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ScienceDirect
Research Policy 36 (2007) 789–806
research policy
www.elsevier.com/locate/respol

Mapping evolutionary trajectories: Applications to the growth and transformation of medical knowledge

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Received 1 August 2005; accepted 1 December 2006
Available online 3 May 2007

Abstract

This paper is concerned with the mechanisms through which medical knowledge emerges, grows and transforms itself. It is a large-scale empirical analysis of the development of treatments for coronary artery disease, which is the most common cause of death in developed countries. We uncover the structure of medical understanding of the disease and the path-dependent co-evolution of scientific and technical knowledge in the search for solutions to the relevant set of problems. After reviewing a broad range of secondary sources and a number of interviews with leading clinicians, we use new tools recently developed for the longitudinal analysis of large citation networks. We apply them to a bibliographic database of 11,240 papers published in the area of coronary artery disease between 1979 and 2003 and to a patent dataset of 5136 US patents documents granted between 1976 and 2003 for angioplasty-related devices. The results are consistent maps, which we critically discuss, of the major scientific and technological trajectories associated with one of the most important medical procedures of the last 30 years.

Keywords: Medical innovation; Technological trajectory; Problem sequence; Longitudinal network analysis

1. Introduction and scope

While more needs to be done to extend the proportion of the world population that benefits from advances in medical sciences and technologies, it is difficult to disagree that these stand among the proudest achievements of the last century. Medical innovation has been and continues to be a source of hope for prevention, effective treatment, and cure of disease; it constitutes one of the obvious areas where progress is made in a non-trivial way to extend the gift of life or improve its quality.

This paper is concerned with the mechanisms through which medical knowledge emerges, grows and transforms itself. This is a process that is distributed across time, space and epistemic domains. It involves the development of correlated understandings about the nature of medical problems and the search for solutions to these problems. It entails a shift from the exploratory undertaking of inquisitive individuals to the more systemic interactions of dispersed groups of practitioners competing and cooperating to solve scientific and technical puzzles in a variety of institutional settings and different incentive structures. How does this happen and how does it lead to improvements in the treatment of diseases? What does the innovation literature have to say on this matter?

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0048-7333/$ – see front matter
doi:10.1016/j.respol.2006.12.007

In a recent contribution on the evolution of human know-how,[1] Nelson (2003) stresses the unevenness with which advance is achieved across different classes of human needs, and these include health needs, many of which have been successfully met and many have insofar eluded satisfactory solutions. With reference to medicine, Nelson emphasises the fundamental role of *practice*, intended as the actual application of human skills to a task, beside the role of articulated blueprint knowledge.[2] He highlights the importance of co-ordinating know-how embodied in different individuals and groups and argues that 'cumulative advance of know-how must be understood as a process of "cultural learning" or evolution' which '. . . in turn, involves the co-evolution of technique and understanding' (p. 1).

On similar lines of thought, Mokyr (1998) discusses the problem of medical knowledge in relation to principles of evolutionary epistemology. He emphasises the key role of scientific and technological capabilities as the necessary pre-condition for induced technical change in medicine and identifies the 'technique' as the main unit of selection. This is defined as '. . . a set of instructions, if-then statements (often nested) that describe how to manipulate nature for our benefit, that is to say, production widely defined' (p. 122). The underlying structure of the system is the set of *useful knowledge* that exists in a society, including untested beliefs and prejudices, which relates to the manifested entity of a set of *feasible techniques* that are tested and evaluated in order to define what technique – or medical routine – will be put to actual use among those available at any moment in time.[3]

Gelijns and Rosenberg (1994) also provide a number of fundamental insights into the dynamics of technological change in medicine upon which we rely for this study. They stress the inadequacy of linear models to account for the salient characteristics of medical innovations. First of all, linear models neglect feedback mechanisms between phases of adoption and use and applied research and development, so as to cancel out the fundamental uncertainty associated with the introduction of innovations into clinical practice and the prolonged need to adapt the technology while drawbacks (i.e. side-effects of drugs) and potential improvements, leading over time to significant incremental change, become apparent through actual use.

Secondly, only 'open', models allow to capture the fact that innovations may come not from biomedical research in the first place, but from other fields.[4] The development of medical devices is especially dependent on a number of technological competences that are not core to health sciences (i.e. optical engineering) and cannot be understood if not in association with the surgical practice in which they are utilised. A third aspect of medical innovation that is not easily accommodated by a liner understanding of its development is the role – and dynamics – of demand. A variety of factors on the adopters end of the spectrum are crucial to the creation of markets for new technologies. Hospital administrators, insurers, patients and regulators are increasingly influencing the rate and direction of medical innovation by explicitly identifying priority needs and re-defining modes of financing that incentivise the emergence and diffusion of cost-reducing technological solutions.[5]

Gelijns et al. (1998) further elaborate on the characteristic uncertainty of medical innovations and the importance of improvements through practice. They argue that 'innovation is a learning process that takes place over time, and a fundamental aspect of learning is the reduction of uncertainty' (p. 694). However – they argue – not all uncertainties can be eliminated in the process and this is valid for both positive and negative unexpected consequences of the application of new treatments. Uncertainty results from the complexity of the human system, which poses severe limits to the possibility of predicting the effects of new procedures.[6] The

[1] Know-how is there defined as 'the wide range of techniques and understandings human societies have acquired over the years that enable them to meet their wants' (2003: 1).

[2] The debate on the tacit versus codified nature of different kinds of knowledge has been explored by a great deal of contributions to the innovation literature. Although awareness of the debate informs parts of our study, this does not constitute its main focus.

[3] Mokyr's discussion of the mapping function connecting knowledge and techniques is extremely interesting and leads to a number of considerations that are very close to the present study, among which the role of rules of falsification, the mechanisms of survival, obsolescence and resistance to change, as well as the problem of the accessibility of knowledge. Space constraints and the empirical nature of this paper do not allow a thorough discussion of so rich a contribution, but traces of its insights can be found between the lines of this study.

[4] This is the rather well known case of ultrasound, laser and magnetic resonance technologies, among the many possible examples.

[5] This is not meant as an endorsement of a 'demand-pull' perspective. Innovation 'on-demand', however desirable in medicine of all fields, does not reflect the long-term struggle of mankind with diseases, many of which cannot yet be solved even if the need for solutions could not be stronger. For a critique of demand-pull models in medicine, see Mokyr (1998).

[6] Metcalfe et al. (2005) note that like all medical innovations, application to the human body is more a matter of engineering than of science. Consequently, as with all engineering innovations, feedback from practical application is of the essence of the development of reliable knowledge (Vincenti, 1990).

typically narrow target of clinical trials and the heterogeneity of the patients recruited to test new drugs and new devices in early phases of development add to the difficulty of finding in the short run unexpected benefits associated with new treatments. As a consequence, the experience gathered in clinical practice and the resulting post-innovation improvements of experimental techniques can hardly be overstated.

Post-innovation improvements provide strong indications that the process of accumulation of medical knowledge occur along *trajectories of change* that emerge over time in the search for better and better solutions to clinical problems (Metcalfe et al., 2005). Innovations are rarely if ever uniquely circumscribed events and outcomes. They are better seen as trajectories of improvement *sequences* in which devices or procedures are progressively refined and extended in their scope of application. Moreover, the devices are only the signatures of knowledge and practice and as one innovation problem is solved so others range into view and form new foci for innovative effort within the broad objective to improve the efficacy of the overarching procedure. As problems are solved, extending the range of application and improving practice, it is inevitable that new problems are defined. All innovation is an exploration of the unknown; it is a discovery process that is neither random nor completely canalised. Rather it proceeds through exploring a *design space* in a largely path dependent fashion within bounds set by the perception of the problem (Metcalfe et al., 2005). Progress means finding new problems and the solutions to these problems lay in different domains of knowledge and communities of practice.

Communities of practice (Brown and Duguid, 1991) are important loci for the development of new knowledge, and it is often at this level that new problems emanate and are formulated. It is through the performance of medical/clinical practice that particular 'glitches' and potential solutions become apparent.[7] The epistemic dimension of the problem sequence cannot be independent of the organisational and institutional bases of relevant networks of individuals. Consequently, scientific and technological knowledge co-evolve with the social networks in which the process is embedded. Not only, in fact, is knowledge distributed within communities, but also distributed across communities linked through a variety of formal and informal mechanisms of exchange.[8] The advancement of medical knowledge heavily relies of continuous feedbacks between science and technology and the nature and intensity of interaction across communities at different points in time are of great importance to the emergence, growth and transformation of medical micro-innovation systems.

