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Network Evolution in the Triple Helix of Particle Therapies: Insights from Bibliometric and Interview Data

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Abstract

This paper seeks to contextualize the discourse on science-technology overlap within the Triple Helix innovation model. It explores the co-evolution of scientific and technological communities relative to two successive research streams within a new scientific paradigm in radiation therapy of cancer: particle therapy. An interdisciplinary community has been emerging across university, industry and government laboratories globally. We structure a theoretical framework which integrates a community-based view of science and technology, "duality" of people and groups, and the triple helix innovation model. We analyze bibliometric and interview data mainly and find overlap between the scientific and technological communities across the triple helix. This overlap occurs via co-authorship of scientific papers, consulting, patenting, informal advice, circulation of scientists and proximity to star scientists. Yet, if science and technology overlap at an international level, the old view of scientific progress based on communities (Kuhn 1962; and Crane 1970) still holds but further research shall clarify if the timing of scientific and technological development is affected and how.

Keywords: triple helix, social network dynamics, particle therapy, star scientists

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S1.1. History and conditions for success

Introduction

The social processes which allow for scientific and technical progress have largely drawn the attention of scholars of science and technical change, and policy-makers for many years. International scientific collaboration has increased due to a number of factors internal and external to science (Wagner and Leydesdorff, 2005). Science and technology developments are intertwined (Price 1984) and can be contextualized in the 'triple helix' of industry-university-government relations (Etzkowitz and Leydesdorff 2000). Scientific and technological networks co-evolve and overlap (Murray 2002) and 'mode 2' knowledge production involves greater transdisciplinarity and collaboration between sites (Gibbons et al. 1994). Overall this is points to the underlying relational nature of innovation which deserves researchers' attention (Edquist 1997; Etzkowitz and Leydesdorff 1997).

Nowadays researchers are puzzled about innovation network dynamics. Generally speaking, this is because a given relationship may change over time (e.g. from weak to strong), and a whole structure of relationships too. When these changes in relationships and structures are a result of a coherent social process, this is termed network evolution.

The coherent social processes we are interested in are scientific and technical progress. Murray (2002) acknowledges that "the old view that 'science' was an exogenous and self-contained process has been replaced by a growing awareness that science may be, to a considerable, extent endogenous. Moreover much work suggests that science and technology may in fact co-evolve and that the nature of such interaction may be much more bi-directional than was originally thought." She provides supportive evidence and a novel methodology to show this. Her distinction between scientific and technological networks is based on the different social structure of science and technology proposed by Dasgupta and David (1994). The literature on scientific (Price 1963; Kunh 1962; 1970; Merton 1973; Pickering 1995; Knorr-Cetina 1999; and Crane 1970) and technological communities (Constant 1984; Assimakopoulos 2007; Dosi 1982) seems relevant in this respect. While these studies focused on science or technology, Murray's contribution is on their co-evolution.

This paper aims to start from exploring this co-evolution and go back to science only. If science and technology overlap, does the old view of scientific progress based on communities (Kuhn 1962; and Crane 1970) still explain the changes in relationships and structure of scientific collaboration? Is the underlying social process of building science still the same in a world in which companies may participate to the scientific community life which has grown internationally? To keep this interrogative close to the current reality we may redress the question in a different fashion. How do social networks of scientists evolve throughout the shaping of intertwined science and emerging technologies within the triple helix?

Different actors and groups shape new technologies (Blosch and Preece 2000) which may be regarded as emerging in configurations of disciplines, skills, and potential users (Leydesdorff and Rafols 2010). If science and technology overlap, these actors and groups may belong to scientific and/or technological communities, while being affiliated to organizations which can be positioned in the triple helix.

Three pillars which are at the basis of the theoretical framework used in this paper: "duality" of people and groups, scientific and technological communities, and the triple helix. These pillars span from the individual to the systemic level, and can be regarded as different layers and aspects of the relational nature of innovation. Social network analyses are suited to bring them together in a single framework. Indeed, a network perspective is applicable at each level–people, groups, organizations, communities, and helices. This would be consistent with the view of multiplex networks.

We sought to map and explore the evolution of triple helix networks by focussing on a new scientific paradigm which led to new technological developments. Particle therapy is a new paradigm in radiation therapy of cancer, having two competing streams using different particles: protons and carbon-ions. Proton and carbon-ion therapies have been emerging at the cutting-edge of cancer treatment as they offer remarkable advantages compared to conventional X-ray therapy of cancer which is widespread in the world. Yet, several barriers (technical and non-technical) shall be overcome for these technologies to be adopted as conventional therapies.

