institutes/Government	2277	7.3	2392	8.7
Other	905	2.9	914	3.3
Total	31126	100.0	27525	100.0

Proportionally, we notice stronger involvement of Universities and University Hospitals in the area of glaucoma, and weaker relevance of General Hospitals than in Cardiology. Part of the reasons for this may reside in the differential success in tackling

[17] In this respect, it is important to emphasise that papers are not always less informative source of applied research output than patents. In the field of medicine, patenting often precedes clinical trials where firms have their proprietary artefacts (be they drugs or devices) tested for performance and safety. As a consequence, publications of the results of trials in the medical literature can be better indicators than patents of impending innovation.

[18] This was based on systematic inspection of address fields and the use of several rules of thumb to allocate to institutional types where it was not clear from the data. The classification proved sufficiently robust against a random selection of the final allocation by internet search of the organisations.

the disease, so that General Hospitals, where 'normal' practice is carried out, play a bigger role in the domain where knowledge of the disease is more advanced. We also noted a stronger presence of firms in interventional cardiology than in glaucoma. This may also signal that involvement in science of drug and device producers grows not only with the size of the market, but also with the stage of development of treatments in relation to fundamental understating of the disease. Inspection of the firms contained in the datasets also reveals that in CAD, small firms (especially engineering-based device producers) are much more numerous and diversified in their range of competences than in glaucoma, where large pharmaceutical companies dominate in spite of a fairly limited range of alternative treatments.

We used the addresses of authors to construct networks that show the linkages among organisations. Figures 7 and 8 illustrate the rich ecologies of organisations from which co-authored papers in our glaucoma and interventional cardiology databases are located. These figures have been extracted from the wider networks that define the collaborative relationships in both fields. In the case of glaucoma the network is made up of 3980 nodes compared to the 3671 nodes for interventional cardiology. As in the country level analysis, the density of the cardiology network far exceeds that of glaucoma, this time by a factor of 5. However as the density figures imply, these networks are only loosely connected internally, 0.1 percent in the case of glaucoma and 0.5 percent for interventional cardiology. Notwithstanding, it is virtually impossible to visualise the underlying structure of these networks given the number of nodes. In order to derive the networks illustrated in Figures 7 and 8 we selected only those nodes with 10 or more connections in the case of glaucoma and 20 or more in the case of angioplasty.[19,20]

The variety of organisations that engage in scientific collaborations are partly explained by the need for innovation to bring together different skills and capabilities that are rarely found embodied in the same institution. Technological breakthroughs often demand the simultaneous use of different sets of skills and knowledge bases in the innovation process (ARORA & GAMBARDELLA, 1990; POWELL et al., 1996).

[19] These thresholds enabled us to view the relationships between 276 glaucoma nodes and 503 interventional cardiology nodes.

[20] Nodes were coded to facilitate visual identification and we privileged in the diagram labelling those nodes that are firms (triangles) and those national/international institutions and foundations (squares). Universities and university hospitals are diamond shaped; general hospitals are coded as white circles while dark circles resisted classification by our schema. Several distinctive clusters connected to the main network by 'gatekeepers' are evident in the diagrams. For example Cluster A in Figure 7 represents a multi-centre in France (DELCOURT et al., 1995) in which the 'gatekeeper' is INSERM, the National Institute of Health and Medical Research.