In this paper, we investigate the recorded history of one of the most important medical innovation of the last decades: Percutaneous Transluminal Coronary Angioplasty, PTCA for short. This innovation emerged in the late 1970s to become a technique that is now more commonly used than the principal surgical alternative coronary artery bypass surgery (CABG), in the treatment of advanced coronary artery disease (CAD) which constitutes the principal cause of death in developed countries (WHO, 1999; OECD, 2003). Not only has PTCA proven with the benefit of experience to be an effective and efficacious mode of treatment, this innovation brought with it a transformation in the division of labour in cardiology so much so that medical boards around the world now recognise Interventional Cardiology as a separate sub-speciality of the broader field of cardiology. To investigate the development of this important domain of knowledge, we apply to two sets of bibliometric data techniques of longitudinal network analysis that to date have not been used to a comparable extent in the study of innovation. These enable us to map in new ways the emergence, growth and transformation of innovation trajectories and allow an appreciation of cumulative, competitive and combinatorial process through which medical knowledge develops in the long-term search for solutions to clinical problems.

2. Data and methodology

Cutler and McClellan (2001) argue that only a focus on the *process* of innovation at a micro level, that is the disease level, has the potential to unpack the relationships that matter in the localised advancement of science and technology in medicine. This is the approach we take here with respect to the problem of coronary artery disease. We developed our methodology accordingly and proceeded as follow. After reviewing the specialised medical literature with the assistance of expert advice,[9] we extracted traces of knowledge codified in scientific

[7] Interestingly, that problems and solutions emanate from the doing of medical practice has clear connections to the notion of 'learning by doing' common in many fields of engineering.

[8] For a general exposition of the means of knowledge transfer in the field of medicine, we refer the reader to Campbell et al.'s (2004) recent review.

[9] In this phase of the research, we were assisted by Dr. Luigi Venetucci, cardiologist of the Manchester Medical School, who was also extremely helpful in validating the datasets constructed for this study.

peer reviewed journal articles and patent documents with the aim to identify and quantify the distributed knowledge base that has developed since the late 1970s in the research domain of interventional cardiology.

Journal articles and patent documents contain a wealth of information, including the authors/inventors' identity, location, institutional affiliation, scientific/technological field of relevance as well as citations to prior art. Citations enable epistemic links to be traced across scientific and technical contributions. On the basis of graph-theoretic principles, they can be used to construct maps where various dimensions of the development of knowledge can be explored synchronically and diachronically. In this study, we use citation graphs to shed light on the evolution of scientific and technological knowledge connected to the emergence of coronary angioplasty. Our main objective is to trace, visualise and critically discuss the complex processes of creation, competition, selection and retention of solutions developed by the medical community in response to the clinical problem of coronary artery disease.

After consulting major university textbooks and with constant feedback from clinicians, we constructed two datasets for the purpose of this exercise. The first is a bibliographic database of papers published between 1979 and 2003. It was extracted from the Thomson/ISI on-line resources and contains basic details and bibliographic citations for 11,240 papers published in the field of interventional cardiology. The second dataset includes patent documents extracted from the United States Patent Office and contains information on 5136 patents granted in the US to angioplasty-related inventions between 1976 and 2003. Both datasets were extracted by keyword searches on titles, abstracts and/or claims ranging from general strategies (e.g. "coronary angioplasty" and "interventional cardiology") to combinations of specific ones aimed at weeding out irrelevant records (e.g. patents related to non-coronary catheters).[10]

On the basis of citations contained in our datasets we constructed a series of graphs that map the development of scientific and technological knowledge in the area of interventional cardiology. Our core analysis rests on the construction of large citation graphs for the scientific/medical domain and one set for the technology domain. From the original data we are able to construct a bibliographic network of slightly more than 300,000 arcs connecting 94,442 nodes. As for patents, we were able to derive a network of 22,095 nodes connected by well over 135,000 arcs. Table 1 provides a synopsis of the data.

Table 1
Data synopsis

	Source	Records	Network nodes
Papers	Thomson/ISI	11,240	94,442
Patents	USPTO	5,136	22,095

Our analysis is underpinned by three algorithms implemented by Pajek.[11] The first, the Main Path algorithm, identifies the most important papers and streams of growth or development in a citation network.[12] It is here used to capture the idea of the problem sequence and visualise the scientific and technological 'trajectories' (Dosi, 1982) associated with the evolution of coronary angioplasty techniques. The second algorithm is a variation of the Main Path as described in Batagelj (2002). While the Main Path provides a parsimonious longitudinal examination of how a citation network or research field evolved through their citation patterns, this variation maps pathways beyond the Main Path and thus provides a visual display of the broader longitudinal connectivity within the system. We use the algorithm to illustrate scientific and technological developments branching out in the search space and their patterns of convergence or divergence over time. Third we use a recently developed algorithm called 'island' (Batagelj and Mrvar, 2003) to further investigate the inner structure of networks. This is a clustering algorithm that enables us to identify and explore small clusters of inventions whose 'local' (internal) connectedness is relatively superior to the strength of their outward connections within the 'global' network. It is especially useful to identify important clusters of contributions in sections of the data where variety is high and the relatively little time elapsed from their appearance to the observation point has not allowed selection mech-

[10] Significant efforts have been made not only to validate the search strategy and results but also to balance the need to be economical in the number of searches and the need to maximise the probability of capturing the relevant patents.

[11] A number of Pajek's functions are here used to find and extract clusters from large networks and show visually the relationships among them. These structures are displayed with standard drawing algorithms such as spring embedders based on minimisation of the total energy of the system (Batagelj and Mrvar, 2003). For further discussion of the data and some of their network statistics, see Ramlogan and Tampubolon (2004).

[12] Hummon and Doreian (1989) devised three indices or weights of edges to computationally identify the (most) important part of a citation network—its main path. Batagelj (2002) developed algorithms to efficiently compute the Hummon and Doreian's indices so that they can be used for the analysis of very large citation networks with several thousands of vertices.

anisms to highlight the most important ones through forward citation patterns.

As we have anticipated, our graphs depict citation-based networks. Bibliographic citations have been acknowledged as explicit linkages between papers that share some content since Garfield's pathbreaking analysis in the 1950s and 1960s (Garfield, 1955; Garfield et al., 1964) and have been extensively used to trace the patterns of scientific advances (DeSolla Price, 1963; Hummon and Doreian, 1989). The greater the number of citations to an earlier work, the greater the likelihood that this paper may be a milestone or key event in that subject field (Garfield, 1970).[13] Citations have also proved invaluable in the study of technical change, as Jaffe and Trajtenberg (2002) discuss at length in their classic volume.[14]

Studying citation patterns between articles, journals and other publications can help provide new insights about the interaction between disciplines, technical fields, individuals, institutions, regions and countries in relation to the growth of knowledge. There are nevertheless obvious limitations in taking bibliographic citations at face value. Differences exist in propensity to cite across countries, cultures and disciplines (Mac Roberts and Mac Roberts, 1989) as well as authors' use of self-citation, inappropriate, indirect and negative citation, window dressing and politically motivated flattery (Hummon and Doreian, 1989). In addition, patent citations are heavily mediated by the examiners who are required to check and eventually integrate the references to prior art. However, neither the appropriateness of the allocation of credit nor the identification of spillovers are *per se* the main concerns of this paper. The nodes of our networks do not represent individuals but discrete pieces of research that embody the codified traces of new knowledge. We treat citations as an 'objective' – or at least standardised – proxy by which we can account for the overall evolution of knowledge systems. Their patterns of accumulation and dispersion reflect the overall result of selective forces operating under a variety of motives in the relevant communities and most importantly are defined by the research community itself and not by the analyst.

With respect to the communities that are relevant for this study, papers and patents are rather reliable indicators of the state of knowledge because in the medical sector the propensity to publish and patent is relatively high (Littell, 1994; Campbell et al., 2004). In the realm of medical/clinical research publishing is clearly associated with academic prestige and carrier opportunities. The emphasis on evidence-based medicine that has emerged over the last four decades has also added to the institutional incentives to publish in scientific journals. For inventors, the incentive to patent is strong both for drug companies and device manufacturers and although the latter tend to be engineering-based firms, where secrecy is often the preferred strategy for protecting new products, the regulatory structure of the medical sector induces patenting because products need to be protected while they are tested in clinical trials and also because patent coverage is taken into account in the market approval process.