As remarked by Baba et al. (2009), different bodies of literature studied university-industry collaborations by focusing on different industries. This is important as: a) innovation processes may vary among industries depending on their knowledge base (Asheim and Coenen 2005, Asheim and Gertler 2005, Moodysson et al. 2008); and b) public research plays a different role among industries (Pavitt 1984). Accordingly, a study on "particle therapy" in the health care sector may offer new insights, given the interdisciplinary nature and public research's focus on such scientific and technological developments.

Theoretical framework

A key contribution (Murray 2002) on innovation, studied the co-evolution of scientific and technical developments. It showed that distinctive scientific and technological networks exist and overlap to an extent. We found interesting to seek and contextualize this explicitly within the triple helix of industry-university-government interactions.

Community and evolution

The social structure of science and technology is different (Dasgupta and David 1994). This is the basis of Murray's distinction (2002: 1390) of scientific and technological networks: "Science they argue is characterized by publication, supported by a priority-based reward system and exists predominantly (but not exclusively) in research universities. This is in contrast to the world of technology in which ideas are produced for economic ends and encoded in patents and other modes of protection to facilitate appropriability. This simplified distinction provides a starting point from which to explore how the individual scientists, scientific and technical communities and their institutions shape the co-evolution and co-production of new ideas."

A stream of authors (Price 1963; Kunh 1962; 1970; Merton 1973; Pickering 1995; Knorr-Cetina 1999) focused on the social organization of science based on communities. By building upon Kuhn's key contribution (1962; 1970), Constant (1984) and Assimakopoulos (1997, 2007) have focused on the social organization of technological practices based on communities. Crane (1972) conceptualizes the evolution of scientific knowledge as growing along an S-shaped curve. Dosi (1982) conceptualizes technological progress similarly as evolving in an S logistic growth curve. Performance is limited and thus individuals and organizations explore alternative approaches to the problem they focus on.

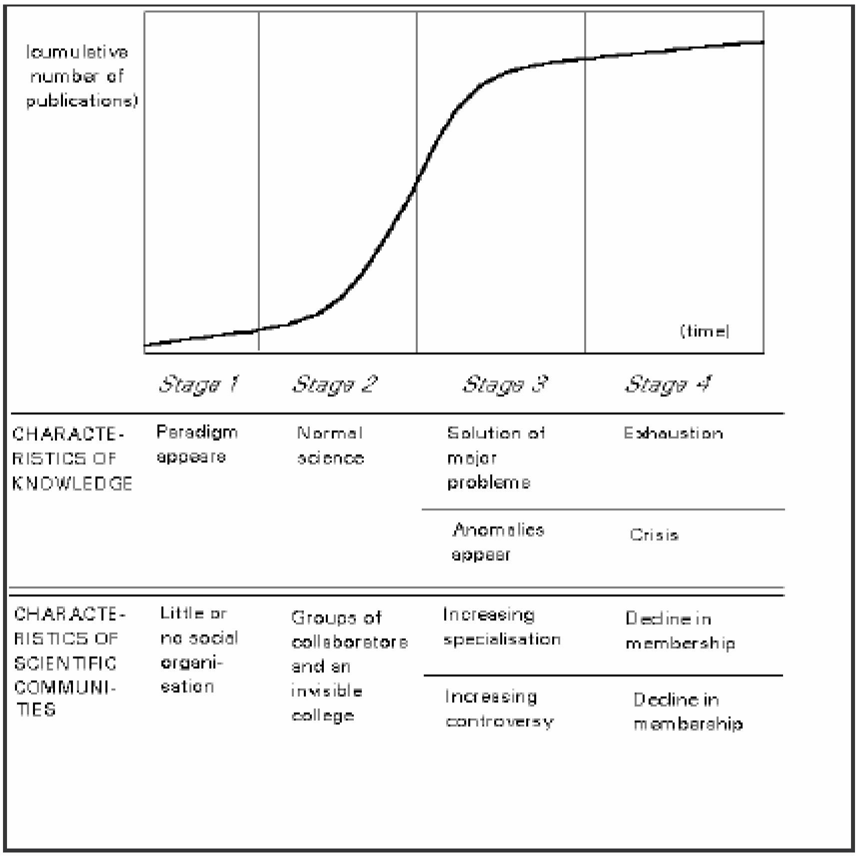
Kuhn (1962; 1970) argues that communities of scientists are the social locus of scientific knowledge. In each community, scientists create and follow a paradigm. This gives specific exemplars and has a narrow and specific usage which is associated to the evolution of scientific knowledge. A paradigm is a set of beliefs regarding several aspects: what the object of research, the methods of approach to it, the concept of science, theories, relevant issues, and the values and meanings of a discipline (Bonet et al. 2009).