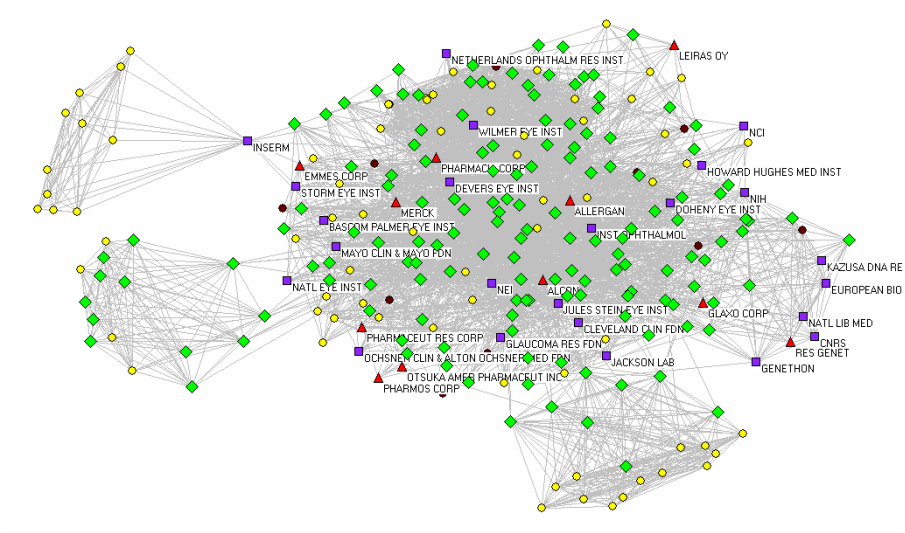

Figure 7. Organisational collaborations in glaucoma

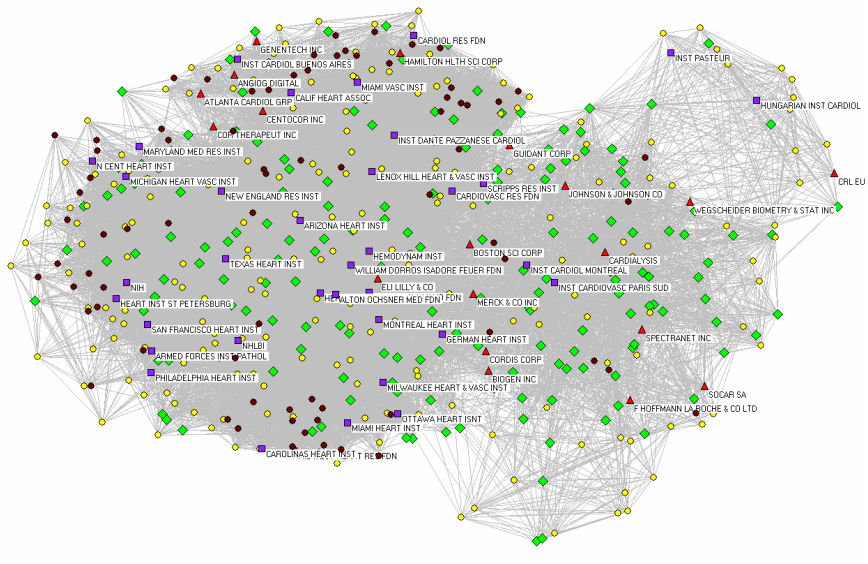

Figure 8. Organisational collaborations in interventional cardiology

The literature on innovation and inter-organisational learning has also highlighted the set of linkages and the resulting collaboration networks are the key vehicles through which organisations obtain access to external knowledge. Interfirm linkages in particular have been shown to provide two kinds of network benefits namely resource sharing, that is, allowing firms to combine knowledge, skills and physical assets; and, access to knowledge spillovers, serving as information conduits through which news of technical breakthrough, new insights to problems or failed approaches travels from one firm to another (AHUJA, 2000). To illustrate the nature of firm involvement in scientific networks and the degree of diversification of research efforts in interventional cardiology and glaucoma, we chose from the dataset a sample of 5 firms with high degree (normalised) centrality scores, of which one, Merck straddles both domains. We then extracted from the main networks subsets of nodes directly associated with these firms to produce a series of firm-centred networks (Figures 9 to 14). We comment briefly on these networks drawing on secondary data:[21]

Figure 9 shows the network of collaborations in interventional cardiology research of Centocor Inc**.** This is a North American biotech company specialising on treatments for heart attack, unstable angina, coronary artery disease, Crohn's disease, and rheumatoid arthritis. In relation to coronary artery disease, its core business is the supply of drugs that are used to complement percutaneous coronary interventions.[22] After joining forces with Fujisawa Pharmaceutical Ltd for market approval and marketing of its leading product in Japan (1996) and with Eli and Lilly & Company for marketing the same product in the US, Centocor merged with Johnson & Johnson, a major player in the broader medical sector, in 1999 but maintained its name.

Centocor's network of collaborations derives from participation in four large US-based randomised trials where its main drug (called ReoPro) for the treatment of coronary conditions was successfully tested in combination with balloon angioplasty, atherectomy and stenting procedures. In the core of the network we find the Research Hospitals where the trials where conducted. We note the presence of some of the key-players in the CAD network, the closest being the Cleveland Clinic Foundation, the Baylor Medical College and Duke University Hospital, who are key research organisations in the field ranked by global centrality indices 2, 70 and 1 respectively.

[21] These are not intended as fully-fledged case studies but simply as ways to enrich our appreciation of the nature of inter-organisational linkages in medical innovation systems.

[22] To be more specific, these are monoclonal antibodies that prevent ischemic complications for patients undergoing PTCA and can function as substitutes for conventional medical therapy when this is not effective in reducing pains from unstable angina.

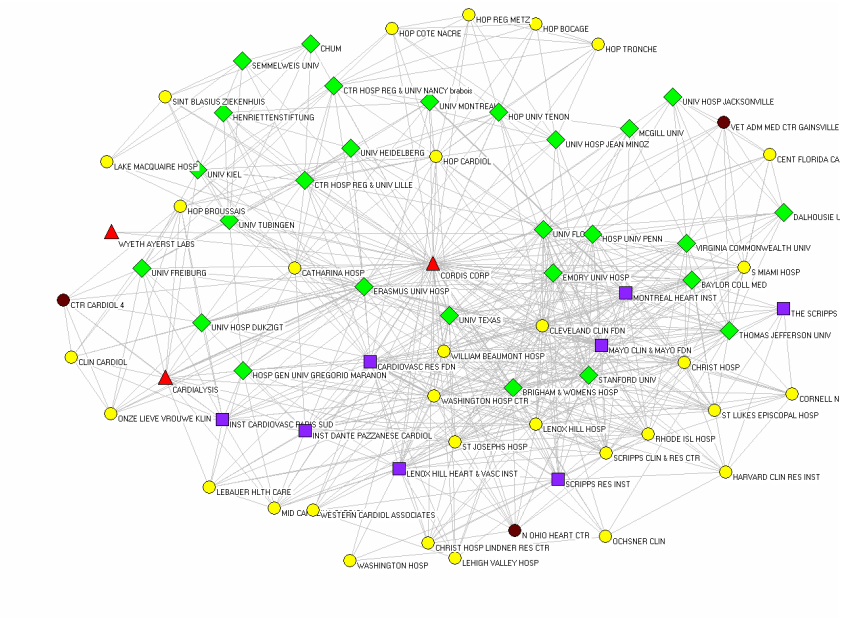

Figure 9. The Cordis network

We note also the connection with Eli Lilly & Co. Inc., who own the trademark of the product, and with Chronolog Corporation, who supply reagents and reagent kits which are used to measure the effects of drugs on the function of platelets[23] and is located, as is Centocor, in Pennsylvania.