It is well known that one of the shortcomings of patents is that while they are reliable indicators of inventive efforts, whose value is highly skewed, they cannot be used to infer too much on the final product market because most of them never reach the market (Griliches, 1990). This is partly due to their uneven value, to lack of financing, or to difficulties encountered in product development phases. In the medical sector, however, these limitations are partly compensated by the fact that scientific papers tell us more on actual applications of knowledge than publications in other fields of science. The clearest hurdle that needs be overcome to bring a product to market is the presence of strong regulatory constraints aimed at testing its efficacy and safety in the interest of the general public before it can be used on eligible patients. Government agencies have exclusive right to confer medical products market approval and market clearance. This depends on submission of scientific evidence on the performance of new drugs and devices in clinical practice. In turn this is systematically published in peer-reviewed journals. The classic objection that scientific publications are rather 'distant' indicators of innovations is therefore weaker in the medical area, where in fact papers reporting the outcomes of clinical trials are often better indicators than patents of developed medical technologies.

3. The Innovation problem and the solution path of Andreas Gruentzig

The German clinician, Andreas Gruentzig performed the first PTCA procedure in 1977. This event would herald a revolution in cardiology that would transform the profession over the following decades and lead to the development of the field of Interventional Cardiology. A recent survey of general internists actively

[13] Garfield (1979) also established that a strong correlation exists between citation rates and peer judgments in several areas/disciplines.

[14] To this, and to the 'classic' Pavitt (1985) and Griliches (1990), we refer the reader for an analysis of the use and shortcomings of patents and patents citations.

involved in patient care by Victor Fuchs and Sox (2001) ranked coronary angioplasty third (only behind MRI and CT scanning and ACE inhibitors) of the 30 most important medical innovations over the last 25 years.

In this section of the paper, we provide a brief overview of the problem of coronary artery disease and the modes of treatment that prevailed before Gruentzig made his mark. As with many innovations, Gruentzig's contribution is premised on antecedents in his case in vascularisation and angiography techniques, it reflected a cumulative and combinatorial growth of knowledge, and temporary setbacks were part of a process in which learning took place in relation to which avenues are feasible and which are not, and why (Ziman, 2000).

4. The disease

Coronary artery disease is the most common cause of death in developed countries. It is the end result of a process called atherosclerosis that occurs when atheroma or plaque forms on the inner layer of the coronary artery and impedes the flow of blood to the heart. In the early stages, the build up of these deposits is silent (symptom-less) but as the disease progresses chest pains of varying degree as well as shortness of breath occur; the eventual outcome may be a heart attack.[15] The chest pain associated with CAD is called angina. It is usually brought about through physical exertion or emotional stress. These increase the heart's requirement for oxygen enriched blood, but with narrowed arteries restricting blood supply, severe discomfort is experienced.

A heart attack occurs when a coronary artery becomes completely blocked and the heart muscle fed by that artery dies.[16] This is usually caused by a blood clot or other blockage in an already narrowed and diseased artery. In some cases people may be unaware they have the disease until they develop symptoms of congestive heart failure—extreme fatigue with exertion, shortness of breath and swelling in the feet and ankles. Congestive heart failure occurs when the heart becomes significantly weakened over a period from insufficient blood supply or as a result of a heart attack, so that it is unable to pump enough blood to meet the body's demands.

5. Treatments for CAD prior to the 1980s

As recently as the decade of the 1960s, treatment options for angina (chest pain) or acute myocardial infarction (heart attack) consisted of few medications (mainly nitroglycerin), rest and hope.[17] In the 1960s and 1970s, respectively, beta blockers and calcium channel blockers were added to the cardiologist's arsenal for dealing with angina. Unfortunately, while these started to provide effective relief from angina by reducing the frequency and force of the heartbeat, they were not a cure for the underlying problem. Surgical treatments also improved from the 1960s with the development of coronary artery bypass surgery (Fig. 1). This is a major invasive and complicated surgical procedure taking between 3 and 6 h to perform. 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.[18] Put simply, the idea behind the procedure is to improve the blood flow to the heart muscle by bypassing the blockages with blood vessels harvested from the leg (saphenous vein) or chest wall (internal mammary artery).[19]

At the time of its introduction bypass surgery was regarded as being truly revolutionary. The idea of stopping a heart, restoring its blood supply then restarting it, bordered on the miraculous. The technique spread rapidly although figures about the volume of procedures undertaken in the early period are patchy. In 1973 around 25,000 operations were performed in the US and this increased to 70,000 by 1977 (OTA, 1978). Elsewhere, the absolute numbers of procedures was small in comparison. In the UK for example 2297 operations were carried out in 1977 and this increased to 4057 by 1980 (British Heart Foundation, 2004).

The diffusion of this procedure was not without controversy and this was primarily related to the evidence base on which bypass surgery was being promoted. A debate raged throughout the 1970s about the quality

[15] It only becomes painfully evident when the vessel is approximately 70% occluded. At this level of closure, the oxygen-enriched blood that the heart receives is only adequate when the body is at rest.

[16] An insufficient oxygen supply to the heart is called ischemia and results in the death of heart muscle cells (myocardium). An unstable lesion, classified as a fibroatheroma, can rupture due to unexpected triggers and, according to recent research, also cause heart attacks.

[17] The use of nitrates (and nitroglycerin) dated back to the mid- to late-1800s. These provided transient relief from angina by dilating vein and arteries thereby enabling more blood to get to the heart. There then emerged a series of competing medical cum technological trajectories each addressing a different perception of the heart disease problem.

[18] Most patients tend to be discharged after 5–6 days and return to work in 5–6 weeks.

[19] The latter artery tends to be favored because it is almost always free of plaque and has an excellent record for long term patency (remaining open) following surgery.

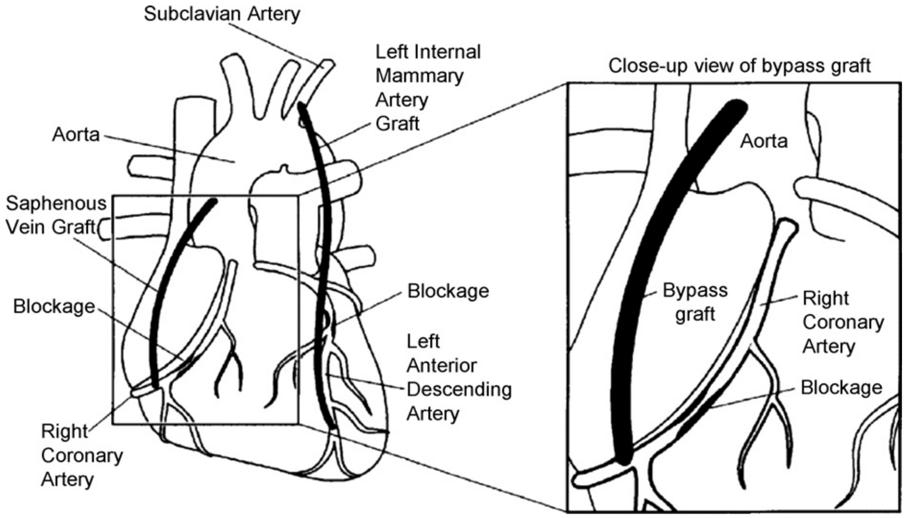

Fig. 1. Coronary artery disease and bypass graft.

of evidence that was being assembled about the efficacy of bypass surgery relative to medical therapy.[20] So much so that the US Office for Technology Assessment (OTA, 1978) was decidedly lukewarm about the procedure arguing that, in terms of survival, the VA randomised trial and a number of others showed that surgery did not appear to bring any appreciable longevity benefit when compared with medically treated patients. The OTA did concede the point that bypass surgery gave 'excellent symptomatic relief from angina pectoris' (p. 43) although it was careful to caution about placebo effects associated with surgery.[21]

5.1. The development of a new treatment modality

It is against this background of uncertainty about the efficacy of coronary bypass surgery that coronary angioplasty was developed. While this achievement secured Gruentzig's name in the annals of medical history, his key insight of using a balloon tipped catheter to dilate the constricted coronary artery was built around cardiac catherization and transluminal angioplasty, established medical techniques.

Cardiac catheterization is a diagnostic procedure in which a catheter (a thin flexible tube) is inserted into the right or left side of the heart. This procedure could be then used to produce angiograms (X-ray images) of the coronary arteries and the left ventricle, the heart's main pumping chamber, and/or used to measure pressures in the pulmonary artery and to monitor heart function. Werner Forssmann is credited with being the first to introduce a (urological) catheter into the right atrium (his own!) in 1929. Branded as "crazy" by his contemporaries, his immediate reward for this achievement was dismissal from his German hospital (he went on to win the Nobel prize in 1956). By the 1950s however, following the work of Cournand, Seldinger and others, diagnostic catherization had become established as the main technique for investigating cardiac function.