Kuhn argues that scientific progress is not continuous and that two periods alternate over times, i.e. "periods of normal science" and "periods of scientific revolutions". In periods of normal science research is undertaken in the scientific community and faith in a paradigm is necessary for people to engage in it. From this, optimism becomes rooted in a scientific community and new theories are created. Periods of scientific revolutions are those in which a paradigm shift occurs. In periods of scientific revolutions consensus is difficult to be reached. When anomalies appear for existing paradigm to be questioned, and there is a rejection of the old paradigm in favour of a new one, this implies the abandonment of the old community for the new one.

Based on Kunh's argument, Constant (1987) draws a parallel and defines technological communities. He argues the communities of technology practitioners are the social locus of technological knowledge. These individuals create and follow technological tradition of practice associated with the evolution of a particular technology. But differently from scientific paradigms, technological traditions have not only a cognitive but also a strong socio-cultural dimension. The cognitive dimension includes scientific theory, methods, but also hardware, and software, implying both tacit and explicit knowledge. The socio-cultural dimension includes communication structures, values and beliefs which are the glue of the community. The key point of contact between the scientific and technological communities is, as it can be expected, surely scientific theory.

By comparing scientific revolution (Kunh 1962) and technological evolution (Constant 1984; Assimakopoulos 2007) it is possible to highlight a key difference as regards the evolution of these different communities. In scientific communities the rejection of an old paradigm for a new one implies the abandonment of one community for the new one. Instead in technological communities there is no implied rejection of old traditions in favour of the new ones: multiple membership to different communities is possible.

Figure 1: Crane's view on the evolution of scientific knowledge and communities



Source: Crane 1972: 172.

Crane (1972:22) argues that scientific knowledge grows in a kind of a diffusion process (see figure above). In turn the growth of publications in any scientific field follows the logistic growth curve depicted for the diffusion of innovations. When a paradigm appears there is little or no social organization in the community. In periods of normal science, there are groups of collaborators and/or an invisible college. When major problems are solved or anomalies appear in the paradigm, there is increasing specialization and controversy within the community. And when there is exhaustion or crisis of the paradigm, a decline in membership can be observed.

Science and technology overlap

Murray (2002) points to the concept of co-evolution of scientific and technological networks and cites Nelson's statement (1995: 63) that scientific progress may in part "reside in the connections between science and technology". She shows evidence on the science-technology overlap and provides a novel methodology to study it empirically. Her contribution explores a number of avenues of science-technology overlap: co-publishing/citation and co-patenting, consulting, informal advising, movement of human capital from academy to industry, proximity to "star scientists, licensing, and company founding. Regarding co-publishing and citation, she found that firms do not participate in science, differently from what found by Henderson and Cockburn's (1994), Arora and Gambardella 1994, and Liebeskind et al. (1996). Their contribution focused on how company ties to scientific communities affect the company performance especially in terms of technological progress for new and science-based technology. In times in which a technological paradigm shift is associated to one in science, firm's publishing is key for a successful transition to the new technological paradigm. Murray (2002) found overlap occurs via licensing, consulting, advising, and company founding by scientists. Regarding the latter, it is important to add when and where companies are found. In this regard, Zucker and Darby (1998) found that most productive "star" bio-scientists played a central role in where and when new bio-tech firms were formed.

An additional avenue may be considered. As remarked by Leydesdorff and Meyer (2007:2), Price (1984:6) proposed the concept of scientific "instrumentalities" (e.g. Galileo's telescope used for momentum discoveries) that mediate between science and technology developments in periods of "normal science" and "normal technology". Price (1984:13) stressed that instrumentalities –unlike instruments– could also set the ground for binding scientists and engineers in invisible colleges through making available a new methodological and technical option to them. A new instrumentality may produce a scientific breakthrough or paradigm shift. And the possibility of making available new technological products that were not around previously. Government laboratories play an important role in providing new instrumentalities (Rosenberg 1992) and methodologies (Salter and Martin 2001). And these can be further developed to adapt to commercial needs (OTA 1995).

Interestingly Breschi and Catalini (2010) explore the co-evolution of science and technology and find that author-inventors who bridge the boundaries between science and technology domains are crucial for allowing connectivity. These gatekeepers can be expected to be important in science or technological networks, yet only only in one of these networks and not in both. They also poin out that European corporate scientists tend to be less present in technological networks than their US counterparts.

Gittelman and Kogut (2003) show how crucial are for bio-tech companies ties with the open science through boundary-spanning 'gatekeepers'. But having bridging ties (i.e. spanning organizational boundaries) is not conducive to innovation per se, as they need to be Simmelian (strong and sticky) ties (Tortoriello and Krakhardt 2010). Zucker et al. (1998; 2002) show the most successful bio-tech companies are co-authoring with university professors. In these contributions, people in a certain position (boundary spanning gatekeepers) in a network of individuals are crucial for producing an outcome for their company. This company outcome, say technical advances, may affect its ties with other organizations and people in these organizations, say other universities and professors.