The second example we selected from the interventional cardiology is Cordis**,** one of the world leaders in research and supply of devices for vascular diseases. It employs 7000 people worldwide distributed in four business units/subsidiaries: Cordis Cardiology for cardiovascular disease management; Cordis Endovascular for the treatment of peripheral vascular and obstructive diseases; Cordis Neurovascular, Inc. for neurovascular management of stroke, and Biosense Webster, Inc. for electrophysiology and medical sensor technology in cardiovascular procedures. In 1996, it merged with Johnson & Johnson Interventional Systems Co. to become a subsidiary of Johnson & Johnson but continues to operate under its original name.

[23] Platelets are those bodies present in blood that form clots to stop bleeding.

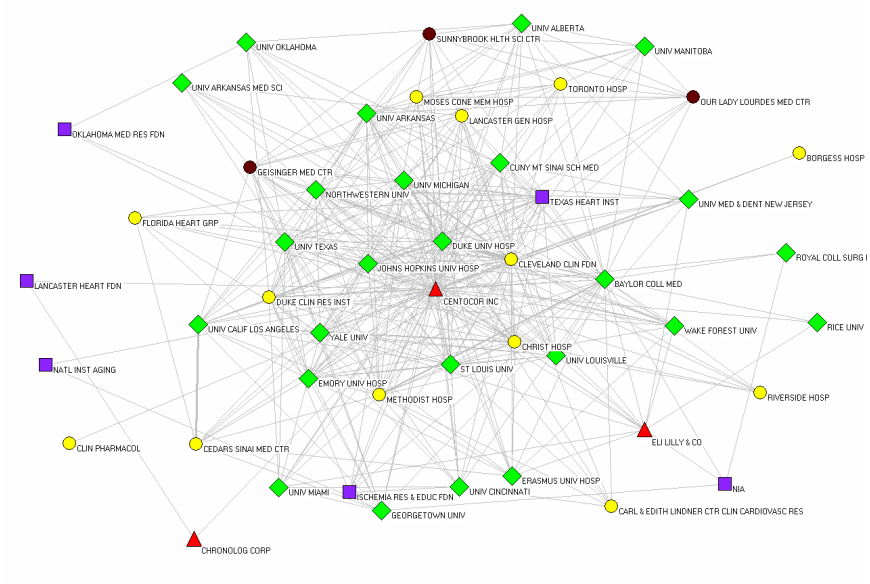

Figure 10. The Centocor network

Since its foundation (1959, Miami) it has maintained a strong record of innovations in less invasive treatments for coronary artery disease. These include some of the first lines of guiding catheters for PTCA and the very first balloon expandable stent (the Palmaz-Schatz stent) which received market clearance for the US in 1994 and is widely recognised as a true step-change in the evolution of interventional technologies. The network of collaborations of Cordis is broad and especially notable if we consider that as a medical device company, as opposed to pharmaceutical or biotech companies, involvement in medical science tends to be limited to the publication of results from clinical trials. In Figure 10 we notice participation in European-based trials (it has a close link with Erasmus University Hospital (Rotterdam), where angioplasty procedures were pioneered in Europe) as well as in US-based trials, which are found in the denser area of the network in the top left corner of the map. We also notice the link with Cardialysis, which is a Rotterdam-based contract research company specialised in the organisation and management of large clinical trials in the field of cardiology. Interestingly, its top three academic partners in research are Tubingen Univerisity (Germany), the Instituto Dante Pazzanese (Brasil) and the Hospital of the University of Pennsylvania (US) which suggest a pattern of international diversification in research strategy.

Allergan is a North American global pharmaceutical company specialised in eye and skin care. It employs 5000 people and has marketing and sales capabilities in 100 countries. As of the beginning of 2002, Allergan had the largest sales force in ophthalmology in North American, Europe, Latin America and Asia, outside of Japan. As far as R&D is concerned, Allergan invest heavily in new ophthalmologic products and couple a diversified range of industrial and academic collaborations with various licensing agreements for compounds at different stages of clinical development.