The American, Charles Dotter coined the term Percutaneous Transluminal Angioplasty (PTA) (Rosch et al., 2003) for a treatment that he developed in the 1960s. During an angiographic examination he inadvertently reopened an occluded right iliac artery (in the lower abdomen) by pushing through it with the angiography catheter. Realising the therapeutic potential for dilating

[20] In a review of the medical literature at the time Mullins and Lipscomb (1977) noted that their analysis was based on incomplete or less that ideally designed studies as few objective randomised studies were available. Given the weight of evidence available they were hesitant to unambiguously recommend surgery other than for a diseased left main coronary artery. For single vessel disease surgery was to be considered an option only after aggressive medical therapy had failed; and in the case of multi-vessel disease cardiologists were divided on whether surgery improved survival rates.

[21] One of the interesting features of the spread of bypass surgery is how quickly it was taken up for cohorts of patients for which the medical evidence was not indicated. Anderson and Lomas (1988) based on a study carried out in Ontario, Canada expressed concern about the apparent change in clinical policies towards the use of bypass procedures in the elderly without solid evidence on efficacy or cost effectiveness in support of such a change. While the increased procedure rates observed might be based on the assumption that the effectiveness demonstrated in the non-elderly could be generalised to the elderly, this assumption may or may not be supportable. The over 65 age groups were not represented in any of the three major randomised trials that had been reported by the early 1980s yet in Ontario and the US, respectively in 1983, they accounted for 23 and 37% of bypass surgeries (p. 253).

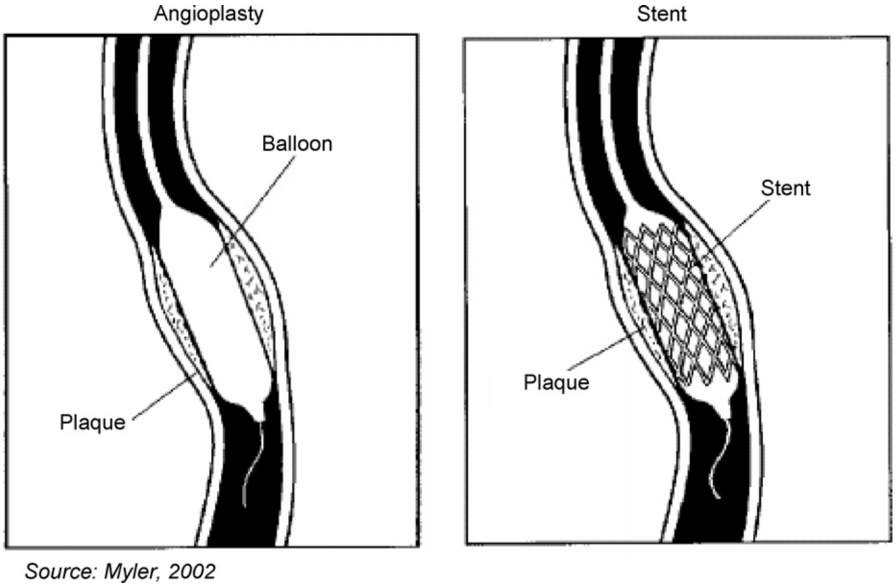

Fig. 2. Angioplasty and stenting procedures.

narrowed arteries, Dotter went on to refine the technique but, as was the case with Forssmann, this was met with scepticism by the American medical fraternity. European radiologists took a more positive view and soon institutionalized the term 'dottering' (of patients) to refer to improving the patency of arteries by the introduction of a series of coaxial catheters. One of Dotter's European followers, Eberhardt Zeitler, who used the technique on a large number of patients would be the one to introduce Gruentzig to PTA.[22]

Gruentzig was exposed to the Dotter method in the mid 1960s at the Ratchow Clinic in Darmstadt (Germany), where he was a Research Fellow in Epidemiology studying coronary artery disease, before deciding to become a cardiologist and move to the University of Zürich in 1974. Here, he began to think about whether the Dotter method could be applied to the heart recognising that 'any application of the dilatation procedure to other areas of the body would require technical changes' (King, 1996: 1624). Encouraged by his colleague and Joint Head of Cardiology, Wilhelm Ruttishauser, Gruentzig proceeded to develop himself a prototype balloon catheter, the foundation for PTCA. Two crucial developments followed. First in 1972, he introduced a PVC balloon, a tough less compliant material than latex, with which he had experimented earlier. In 1975, he developed a single and then more importantly a double lumen catheter—one for inflating the balloon and the other for injecting contrast media and monitoring intravascular pressure. By 1976 he was presenting the results of animal experimentation to a less than enthusiastic audience at the American Heart Association meeting but by 1977 he had succeeded in doing the first PTCA on a patient in Zürich. The technique spread quickly thereafter particularly in the US.

The growth of practice was naturally associated with a vast number of improvements in devices and practice including the invention of the steerable balloon catheter by Simpson in the early 1980s (Simpson et al., 1982). Most importantly, the structure of these many contributions to the innovation sequence also reflects the shift in the nature of the dominant problem. 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 restenosis – the reformation of the plaque after the procedure – occurred in a significant number of patients drastically reducing the efficacy of the treatment and raising its real cost. The solution to this problem (see Fig. 2) was the invention and innovation of the stent, an expandable metal device to give support to the blood vessel wall (Eeckhurst et al., 1996).

Stenting cuts residual restenosis by over 50% and is a major complementary development in PTCA technology. Even this solution is not complete for restenosis can occur on the inside of the stent – this is called 'in-stent restenosis' – and attention has shifted to the design of drugs to coat the stent, and other techniques, that will serve to prevent this occluding process (Serruys et al., 1991; Linkoff, 2000; Suwaidi et al., 2000). In the devel-

[22] This account draws in part on King (1996, 1998).

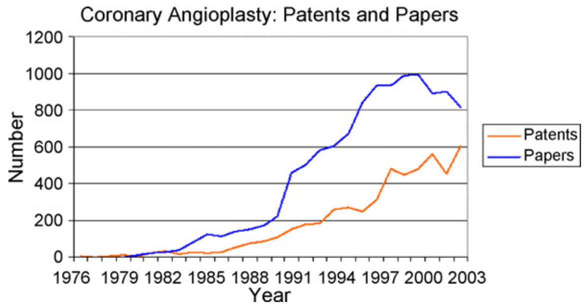

Fig. 3. Coronary angioplasty papers and patents 1976–2003.

opment of this extended problem sequence published clinical research, including reports of evidence on procedures, has been of paramount importance. Here, we use it to capture the growth of understanding in the community of PTCA practitioners.

6. Scientific and technological trajectories of coronary angioplasty

The nature of the innovation process in relation to PTCA mirrors that in other significant medical innovations where there is a dialogue between devices and practice. Studies by Gelijns and Rosenberg (1994), Gelijns et al. (1998, 2001) aptly characterise it as an uncertain co-evolutionary process of technique and knowledge. Fig. 3 shows the tremendous growth both in publication and in patenting activities, as it were, post-Gruentzig. The two curves show the incipient logistic tendencies characteristic of evolutionary processes, whose composition we shall explore in detail in the following paragraphs.

6.1. Synthesis of the evolution of scientific knowledge

Fig. 4 shows a reduced version of the rich ecology of contributions that grew from Gruentzig's efforts. The map comprises the 689 papers that have been the most highly cited over the period considered.[23]

While revealing a tightly connected network, this graph provides only limited information on the dynamics of the systems. In other words, it needs more structure to be meaningful. Fig. 5 restructures the same data by means of a variation of the Main Path algorithm that organises the papers in layers corresponding to the citations ordered in time so that we can observe the time evolution of the network by moving along the vertical axis.[24]

In the figure, at each time period we capture diverging and converging streams of developments as the medical communities search the epistemic space of the problem of coronary artery disease. After the initial exploratory phase stimulated by Gruentzig's findings we observe a distinctive pattern of closure in the network around the mid 1990s. We analyse a number of these papers to understand what were the issues being address at that time and find that they relate to the efficacy of stents.[25] The clinical experience with stents up to that time did not meet up to the expectations that were raised. The principal reason was the great variability in the results obtained. A more wide spread acceptance of stenting came with the Benestent and Stent Restonsis studies of the early 1990s.[26] Colombo et al. (1995) deals with the results obtained from these extensive clinical trials and stands out in our map as a watershed in the debate for two reasons. Firstly, it provided persuasive evidence of the advantages of stenting compared to ‘simple’ balloon angioplasty and, secondly, it proved that the success rate of the procedure heavily depended on the placement of the stent graft. On the one hand this fostered further research on stents aimed at improving the procedure and on the other it opened up the search for solutions to in-stent restenosis which proved to be one of the drawbacks of stent deployment.