From people to the Triple Helix: a chain of dualities

When science and technology overlap (Murray 2002), the different actors and groups which shape new technologies (Blosch and Preece 2000) may belong to scientific and/or technological communities, while being affiliated to organizations which can be positioned in the innovation triple helix. If we shift the focus from communities to actors, we may seek to contextualize them in a single system of innovation: the triple helix. We can move from people to groups and organizations, and position them in the Triple Helix. We can also move along a chain of "dualities": people and groups, groups and organizations, organizations and helices. This "duality chain" may be used to look at the overlap between science and technology.

Breiger (1973) initiated the research tradition on "duality" of people and groups and Lazega et al. (2008) recently contributed to it. They looked at multi-level networks of superposed and partially connected interdependencies between actors in different networks, i.e. inter-personal, and inter-organizational. Lazega et al. created a method of structural linked design which articulates these different levels. First the analysis of the whole networks at each level is carried out. Then, the two levels are put in relation to each other by looking at the organizational affiliation of individuals and how each pairs correspond in the two levels, as in bipartite networks. This way they can look at centrality measure in both levels and identify small and big fishes (cancer researchers) and small and big ponds (labs). Finally they look at (scientific) outcomes measures to identify catching up strategies of small fishes adopt. They argue this adds a new dimension to the sociological study of outcomes, meso-level phenomena (e.g. opportunity structures), and macro-level phenomena such as social inequality.

When the outcomes obtained by an organization affect the resources obtained by another organization in the same network or outside of it (e.g. a successful university lab may obtain more resources over time and, since public budgets are shrinking, other labs may see their pond shrinking). We may use they example of research funding of HIV cures vis-a-vis particle therapy. If a university lab is successful in its HIV research leading to a new cure which is highly cost-effective, then the respective government will be confronted with funding one stream or the other to the benefits of industry and of society at large. This links the duality of people and groups with the triple helix model of university-industry-government relations.

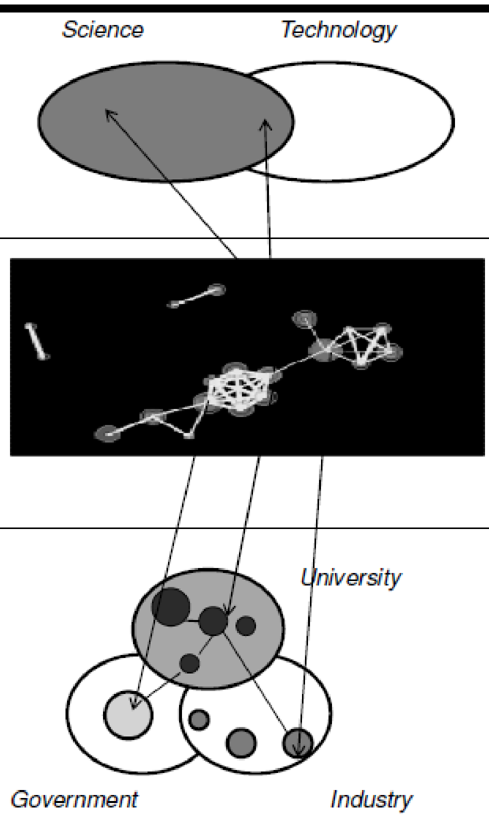
The three pillars emerge from the above discourse. These are: "duality" of people and groups, a community-based view of science and technology, and the triple helix innovation model. These may be regarded as three pillars of a framework which spans from the individual to the systemic level of analysis, and can be regarded as different layers and aspects of the relational nature of innovation. Social network analyses are suited to bring them together in a single framework. Indeed, a network perspective is applicable at each level–people, groups, organizations, communities, and helices.

One may recall a classical interrogative in social theory: does position determine the actor outcome, or vice versa? By adding the time variable, which position at a given point in time does determine which outcome at a given point in time, and vice versa? Now, which position of an actor does determine which outcome in a inter-group or inter-organizational structure, and vice versa? (fish-pond "duality"). And which position of an organization does determine which outcome in the triple helix? (pond-helix "duality"). By adding the time variable, when are these positions determining these outcomes or vice versa?

We may rename these two dualities by using astronomic metaphors which we can refer to in the empirical analysis. First a star-constellation "duality" would include scientists and their research groups. The most cited and prolific scientists are big stars and have a position in the constellation structure. Young scientists (small stars) are more pheripheral but "gravitating" around big stars. Their research groups may be bigger or smaller (in terms of resources, expertise, and number of scientists) and may collaborate with other groups or not: the size and structure of the constellation depends on these differences. Yet, these groups belong to an organization which can be positioned in the triple helix galaxy (constellation-galaxy "duality").