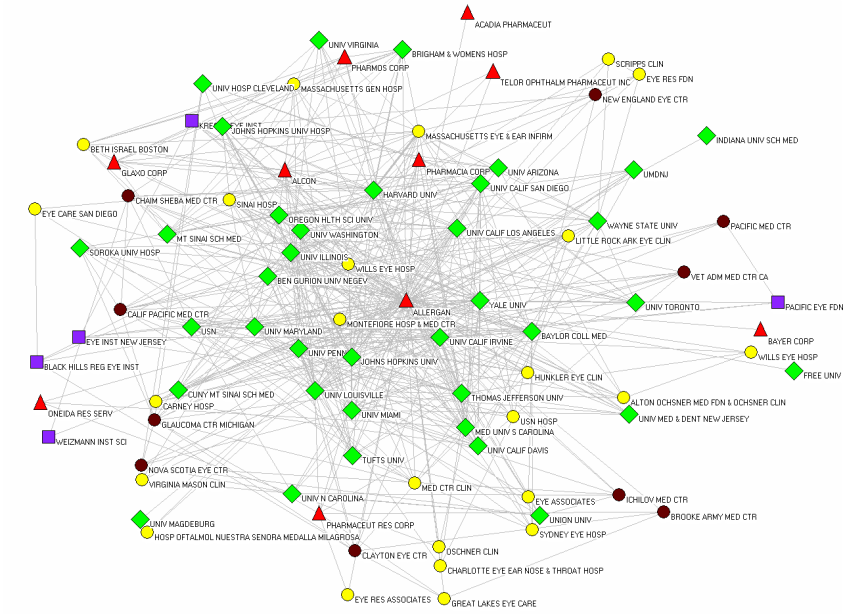

Figure 11. The Allergan network

With respect to glaucoma, their central presence in the network represented in Figure 11 is due to their research in products for the reduction of IOP (Lumigan®, Alphagan® and Alphagan®P).[24] The institutions with which Allergan have collaborated most often are the University of California Irvine, the University of Arizona and the Weizmann Institute (Israel). Their centrality scores are 34, 122 and 350 respectively. It is interesting to note the close proximity of Allergan, whose

[24] The three drugs are all indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Alphagan®P is a reformulation of Alphagan® to reduce the incidence of ocular allergies. Lumigan® is used for patients who are either intolerant or weakly responsive to other IOP-lowering medications.

headquarters are in California, to the University of California Irvine and a crown of North American academic partners (which also include the other campuses of the University of California). A number of connections with large industrial partners can also be found: note the links, among others, with Acadia, Pharmacia, Bayer and the joint participation of Allergan, Glaxo, Pharmos, and Alcon in a 1996 research trial (centre-right side of the map) with major academic institutions including Harvard University, Beth Israel Hospital and City University of New York.

Alcon is a Nestlé-owned pharmaceutical company specialised in ophthalmic pharmaceutical, ophthalmic surgical, vision care and optic products. To date, it runs operations in more than 70 countries and sells in more than 180. It has 12,000 employees worldwide, of which approximately 1000 scientists, engineers and support staff for research. It cooperates in research with major general pharmaceutical companies for the discovery of compounds and develops and tests a limited number of its own chemicals and devices in collaboration with leading academic centres (Figure 12). Among its most recent products in the area of glaucoma is Iopidine®, which is an alpha agonist to treat the end-stage of disease. Its major partners in scientific research are the University of Iowa, the University of North Texas and the University of Pennsylvania, ranked 144, 416 and 38 by global centrality score. Again, we note a pattern of geographical co-location between the firm and one of its most important partners, since Alcon's headquarters are in Forth Worth, Texas.

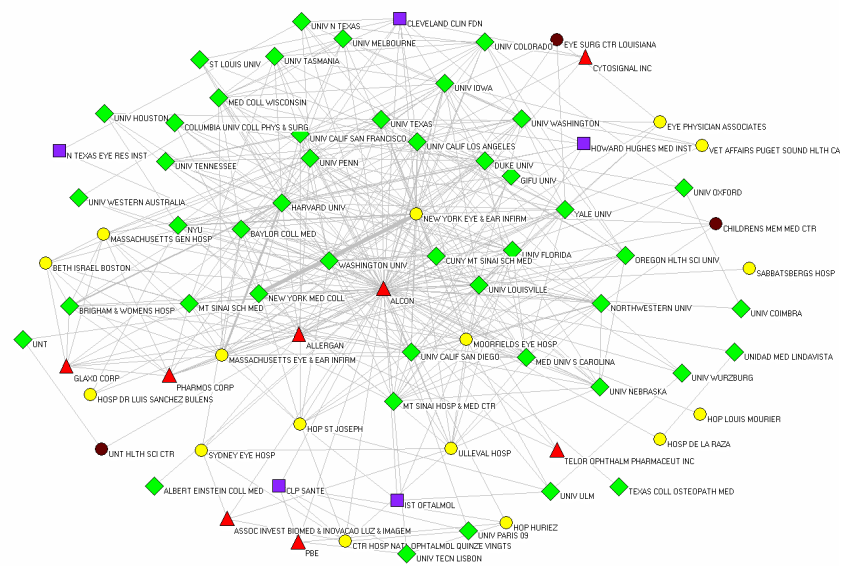

Figure 12. The Alcon network

Merck (Figure 13) is a multinational pharmaceutical company that discovers, develops, manufactures and markets vaccines and medicines in over 20 therapeutic areas. It figures prominently in both networks. It has approximately 60,000 employees, manufactures products in 32 facilities and sells products in approximately 150 countries. It conducts research at 11 major research centres in the United States, Europe, and Japan on a broad range of clinical conditions including high blood pressure, heart failure, cholesterol levels, osteoporosis, arthritis, glaucoma, ulcers, pneumonia and hepatitis A and B. In the late 1980's and throughout the 1990's, Merck established a number of alliances and collaborations under a variety of contractual arrangements. Among others, it joined forces with Johnson and Johnson for over-the-counter medicines, with Astra, who later merged with Zeneca, for certain prescription medicines, with DuPont for basic research, with Pasteur Merieux (now Aventis) for research and marketing of vaccines in Europe, with Rhone-Poulenc (now also Aventis) for animal health and poultry genetics and with Schering-Plough for cholesterol management and respiratory products. To date, they are involved in hundreds of academic collaborations and significant external arrangements with biotech companies as well as other large pharmaceutical companies not only for basic research and compound development, but also for drug delivery technologies and enabling/platform technologies.