By using the Main Path algorithm, we are able to further ‘distil’ the data and visualise a highly synthetic summary of the development of scientific knowledge in the area (Fig. 6). The Paper Main Path comprises 61 nodes, each node corresponding to a paper.[27] We interpret it as an illustration of the dominant scientific trajectory that emerged out of the dispersed and yet interdependent research efforts that were made in the surgical treatment of coronary artery disease over the past 30 years.

We stress that the sequence here illustrated does not result from a horizontal count of the paper yields of the different years considered, which would result in a trail of the papers with the highest citation counts per year. This would not serve the purpose of showing the diachronic connectedness of the system, which is instead what we

[23] For presentational purposes, we have limited the labelling of nodes. We have used the Kamada Kawai (Kamada and Kawai, 1989) algorithm embedded in Pajek for visualising the network. The bibliographies for Section 4 of this paper are available from the authors upon request.

[24] We follow the procedure outlined in Batagelj (2002).

[25] See, for example the discussion in Foley et al. (1993), Holmes et al. (1994) and Colombo et al. (1995).

[26] See in particular Serruys et al. (1994) and Fischman et al. (1994).

[27] The respective bibliographies are available upon request from the authors.

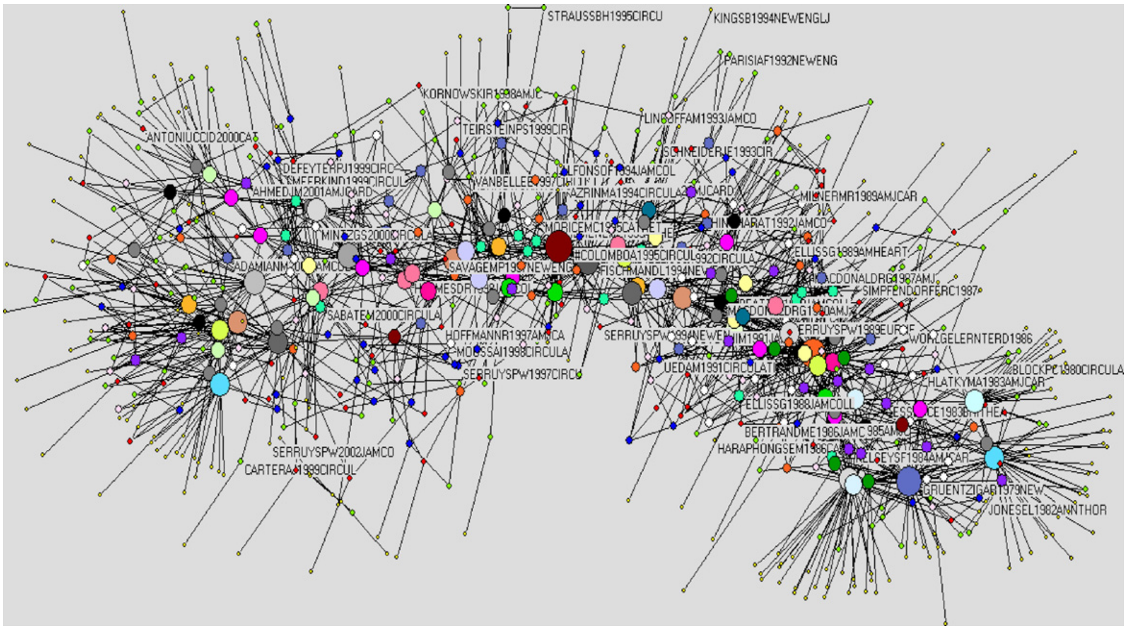

Fig. 4. Ecology of coronary angioplasty medical research.

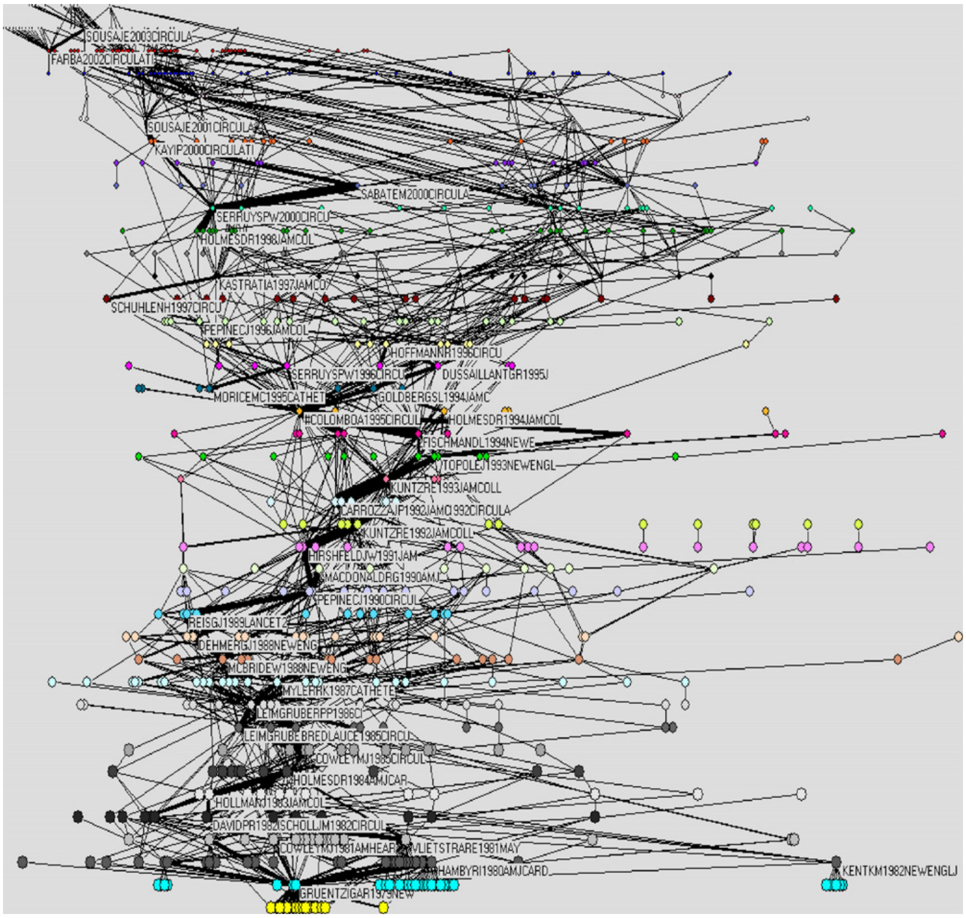

Fig. 5. Time evolution of the scientific network.