Even though this is outside the scope of the paper, such a framework might be linked to the research efforts in developing new science, technology and innovation indicators. Lepori et al. (2008) stress that changes of indicators of science, technology and innovation are linked to shifts in the research and innovation system, as well as to the transition from a centralized to a distributed intelligence. They call for a change of rationale from an input/output to a positioning indicators framework, focusing on flows and linkages between actors in the innovation system. Thinking of a chain of duality and looking at network positions data (e.g. centrality and betweeness measures) as well as outcomes may link to their call.

Figure 2: The ‘chain of dualities’ framework



Perspective	Illustration	Key references	
Community – Social organization		Scientific Communities (Khun 1962;Crane 1972) Tech communities (Constant 1987; Assimakopoulos 2007; Dosi 1982)	
		Overlap of Science &Technology networks (Murray 2002)	
Networks of: a) Individuals •Scientific authors •Inventors b)Groups or Organizations		Social Newtorks •Simmelian ties (Tortoriello & Krackhardt 2010) •“Duality” (Breiger 1974; Lazega et al. 2008) University-Industry Collaboration	SN research on innovation networks Other streams using SNA as a method
		TH indicators based on research production (e.g. Park and Leydesdorff 2010)	
Innovation System		Triple Helix (2000)	

Source: elaboration of the authors.

As shown in the figure above, such framework may be used to map these literature bodies more comprehensively. Even though this is not within the scope of our paper, one simple consideration can be done by referring to some relevant references in these research streams: on the one hand, bibliometric and social network analyses are used to study respectively the science-technology overlap (Murray 2002) and the evolution of scientific collaboration (Barabasi et al. 2002); on the other hand social network theory is built by using data on scientists and technological practitioners (Lazega 2008; Tortoriello and Krakhardt 2010). This is what may make these different literature bodies informative of each other. The table can further be filled with a section on methodologies used, and industries studied etc.

Methodology and data sources

First, semi-structured interviews have been carried out with leading experts in order to explore and refine the scope of the study. They have also pointed to key secondary data such as reports and scientific publications that it was worth analyzing.

Second, co-authorship and co-citation networks of scientific papers for both routes have been studied. The corresponding data sources are the Science-Citation-Index-Expanded and Conference-Proceedings-Citation-Index-Science. In the first interviews, the interviewees have been asked what they consider as the relevant search strings to be used for the bibliometric data gathering. A small online survey has been administered to them to give time to reflect and list relevant strings. Two datasets have been generated covering mostly the clinical side and including 1920 and 440 records for route 1 and 2 respectively.[2] Then two other datasets of 1634 and 1024 records have been generated for route 1 and 2 respectively and covering the spillovers from accelerator science to the other disciplines. With the second datasets, the network evolution visualization has proceeded by ten-year-slices (5 for proton, and 2 for carbon-ion).

Finally, semi-structured interviews with leading experts (identified through the bibliometric analyses and interviews) have been carried out with the aim of triangulating the findings obtained in the first two steps of the research design. So far we have interviewed 12 key scientists who have been active in the US, Europe and Japan.

Bibliometric data gathering approach

Step 1: Retrieval of two general datasets. A formal 'nominalist' search has been based on search strings which have been collected by asking experts in the field of particle therapy. These strings have been used to generate two initial datasets, i.e. one per route, which included more than 100,000 records each. These datasets included also irrelevant data and therefore the following steps have been taken to get rid of such data.

Step 2: Refining by document type (articles and proceedings papers). Both published articles and conference papers have been included in the dataset as they represent the outputs of research to be disseminated. This search limitation allowed excluding other irrelevant records from the datasets. Although journal publications and proceedings papers may be considered as overlapping, we have include both for the following reason. Conference papers seem to be particularly relevant as semi-structured interviews have highlighted the important role played by certain conferences in the field. Several star scientists stressed that important decisions are taken at conferences, and that some proceeding papers which have been key for future developments, have not been followed by a publication, though becoming highly cited.

Step 3: Combination with an 'organizations' search string. Both datasets have been combined with a new search for organizations. These organizations have been again identified together with particle therapy experts and include all major centers of research and technological development (RTD) in the area of proton and carbon-ion therapy. These centers are universities, government labs and companies; they include both physics and clinical research (university hospitals).

[2] We number the routes in order to better communicate the historical sequence of proton and carbon-ion routes. The aim is to ease the reading as we acknowledge the complexity of this particle therapy study.

The companies involved can easily be listed by experts in the fields as they are limited in number worldwide. This is due to given the high level of risk-bearing, expertise and investments required to participate in the RTD of particle therapy facilities. Likewise, the government labs and universities involved in such a research can easily be traced into the data for one key reason: there are a limited number of accelerator facilities (clinical and non-) worldwide where such research could be carried out, and this is due to the high construction costs of these facilities (i.e. hundreds of millions of dollars). Overall, this is consistent with the concept of scientific instrumentalities which function as the "glue" of the community (see theory section).