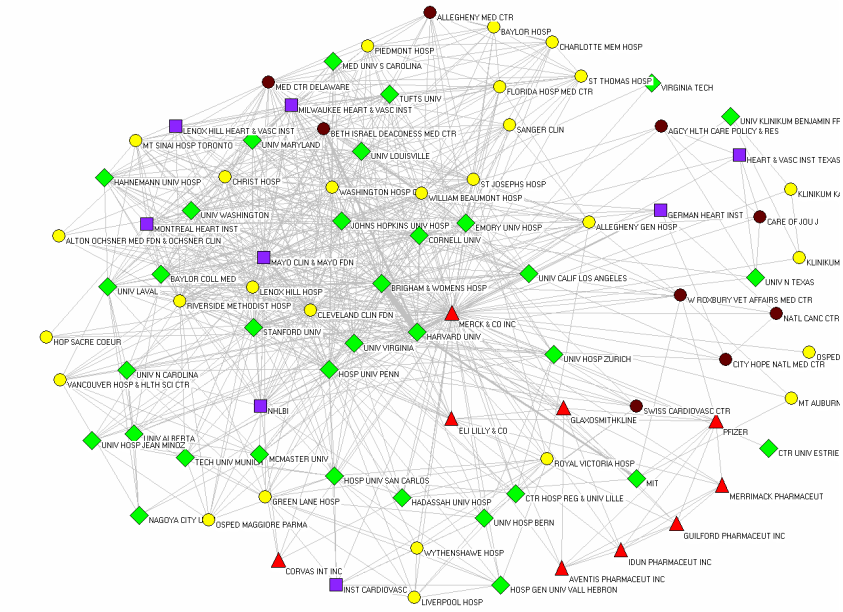

Figure 13. The Merck cardiology network

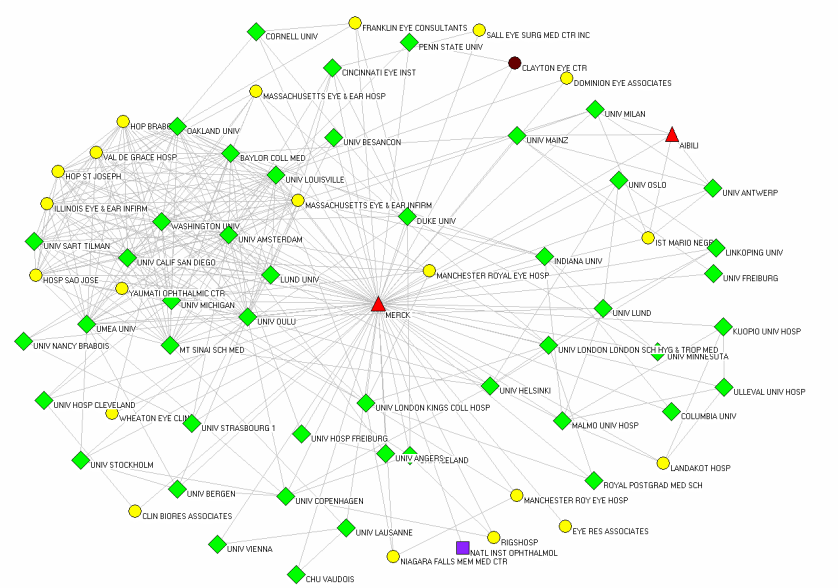

Figure 14. The Merk galucoma network

In the CAD network (Figure 13), Merck researches heavily in cholesterol-lowering drugs. Its leading new products in the area are Zocor (simvastatin), which reduces the incidence of coronary heart disease and limits the need for surgical revascularisation procedures, Zetia which reduces absorption of cholesterol in the digestive tract and further improve the effectiveness of statins, and Vytorin, which is a combination of the previous two. Its main partners in interventional cardiology research are among the top 10 centrality-ranked organisations and include the Mayo Clinic & Foundation (7th), Emory University (where Gruentzig pioneered angioplasty in the US) (10th) and Cleveland University (2nd). In the area of Glaucoma (Figure 14), Merck's leading product is Cosopt. This is indicated for the reduction of high intraocular pressure (IOP) in patients who are affected by open-angle glaucoma or ocular hypertension and do not respond satisfactorily to beta-blockers. Although Merck is one of the top firms by centrality, its main academic partners in glaucoma research are lower-ranked than its cardiology partners (Amsterdam University (36th), Wheaton Eye Clinic (379th) and Clayton Eye Clinic (160th).