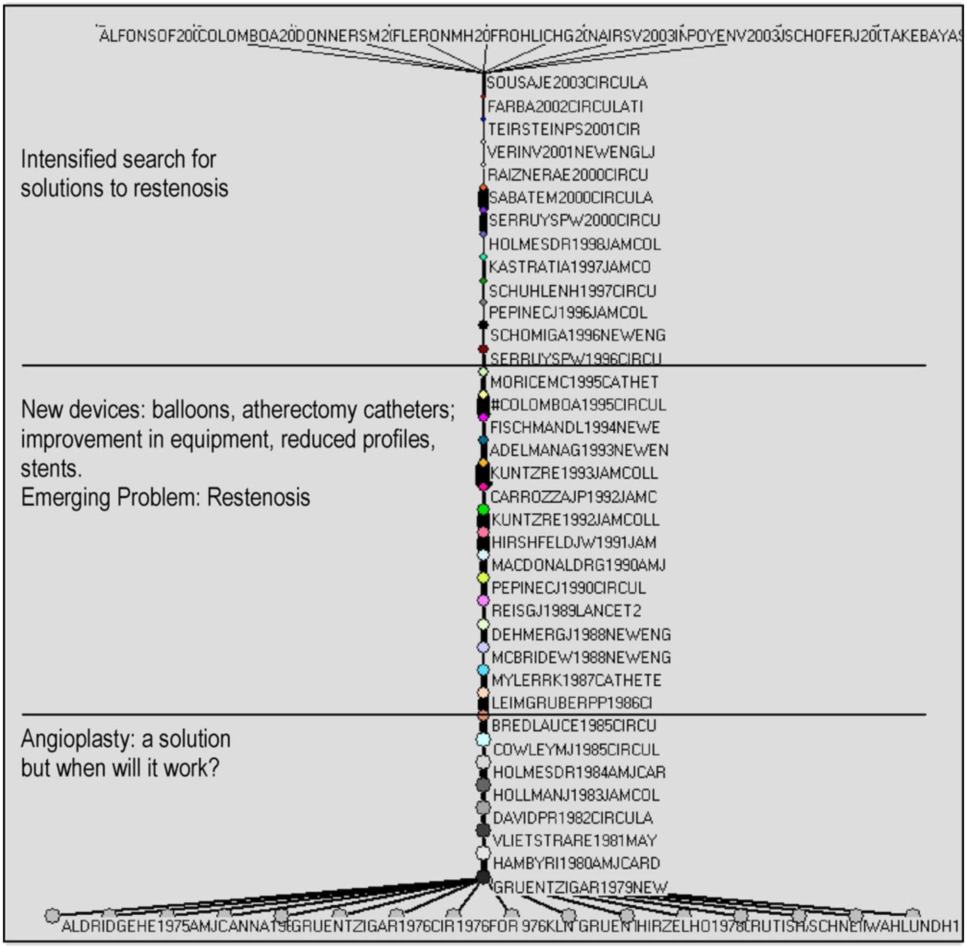

Fig. 6. Papers Main Path.

set out to do. The Main Path results from the identification of the path that is most frequently used to 'walk' from to the top to the bottom (that is back in time) of 'field' of papers. This does not involve the discrete count of the maximum number of citations received, but the simultaneous computation of all the possible paths through the whole dataset and the choice of the one that is most frequently encountered through time.

Starting from the paper Main Path, we studied the abstracts associated with each node and found that they generally confirm the qualitative account of the main developments in angioplasty that have been reported in several specialised studies (Mueller and Sanhom, 1995; Myler, 2002; King, 1996, 1998).[28] Analysis of the papers along the spine in both diagrams provides evidence of the notion of the problem sequence that we discussed in the introduction. Gruntzig et al.'s (1979) paper (node 2) lies at the bottom of the papers Main Path perpendicular. The nodes below Gruentzig to some extent represent some of the foundation from which the angioplasty community emerged. Nodes to the top of the diagram on the other hand are a sample of the state of the art by 2003.

Following Gruentzig's breakthrough, the concerns of practitioners were with identifying the medical conditions under which this new technique would provide benefits to patients under tolerable margins of risk (nodes 2 up to 18). The study by Cowley et al. (1985) (node 3) is one of a number of foundation papers that were produced under the sponsorship of the National Heart Lung and Blood Institute in this early period. These provided early evidence from a Registry set up in 1979 to collect, analyse and disseminate the results from using the balloon angioplasty procedure in medical centres across the US and in other countries (Mullins et al., 1984).

As operational experience was gained, the medical community began to recognise a number of prob-

[28] Abstracts were obtained from the Medline database and for those that were not electronically available, we read the papers.

lems. First, in a small but significant number of cases, the procedure resulted in weakening and collapse of the internal structure of the artery necessitating emergency bypass surgery. Thus in the early days, coronary angioplasty could not be performed in locations where emergency operating facilities were not available. Second, tissue trauma at the site of the procedure sometimes triggered blood clotting which, depending on severity, would require major invasive treatment. Over time however the occurrence of this would be addressed with anti-thrombolytic drugs. The third problem was restenosis—the appearance of a new constriction in the artery. This tends to occur during the first 3–6 months after the procedure. It is not atherosclerotic in nature but results from the outgrowth of "endothelial" cells that normally line blood vessels. It has been likened to "over exuberant" tissue healing and regeneration similar to scar formation after the trauma of angioplasty.

Between 1986 and 1995 (nodes 10 up to 7) together with developments of the technique (e.g. node 8: applications new balloon on wire device) the problem of restenosis acquired increasing relevance and prompted the emergence of various attempts at solution (e.g. example, nodes 22 (n3 fatty acids), 37 (fish oils) and 39 (corticosteriods). During the latter part of the 1980s the solution of the stent gathered momentum. This consisted of a scaffolding structure, applied either with balloon angioplasty or on its own (self-expanding stent) which resolved two problems; first, it would act as a support structure to prevent the collapse of the inner vessel which sometimes occurred thus limiting the need for emergency surgery and second, it would reduce the impact of restenosis by mechanically maintaining the artery patency and thus the need for multiple angioplasty procedures. Nodes 1 up to 28 represent the period from the mid 1990s up to 2003. At the start of this period the beneficial deployment of stents was confirmed by major studies (nodes 7 and 1) while others addressed the major issue of in-stent restenosis. It was soon found that scarring occurred within stents restricting blood flow. Among the various solutions that have been explored are coated stent (nodes 17), medical therapies before and after stenting (node 21) and radiation (nodes 20 and 30). The question we pose now is: will we find similarities in the evolution of technical knowledge as documented in patents?

6.2. Synthesis of the evolution of technical knowledge

The exploration of the complementary technological is illustrated in Fig. 7. This highlights the variety of contributions that were diachronically associated with developments in coronary angioplasty. We can note that there were versions of balloon catheters parallel to Gruentzig's which emerged as the most successful and that a number of complementary developments followed the introduction of Gruentzig's double lumen cathether. The literature points out that especially important were the contributions of Simpson (Pat No. 4323071) who developed the steerable guide wire in 1982. This device enabled operators to access the most distal lesions by allowing greater direction control of the catheter through the coronary system. It led to an increased success in the angiographic success rate from 83 to 93%, a clinical success (angioplasty) rate from 79 to 91% and a lowering of the emergency bypass surgery rate from 7.2 to 2.8% by 1984 (King, 1998: 68).

In the same cohort of patents we find Gianturco's (Pat No. 4580568) which is a fundamental precursor of the previously mentioned Palmaz stent (Pat No. 4733665). This latter development appears to be the source of several streams of research branching rather neatly from the left lower section of the graph that relate to improvement in stent devices. Prototypes of the Palmaz design were used for two early randomised trials whose results were included in an evidence based consensus document published by the American College of Cardiology (ACC) in 1996. By the time this document appeared stents were being used in more than 50% of PTCA procedures. The pace of scientific and technical knowledge about stent improved rapidly so much so that by the time the ACC published a second consensus document 2 years later neither of the two stents approved by the FDA for use in the treatment of discrete de novo lesions to prevent restenosis and acute or impending artery closure were in use having been replaced by improved versions (Suwaidi et al., 2000). By 1993 and 1997 stents became widely used and the end of the decade they accounted for 80% of all angioplasty procedures (Schaaf, 2001).

Fig. 8 contains the Main Path of patent document, which summarises the main technological trajectory of surgical treatments of coronary artery disease. An analysis and evaluation of the patent documents associated to the Main Path reveals a trajectory that is broadly similar to the problem sequence that we observed with the bibliographic data.

Recall from our earlier discussion that one of Gruentzig's major achievements was creating a double-lumen balloon catheter specific to the problem of coronary artery disease. The prototype catheter was developed of all places, in his kitchen. He later entered