Step 4: Reiteration of previous steps to include and exclude records. Some key terms have been excluded and new key terms and organizations have been included in the search strings and the differences with previous datasets have been analyzed. Not only have the number of records been monitored, but also the presence of records from different disciplines. In this reiterative process, the opinion of experts has been asked.

Empirical study

Our study started by discussing with experts in accelerator physics about different scientific developments which followed improvements in the accelerator science and allowed for relevant technological applications. While some developments regarded industrial facilities, we found the particle therapy of cancer interesting for several reasons: mainly its interdisciplinarity, international dimension, and the fact that the new clinical applications developed are associated with a new paradigm in radiation therapy of cancer. Below we provide more detailed preliminary findings on the history and characteristics of the particle therapy community, based on interviews and bibliometric data mainly. On a minor extent, we also analyzed reports and scientific papers, and observed directly: a) an international scientific workshop in which the core of the particle therapy community reunites (including mainly scientists from university, government labs and companies), and b) the functioning of research facilities as well as commercially oriented clinical facilities.

Two routes of Particle Therapy

The evolution of scientific knowledge on "particle therapies" of cancer has been intertwined with the development of cutting-edge technologies based on proton and carbon-ions since the 1950s and 1990s respectively. Both proton and carbon-ion routes are at the intersection of physics, bio-medicine, biology and bio-chemistry, and resulted from the collaboration among several universities, companies, government laboratories and agencies mainly in the USA (e.g. Loma Linda University, LBL Berkley[3], Varian), Japan (e.g. Chiba University, NIRS, Hitachi) and Europe (e.g. CERN, GSI, Siemens).

Particle therapy (also known as hadrontherapy)[4] offers one key strength vis-à-vis conventional radiation therapy of cancer (i.e. based on beams of X-rays). In particle as well as in conventional radiation therapy, beams are delivered to the patient to destroy tumor cells. As inevitable, the surrounding healthy tissues also receive some radiation doses. The damage is

[3] A U.S. Department of Energy National Laboratory Operated by the University of California.
[4] In this paper the terms "particle therapy" will be used only in the sake of clarity.

lower with charged protons and carbon-ions than with X-rays. Both protons and carbon-ions offer higher precision when irradiating the target region (Dosanjh et al. 2007; Enlight, 2010).

Route 1 technologies (i.e. based on protons[5]) are nowadays maturing after more than 50 years of research and technology development (RTD). Route 2 technologies (i.e. based on carbon-ions) are emerging after two decades of RTD yielding potentially dramatic improvements vis-à-vis route 1 but also higher uncertainty about their biological effects. In the US, route 1 has been developed importantly while route 2 has not been backed with the necessary support by companies and government, having not been approved by the corresponding US agency within the U.S. Department of Health and Human Services –the Food and Drug Administration (FDA). The US research involvement in technology 2 RTD has therefore shifted to collaborations with European actors significantly.

Interviews and papers analyses (Dosanjh et al. 2007; Enlight, 2010) show that research on the proton route originated in the US in 1946 and the first patients were treated in the 1950s by using non-dedicated accelerators. At that time only a few parts of the body could be treated due to the low power of accelerators. However until that time proton therapy was only at its outset. It was in the the late 1970s that proton therapy started becoming viable for clinical applications thanks to the advances in accelerators, medical imaging and computing. This links back to the concept of scientific instrumentalities which allowed mediation between science and technology and bound together different experts from different disciplines. Proton facilities entered medical clinics only in the early 1990s. Nowadays there are about thirty proton centers in the world.

Research on the carbon-ion route originated in the US in the late 1980s and migrated to Europe and Japan in the 1990s after the closure of the Bevalac accelerator in Berkeley, California. The most significant contributions have been achieved in Germany and Japan under the leadership of two scientists who had previously carried out research at Berkeley. In 1994 a first dedicated facility was operational in Japan. In 2009 a first facility which could use both protons and carbon ions started treating patients in Germany (HIT). Other facilities of this kind have been or are being constructed in Europe and Japan.

In both technologies' RTD work some land-mark phases can be identified:

- The *development* of scientific knowledge on particle therapy which results into publications and the application of this knowledge, protected through patents. This phase requires adaption of non-dedicated facilities, or design, construction, and testing of new facilities. The relationship with firms is limited to commissioning parts of the designed facilities.

- *Transfer of expertise to industry* for the construction of commercial facilities to be possible. This tends to happen with the commissioning of the construction of research-oriented facilities designed by government lab or university scientists, a phase in which the interaction between firms; university and PROs is key.

- *Initial commercialization* of clinical facilities (construction and operation) limited to further clinical trials.

[5] We number the routes in order to better communicate the historical sequence of proton and carbon-ion routes. The aim is to ease the reading as we acknowledge the complexity of the particle therapy case.