Although the evidence we have gathered at the firm level is anecdotal, we cannot fail to notice different patterns of collaboration seem to characterise the two research areas. When the top three partners are considered for each of the firms from the cardiology network, computation of the global degree centrality scores indicates strong

association with top players in the field and weak geographical ties. On the contrary, in relation to glaucoma, the association with top players is weaker while a strong geographical link appears in two out the three cases between firms and academic partners being co-located in the same state/country. The contrast is interesting and may reflect the different stages of understanding and treatment of the diseases. In the case of interventional cardiology solutions have been found and incentives in applied research are very strong for those firms that seek opportunities for entry or growth in the associated market.[25] Research in glaucoma, although as lively as research in interventional cardiology (recall that the number of publications in the two fields is roughly the same and that large firms are present in both), is correlated with fewer treatment options.[26] It seems to be more basic in orientation as the problem of glaucoma is yet to be clearly defined. Firms may prefer to focus on absorbing information flows about the state of the art, but for this it appears that they would not need to connect with institutions of the highest ranking.

Conclusion

In this paper we have applied empirical network analysis to help illuminate the study of medical innovation. We focused broadly on two medical problem areas – coronary artery disease and glaucoma – and used large quantities of bibliometric data from the medical literature to construct respective network structures. We argued that innovation in medicine is a complex process that unfolds unevenly in time and space; that research paradigms emerge through these complex processes; and, that we can perceive these processes partly through the highly dispersed activities of practitioners connected through the institutional ties of the respective communities. Our main purpose therefore was to illustrate, analyse and compare the trajectories of scientific knowledge and medical practice as the respective communities searched for solutions to these medical problems. We further used the network methods to discuss the distributed nature of these medical innovation systems by considering the associated geographical and organisational domains.

Even a casual glance at the two citation networks suggests different patterns of behaviour in these two medical communities. A detailed analysis of the underlying literature enabled us to conclude that this reflects substantial differences in the rate and direction of progress in the relative clinical areas. Given the current understanding of

[25] Connection with top players for development and testing of new products is also likely to augment the chances of product approval by regulatory authorities because of reputation effects.

[26] In fact, inspection of the number papers related to clinical trails, which imply applied research, reveals that over the period 1985-2003 791 documents are found for interventional cardiology as opposed to 415 over a period longer by 20 years (1965-2003) for glaucoma. The figures for randomised trials, which involve stricter control and therefore more advanced stages of research, are 96 for the former and only 32 for the latter.

coronary artery disease, coronary angioplasty presents itself as a viable solution as we observe a fairly coherent trajectory of research. By contrast, following the debunking of the intraocular pressure (IOP) pressure paradigm which existing until the 1950s, glaucoma research has followed several distinctive pathways in search of a more elusive solution and has resulted in rather dispersed longitudinal citation patterns.

Our understanding of the underlying behaviour of these two communities was further enhanced by considering other features of the bibliometric data. Medicine heavily relies on extensive collaborative within and across organisations. In this respect different patterns have been found to characterise research in the two clinical areas. For example the size of teams, a joint effect of different cultures and incentives, is considerably larger in interventional cardiology than in glaucoma research. Moreover, the density of collaborative efforts differs between the networks. Analyses of the geographical distribution reveal that agglomeration effects generate a distinctive polarisation between US states and European countries but this is stronger in the case of interventional cardiology than in glaucoma. Also the relative intensities of collaborative research are stronger within the US than across Europe, a clear reflection of the scale of investment in health technology research in the two regions.

With respect to the organisational composition of the research networks, we showed the presence of rich ecologies where universities, hospitals, dedicated research institutes and firms closely interact in the development of medical innovation. These contribute to the advancement of medical knowledge through distinctive sets of complementary competencies that need to be effectively coordinated to create, improve and diffuse innovative health technologies. We showed that more firms are involved in angioplasty research than in the development of treatments for glaucoma. We interpret this as a result of better windows of opportunities for profit in the area where scientific understanding is less ambiguous. Firms also appear to show different behaviours between the networks in relation to the choice of collaborative partners with a stronger preference for research organisations ranked at the top by degree centrality in cardiology than in glaucoma. We take this as an indication that firms act strategically by forging the best possible alliances in areas where the rate of progress appears to be higher and can translate more easily into technological developments in rapidly changing product markets.

Inevitably, no single study can exhaust the variety of theoretical and empirical aspects of the problem of medical innovation and this paper has the limited ambition to contribute to our understanding of the nature, rate and direction of the growth and transformation of medical knowledge in the two specific areas. As a consequence, and although the amount of data we used and elaborated is considerable, its findings should only be generalised with care.

We hope to address lack of systematic econometric analysis in future work. On this occasion we privileged different quantitative methods that could allow us to map and visualise network structures (of articles, countries and organisations) so that we could explore in some detail the nature of the connections (epistemic, geographical and organisational) that comprise the system. It is also clear that inferences on the structure and evolution of innovation systems made on the basis of scientific publications should be complemented with data on other research output (patents) and data on market approvals and actual sales.

Medical research is of enormous significance to society and constitutes a rich field of investigation for the study of innovation especially as new and urgent issues are emerging with respect to economic sustainability, social acceptance and access and ethical conduct of the industry. Further elements of interest in the process of innovation in medicine stem from the interdependence between the service economy and the manufacturing economy. Medical progress is crucially dependent on the interaction between the clinical delivery of health care services and an international manufacturing system that develops and delivers new drugs and new devices to enhance the delivery of local clinical services.