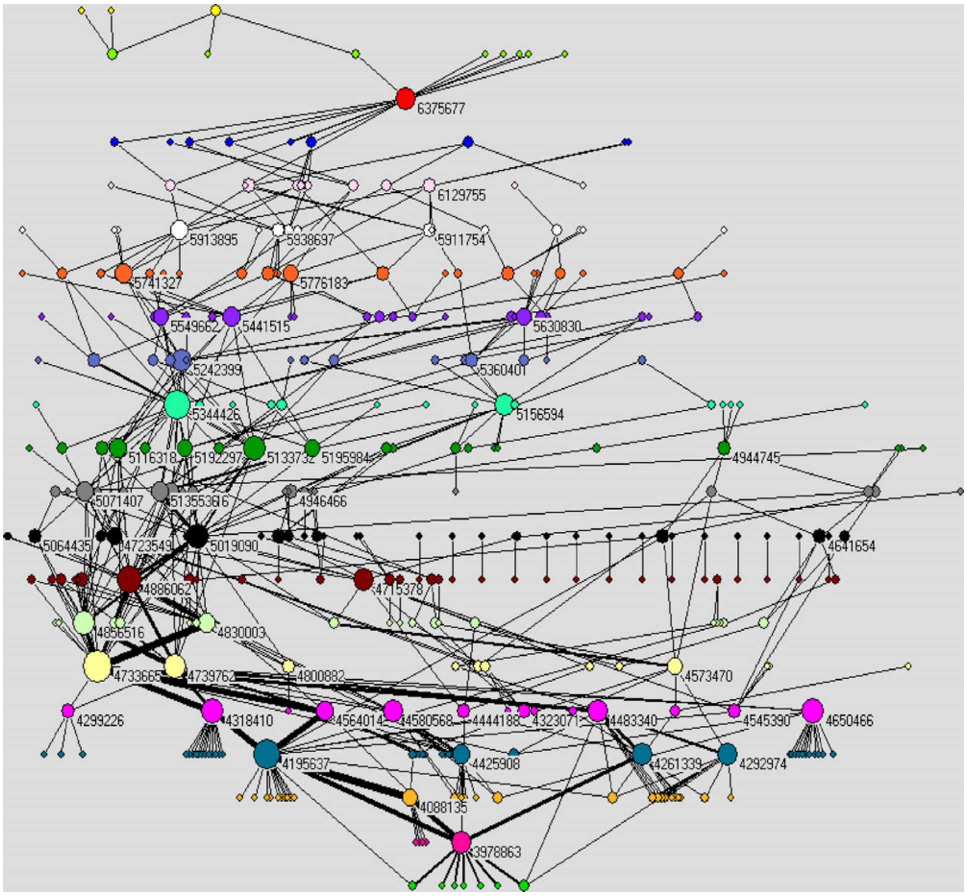

Fig. 7. Time evolution of technological network.

into a relationship with Schneider, a Swiss medical needle manufacturing company based in Zürich, for manufacturing a marketable device and applied for a patent with the US Patent and Trademark Office in 1977. This was granted in 1980 and paved the way for the diffusion of coronary angioplasty in the US. Citations reveal that Gruentzig's patent (number 4,195,637) built upon surgical and other catheters (bottom layer of the graph and node 3,798,863). A second wave of technological development started with Palmaz who was the first to receive a patent for a stent for the coronary arteries in 1988 (node 733665). Thereafter on the Main Path we observe an expansion of stent delivery systems which typically include the specially designed catheter apparatus. In the second half of the 1990s there appears to be a greater degree of specialisation reflected by a number of stent designs patented independently of catheter systems.

The Main Path analysis has enabled us to reduce the full data sets to the main trajectories in medical science and the associated and co-evolving technological knowledge. However, while we can identify the direction of the growth of research efforts, we are unable to appreciate the full scope of experimentation and the variety of complementary and competing solutions to different facets of the problem of coronary artery disease (and this is especially the case for patents with respect to papers). Main Path analysis privilege diachronic connectedness throughout the whole period considered and is not sensitive to the presence of local horizontal 'cliques' of innovative ideas. As a consequence, it tends to suppress extreme diversity and neglect important radical breakthroughs with a short history. To remedy, different tools are needed to investigate the composition of the patent cohort of the last decade.

To probe further into the inner structure of the network of recent patents, we use a 'clustering' algorithm which is capable of identifying areas of the entire search space where the local – 'internal' – connection between patents is relatively stronger than the global – 'external' – one. This allows us to account for the variety of complementary and competing areas of technical expertise

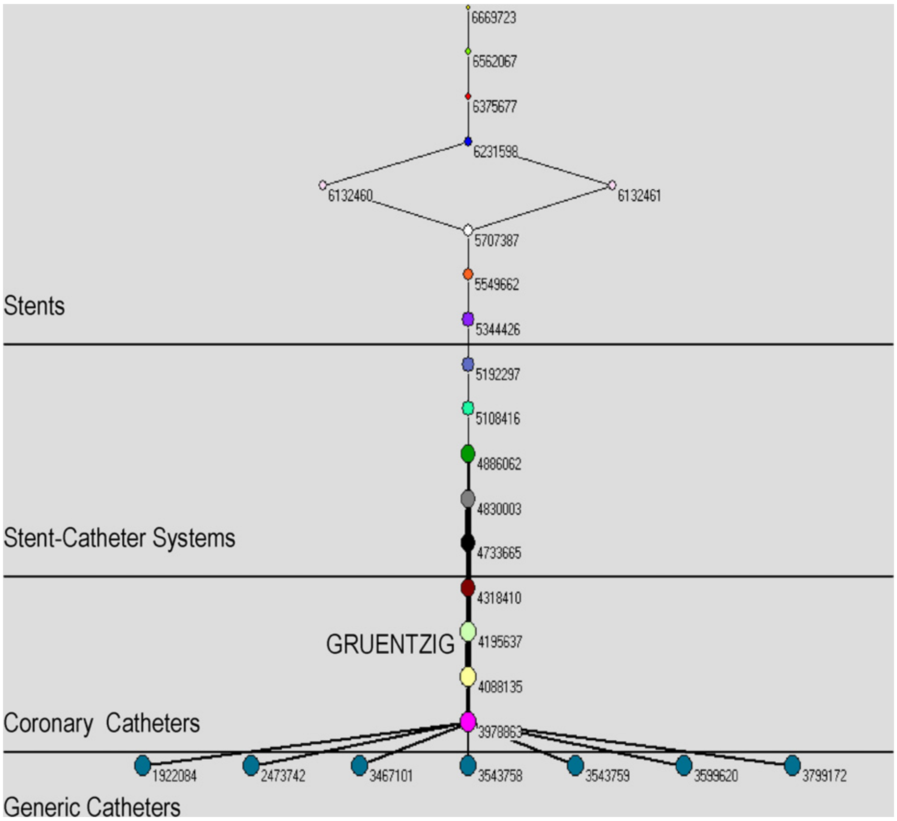

Fig. 8. Patents Main Path.

that contributed to the advancement of PTCA.[29] Because of space constraints we present only a selection of the clusters that emerged from analysis. Fig. 9 shows four clusters that have been extracted.

These groups of patents represent technical solutions which are complementary to stent and catheter devices but which are distinctive because they address different facets of the problem. Magnetic Resonance Imaging devices[30] for example are being developed as a non-invasive and potentially better performing alternative to traditional angiography procedures in the diagnosis of the disease. Atherectomy devices address the problem of reducing and removing the bulk of the plaque that occludes the vessel. They can embody rotor blades or laser emitting tips and be used for the treatment of restenosis before and after the placement of stents. Brachytherapy (radiation) is a potential solution to the problem of in-stent restenosis as it prevents an exaggerated healing response at the site of the lesion. It has been shown to reduce the recurrence of further blockages in the vessel (French and Faxon, 2002). However, the technique that has gained the most momentum against in-stenosis is the 'coated' stent.

This consists of stenting grafts that provide localised drug delivery. A variety of therapeutic substances (fibrin or other drugs) can be embedded on a thin polymer layer and are released over a period of time to inhibit the biological processes that are thought to cause restenosis. The last of the clusters presented in Fig. 9 illustrates a group of chemicals deployed for coating. Other interesting examples discovered in the data, which nicely prove the presence of a rich ecology of innovative efforts associated with widely different technological capabilities and niches of specialised know-how, include: CT scanners, anti-inflammatory compounds, digital image processing systems, angioplasty specific surgical tables, blood flow measurement detectors, filtering devices and contrast media for angiography.

[29] Interestingly, as the problem sequence evolved, different competence bases acquired relevance and provided windows of opportunities for new entrants thus renewing over time not only scientific understanding of the disease but also the composition of the industry (Mina, 2006).

[30] For a thorough discussion of the imaging industry, see Gelijns and Rosenberg (1999).