- The *clinical trials* are carried out to reach the statistical evidence required by medical doctors for the acceptance of these technologies for standard clinical practice. This produces further publications, patents, standards and protocols for the use of machines and therapy administration.
- *Wider commercialization* of the technology is possible as the technology is considered to be “ready” by medical doctors, based on extensive statistical evidence.

These phases are reiterative and overlap over time, underlying a non-linear innovation process. This seems to be in line with previous contributions. Indeed, government laboratories play an important role in providing new instrumentalities (Rosenberg 1992) and methodologies (Salter and Martin 2001). And these can be further developed to adapt to commercial needs (OTA 1995).

First bibliometric analysis: from the clinical side

The first data gathering includes 1920 records for route 1, and 440 records for route 2. It shows the latest scientific progress especially within the clinical side (See key subject areas around biomedicine and clinical science in the table below).

Table 1: Number of records by top Subject Areas retrieved Science-Citation-Index-Expanded and Conference-Proceedings-Citation-Index-Science

Proton (1920)	Carbon ion (440)
RADIOLOGY, NUCLEAR MEDICINE & MEDICAL IMAGING (988)	RADIOLOGY, NUCLEAR MEDICINE & MEDICAL IMAGING (209)
ONCOLOGY (537)	ONCOLOGY (129)
NUCLEAR SCIENCE & TECHNOLOGY (265)	NUCLEAR SCIENCE & TECHNOLOGY (70)
ENGINEERING, BIOMEDICAL (206)	BIOLOGY (54)
CLINICAL NEUROLOGY (157)	INSTRUMENTS & INSTRUMENTATION (49)

This corresponds to the early stages of the particle therapy community social organization. The yearly peaks of 60 publications in carbon ion and 198 in proton amount to a total of 258, and can be compared with the peak in conventional radiation therapy publications, i.e. 420 records. This may be an indication that particle therapy is entering stage 3 in Crane's S-shaped curve of publications.

Figure 3. Crane's S shaped curve

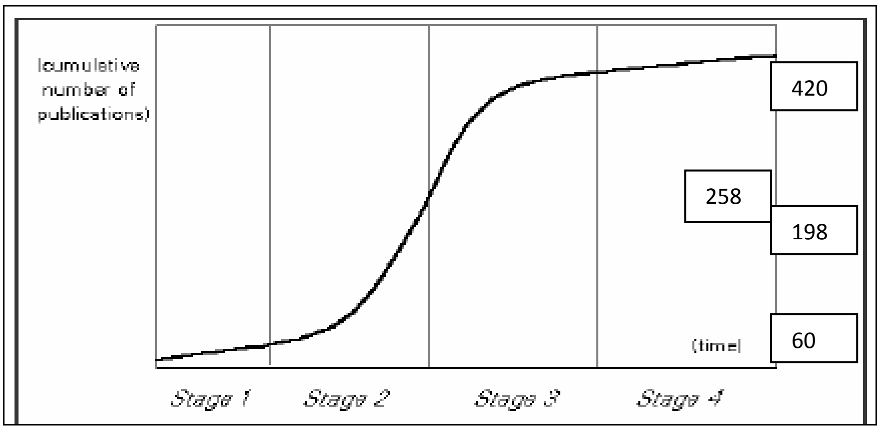
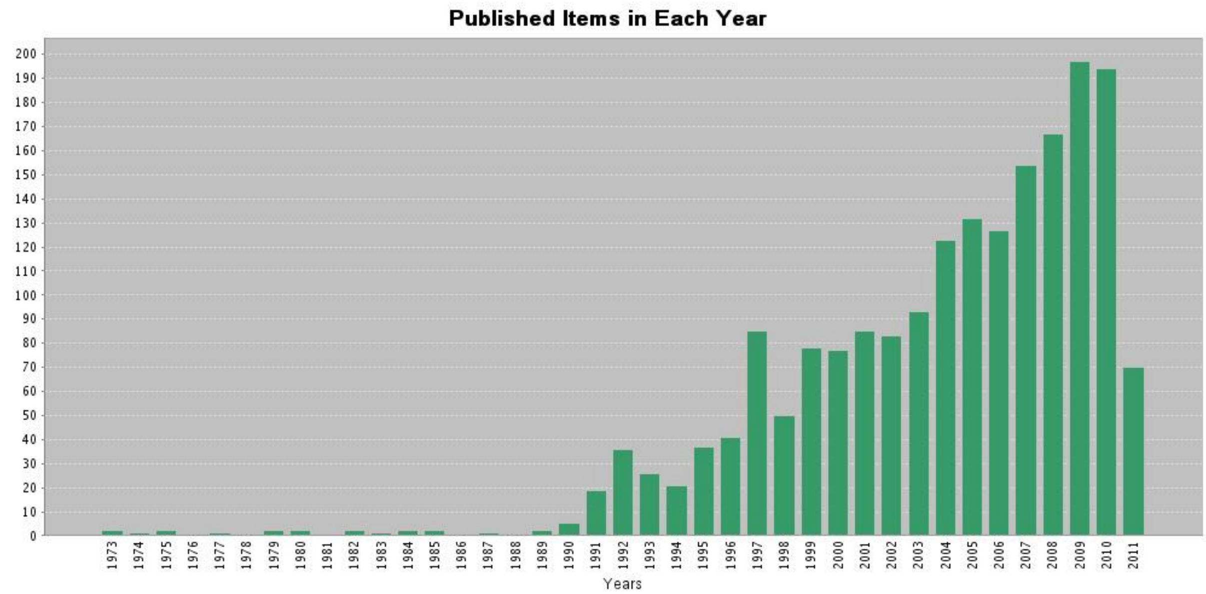
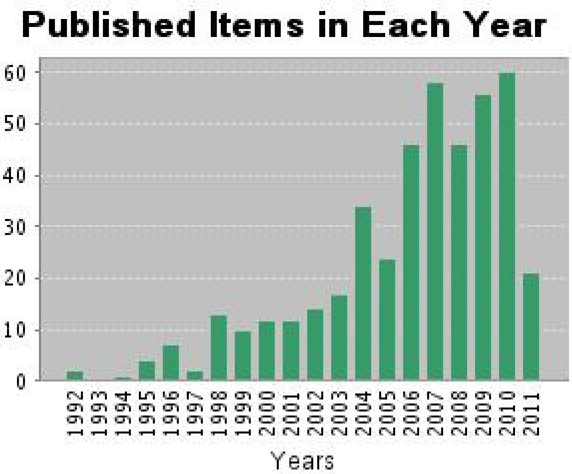