So close is the degree of supply chain interdependence that the medical service economy and the medical industry economy are effectively one. Secondly, feedback from clinical practice is essential to advancement in medical science and technology as in few other sectors of the economy. The highly experimental nature of medical knowledge resides, in fact, in the tight connection between the provision and use of new treatments where feedback from intermediate adopters (clinicians) and final beneficiaries (patients) is essential in shaping the innovation process. Thirdly, the health sector is a typical example of a system in which public and private organisations closely co-operate and compete to meet socially recognised needs. However – and it is here that we believe further research should focus – the question where boundaries should be set with respect to funding and governance is of concern because of the need to (i) restrain the escalating growth of health costs – of which innovations constitute a sizeable proportion; (ii) improve the welfare efficiency and efficacy of innovation processes; and, (iii) guarantee objective evaluations of new drugs and technologies.

*

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References

AHUJA, G. (2002), Collaboration networks, structural holes and innovation: A longitudinal study, *Administrative Science Quarterly*, 45 (3) : 425–455.

AIRAKSINEN, P. J., HEIJL, A. (1983), Visual field and terinal nerve fiber layer in early glaucoma after optic disk hemorrhage, *Acta Ophthalmologica*, 61 (2) : 186–194.

ARORA, A., GAMBARDELLA, A. (1990), Complementarity and external linkages: The strategies of large firms in biotechnology, *Journal of Industrial Economics*, 38 (4) : 361–379.

BARABASI, A. L. (2002), *Linked: The New Science of Networks*, Perseus Publishing, Cambridge MA.

BARKAN, O. (1954), Narrow angle glaucoma–pupillary block and the narrow angle mechanism, *American Journal of Ophthalmology*, 37 (3) : 332–350.

BHATTACHARYA, S., KRETSCHMER, H., MEYER, M. (2003), Characterizing intellectual spaces between science and technology, *Scientometrics*, 58 (2) : 369–390.

BATAGELJ, V. (2002), *Efficient Algorithms for Citation Network Analysis*, Working Paper, Deptartment of Theoretical Computer Science, University of Ljubljana.

BATAGELJ, V., MRVAR, A. (2003), *Pajek: Analysis and Visualization of Large Networks*, Institute of Mathematics, Physics and Mechanics, Department of Theoretical Computer Science, University of Ljubljana, Preprint series 41, pp. 871.

BLUME, S. (1992), *Insight and Industry: On the Dynamics of Technological Change in Medicine*, MIT Press Boston.

BLUME, S. (1995), Cochlear implantation: Establishing a clinical feasibility 1957–1982, In: N. ROSENBERG et al. (Eds), *Sources of Medical Technology*, National Academy Press, Washington.

BORGATTI, S. P. (2005), Centrality and network flow, *Social Network*, 27 (1) : 55–71.

CARLSSON, B. (Ed.) (1995), *Technological Systems and Economic Performance: The Case of Factory Automation*, Kluwer Academic Publishers, Dordrecht and London.

CHANDLER, P. A. (1952), Narrow-angle glaucoma, *AMA Archives of Ophthalmology*, 47 (6) : 695–716.

CONSOLI, D., MCMEEKIN, A., RAMLOGAN, R., MINA, A., TAMPUBOLON, G., METCALFE, J. S. (2005), *Progress in Medicine: The Structure and Evolution of Know-How for the Treatment of Glaucoma*, Paper prepared for the DRUID Conference, June 27–29, Copenhagen.

COOKE, P., URANGA, M. G., ETXEBARRIA, G. (1997), Regional innovation systems: institutional and organisational dimensions, *Research Policy*, 26 (4/5) : 475–491.

COOMBS, R, HARVEY, M, TETHER, B. (2003), Analysing distributed processes of provision and innovation, *Industrial and Corporate Change*, 12 (6) : 1125–1155.

DELCOURT, C., VILLATTECATHELINEAU, B., et al. (1995), Visual impairment in type-2 diabetic patients – a multicenter study in France, *Acta Ophthalmologica Scandinavica*, 73 (4) : 293–298.

DOSI, G. (1982), Technological paradigms and technological trajectories: A suggested interpretation of the determinants and directions of technical change, *Research Policy*, 11 (3) : 147–162.

DRANCE, S. M., AIRAKSINEN, P. L., PRICE, M., SCHULZER, M., DOUGLAS, G. R., TANSLEY, B.W. (1986), The correlation of functional and structural measurements in glaucoma patients and normal subjects, *American Journal of Ophthalmology*, 102 (5) : 612–616.

EDQUIST, C. (Ed.) (1997), *Systems of Innovation: Technologies Institutions and Organization*, Pinter, London.

FISCHMAN D. L., LEON, M. B., BAIM, D. S., SCHATZ, R. A., SAVAGE, M. P., PENN, I., et al. (1994), A randomised comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease, *New England Journal of Medicine*, 331 : 496–501.

FREEMAN, C. (1991), Networks of innovators: A synthesis of research issues, *Research Policy*, 20 (5) : 499–514.