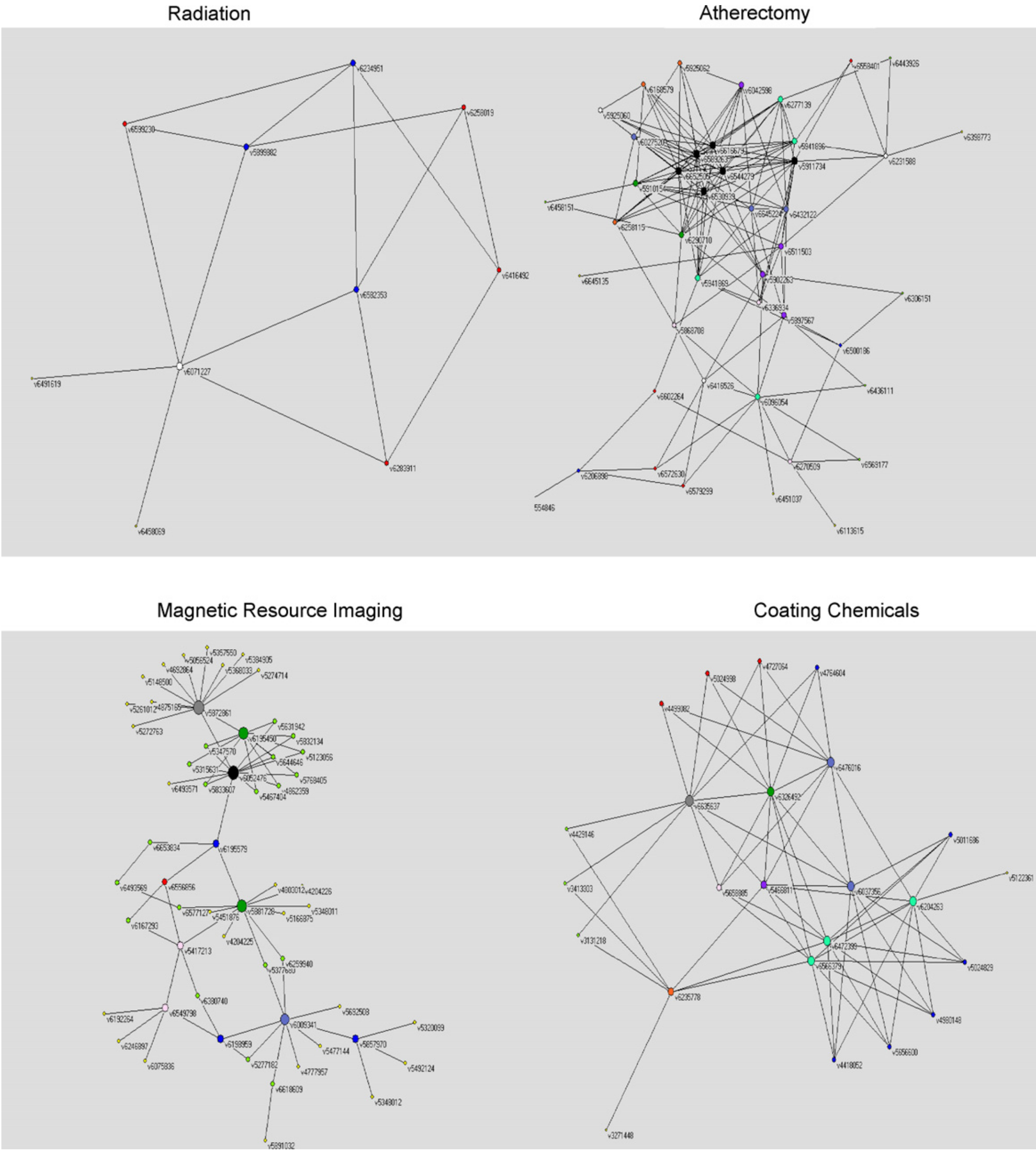

Fig. 9. Technology islands.

7. Discussion and conclusion

Over the past two decades innovation in health has emerged on the top of policy agendas across many countries, largely driven by the severe burden that health provision places upon their financial resources. Allocation problems are urgent and tend to dominate the debate. However, a dynamic view of innovation that recognises the long-term, path-dependent and complex nature of change in health technologies and systems, is equally important, but needs a different framework of analysis where processes of knowledge emergence, development and transformation are core.

The foundations of this paper are in the discussion of the uneven, uncertain, distributed and evolutionary traits of the innovation process. They incorporate the fundamental role of practice, that is the actual application of human skills to a problem, and its impact on the development of new knowledge. Such a perspective, very familiar to historians of medicine, encompasses feedback mechanisms between applied research, adoption and use and emphasises the open-ended nature of progress. Importantly, this is a process that is not deterministic. Its outcomes can hardly be foreseen yet they cannot be said to have emerged randomly and trajectories of change can be observed ex-post as a result of the process of accumulation of knowledge.

We have used the notion of a problem-sequence as a focussing device to uncover the nature of the discovery process and tested it through the extensive empirical analysis of the long-term development of one specific clinical area. We have taken as a unit of analysis a whole field of clinical research, namely interventional cardiology, and applied a combination of qualitative and quantitative techniques to map its global development over a period of nearly 30 years. By coupling the investigation of secondary sources and interviews to leading practitioners with new techniques of longitudinal network analysis, we have provided systematic empirical evidence of a set of scientific and technological trajectories and the way in which developments in the surgical treatment of coronary artery disease have unfolded over time. These display substantial co-evolutionary patterns. In addition, in-depth analyses of the main paths have enriched our understanding of the converging and diverging lines of contributions through time as well as our appreciation of the epistemic variety of complementary and competing techniques used in this clinical practice and widely discussed in the medical literature.

The long-term perspective we have adopted also stresses another important, and nevertheless often forgotten, feature of the process of emergence, growth and transformation of radically new understanding and treatment of diseases: its characteristically irregular tempo. The pace of innovation is uneven through time and the benefits that are now associated with successful new techniques are nowhere to be found in the performance of their first applications. The most relevant gains were usually obtained well after the original insights (and devices) were conceived and only in combination with other developments that were not at all foreseeable in the first place. Technologies that in the long-run have proven remarkably successful initially grew, and often did so for several years, in conditions of uncertainty with regard to their relative efficiency but on the basis of an increasingly collective vision of their potential benefits.[31] Diversified incremental change through shared practice, and not the genius of pioneers alone, was the key to their long-term affirmation.

How reliable a picture of the development of coronary angioplasty have we provided through our bibliographic network analysis? Are we sure we have explored trajectories of innovation and not just purely of inventions? First of all, the algorithms we deployed on the paper and patent datasets produce results that correspond very closely to the qualitative evidence available in numerous surveys to be found in the best medical journals and to specialised interventional cardiology device market reports. Secondly, all the results have been validated by a number of international experts we consulted during and after the study. Thirdly, the major technological shift from catheterisation to stenting, with windows of opportunities for alternative techniques, is clearly mirrored by data on the market approval of devices released by the FDA.[32]

We believe the methodology we have developed is capable of generating robust evidence of micro-processes of innovation and yield interesting potential for applications in other research domains. At the same time, the limitations of this essay are of course numerous. To begin with, this is a single disease area study and the results it produces, although based on rather comprehensive quantitative and qualitative data, should be generalised with care. Secondly, a number of factors have been left in the background, for example the role of institutional change that accompanied the development and diffusion of innovative treatments of CAD; the competing development of non-surgical solutions (i.e. entirely pharmacological and pharmacogenetic remedies) which may displace angioplasty in a not-so-distant future; the geographical and organisational distribution of fundamental and applied research. While some of these issues have been investigated in some details in other contributions (for example, Ramlogan et al., 2007; Mina, 2006), others clearly go well beyond the scope and space constraints of the present study and provide opportunities for further research.

Acknowledgements

While developing this paper we greatly benefited from comments by the participants of ‘The Uneven Growth of Knowledge’ Workshop (Florence, March 12–13, 2004) and the ‘Healthy Innovation’ Workshop (Manchester, July 8–10, 2004). We wish to express

[31] In this light, we might ask, would coronary angioplasty (but also by-pass surgery) have come about if cost-effectiveness criteria had been enforced at the time of their initial development the way they are now increasingly enforced by regulatory agencies to contain health costs?

[32] Available at http://www.fda.gov/hearthealth/treatments/medicaldevices/medicaldevices.html.

our gratitude to Professors Richard Nelson and Andrew Webster, who were so generous with their advice and support. We also thank Professors Cristiano Antonelli, Giuseppe Clerico, Salvatore Rizzello, Mark Dodgson and Annetine Gelijns (and her colleagues at the International Center for Health Outcomes and Innovation Research of Columbia University). Finally, we would like to thank Dr. Luigi Venetucci and Prof. Anthony Heagarty from the Manchester Medical School, and Prof. Spencer B. King III (Fuqua Heart Center, Piedmont Hospital, Atlanta), Martin B. Leon MD and Eric A. Rose MD (Columbia Presbyterian Hospital, New York). We acknowledge the financial support from the UK ESRC and MRC IHT (Innovative Health Technology) Programme, co-ordinated by Prof. Andrew Webster.

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