FREEMAN, C. (1995), The national systems of innovation in historical perspective, *Cambridge Journal of Economics*, 19 (1) : 5–24.

FUCHS, V. R., SOX, Jr. H. C. (2001), Physicians' views of the relative importance of thirty medical innovations, *Health Affairs*, 20 (5) : 30–42.

GELIJNS, A., ROSENBERG, N. (1999), Diagnostic devices: An analysis of comparative advantages, In: MOWERY, D., NELSON, R. (Eds), *Sources of Industrial Leadership*, Cambridge University Press, Cambridge.

GELIJNS, A. C., ROSENBERG, N. (Eds) (2005), *Sources of Medical Technology: Universities and Industry*, Institute of Medicine, National Academy Press, Washington.

KATZ, J. S., HICKS, D. (1997), *Bibliometric Indicators for National Systems of Innovation*, IDEA Paper Series 12, available at: www.sussex.ac.uk/Users/sylvank/best/nsi/index.html

HUMMON, N. P., DOREIAN, P. (1989), Connectivity in a citation network: The development of DNA theory, *Social Networks*, 11 (1) : 39–63.

JONAS, J. B., GUSEK, G. C., NAUMANN, G. O. H. (1998), Optic disk morphometry in chronic primary open angle glaucoma, *Graefes Archive for Clinical and Experimental Ophthalmology*, 226 (6) : 522–530.

KRUPIN, T., MITCHELL, K. B., JOHNSON, M. F., BECKER, B. (1978), Long term effects of iridectomy for primary acute angle closure glaucoma, *American Journal of Ophthalmology*, 86 (4) : 506–509.

LEYDESDORFF, L., MEYER, M. (Eds) (2003), The Triple Helix of university–industry–government relations, *Scientometrics*, 58 (2) : October 2003.

LUNDVALL, B. Å. (Ed.) (1992), *National System of Innovation: Towards a Theory of Innovation and Interactive Learning*, London, Pinter.

MALERBA, F. (Ed.) (2004), *Sectoral Systems of Innovation*, Cambridge University Press, Cambridge.

METCALFE, S. J., JAMES, A., MINA, A. (2005), Emergent innovation systems and the delivery of clinical services: The case of intra-ocular lenses, forthcoming in *Research Policy*.

MINA, A., TAMPUBOLON, G., RAMLOGAN, R., VENETUCCI, L., MCMEEKIN, A., METCALFE, J. S. (2004), *Problem Sequences and Innovation Systems: Emergence, Growth and Transformation of a Medical Sector*, CRIC Working Paper No. 14, University of Manchester.

MURRAY, F. (2002), Innovation as co-evolution of scientific and technological networks: Exploring tissue engineering, *Research Policy*, 31 (8/9) : 1389–1403.

NELSON, R. R. (1993), *National Innovation Systems: A Comparative Analysis*, Oxford University Press, Oxford.

NEWMAN, M. E. J. (2000), *Who is the Best Connected Scientist? A Study of Scientific Co-authorship Networks*, SFI Working Papers No. 00-12-064, Santa Fe, New Mexico.

OWEN-SMITH, J., POWELL, W. W. (2003), The expanding role of university patenting in the life sciences, *Research Policy*, 32 (9) : 1695–1711.

POWELL, W. W., KOPUT, K. W., SMITH-DOERR, L. (1996), Interorganizational collaboration and the locus of innovation: Networks of learning in biotechnology, *Administrative Science Quarterly*, 41 (1) : 116–145.

POWELL, W. W., GRODAL, S. (2005), Networks of innovators, In: FAGERBERG, J., MOWERY, D. C., NELSON, R. R. (Eds), *The Oxford Handbook of Innovation*, Oxford University Press, Oxford and New York.

POSNER, A., SCHLOSSMAN, A. (1948), Syndrome of unilateral recurrent attacks of glaucoma with cyclitic symptoms, *Archives of Ophthalmology*, 39 : 517.

QUIGLEY, H. A., ADDICKS, E. M., GREEN, W. R., MAUMENEE, A. E. (1981), Optic nerve damage in human glaucoma, *Archives of Ophthalmology*, 99 (4) : 635–649.

QUIGLEY, H. A. (1982), Childhood glaucoma – Results with trabeculotomy and study of reversible cupping, *Ophthalmology*, 89 (3) : 219–226.

RAMLOGAN, R., TAMPUBOLON, G. (2004), Paper presented at the *Uneven Growth of Knowledge*, Workshop, European University Institute, Florence 12-13th March.

TETHER, B. S., METCALFE, J. S. (2003), Horndal at Heathrow? Capacity expansion through co-operation and system evolution, *Industrial and Corporate Change*, 12 (3) : 437–476.

UTTERBACK, J. M. (1994), *Mastering the Dynamics of Innovation*, Harvard Business School Press, Boston.

WAGNER, C. S., LEYDESDORFF, L. (2004), *Network Structure, Self-Organizationa and the Growth of International Collaboration in Science*, Amsterdam School of Communications Research, University of Amsterdam, available at: http://users.fmg.uva.nl/lleydesdorff/cwagner/collabnets.pdf

WALSH, J. P., BAYMA, T. (1996), The virtual college, *Information Society*, 12 (4) : 343–363.