Figure 4. Number of papers per year retrieved in the Science-Citation-Index-Expanded and Conference-Proceedings-Citation-Index-Science; 1972-2011.

R1: Proton route





R2: Carbon ion

Regarding key authors by records count (see table below), a number of names is found to correspond to top cited authors, top co-cited in co-citation networks, and nominated by interviewees. For route 1, the overlapping names across these data are in particular the Medical Doctors Slater JD and Slater JM (Loma Linda University), Medical Doctor Suit from MGC (USA), and Eros Pedroni from PSI (CH). For route 2, for route 1, the overlapping names across these data are Tsujii, Kraft, Kanai, Debus, Sholz, Kato, Durante and Kramer. Both Kraft and Tsujii did research in California, where route 2 idea originated, and then brought it to Germany and Japan and developing extensively this research there. Let us recall that carbon ion route was not approved by the FDA and, in turn, it could not develop extensively in the USA.

Table 3: Top 40 authors based on records count in the Science-Citation-Index-Expanded and Conference-Proceedings-Citation-Index-Science

R1: Proton route

Top 5	Top 10	Top 15	Top 20	Top 25	Top 30	Top 35	Top 40
LOMAX, AJ (57)	NEWHAUSER, WD (38)	AKINE, Y (29)	HABRAND, JL (24)	TITT, U (20)	FERRAND, R (18)	MAZAL, A (17)	EGGER, E (16)
PAGANETTI, H (48)	CUTTONE, G (34)	GOITEIN, M (29)	GOITEIN, G (23)	BORTFELD, T (19)	GRAGOUDAS, ES (18)	MILLER, DW (17)	GEORG, D (16)
SLATER, JD (48)	TOKUUYE, K (32)	SUGAHARA, S (28)	GLIMELIUS, B (22)	LOEFFLER, JS (19)	LIEBSCH, NJ (18)	SUIT, HD (17)	GRIDLEY, DS (16)
SLATER, JM (46)	MOHAN, R (30)	HUG, EB (25)	SCHNEIDER, U (21)	OLKO, P (19)	NOEL, G (18)	CHAUVEL, P (16)	GRUSELL, E (16)
MUNZENRIDER, JE (38)	PEDRONI, E (30)	CIRRONE, GAP (24)	OHARA, K (20)	DESJARDINS, L (18)	DELANEY, TF (17)	DELACROIX, S (16)	MIRKOVIC, D (16)

R2: Carbon ion

Top 5	Top 10	Top 15	Top 20	Top 25	Top 30	Top 35	Top 40
TSUJII, H (69)	ANDO, K (26)	MIYAMOTO, T (23)	YANAGI, T (19)	BABA, M (16)	KOIKE, S (14)	IWATA, Y (12)	KATO, S (11)
YAMADA, S (41)	FURUSAWA, Y (26)	KRAFT, G (22)	YOSHIKAWA, K (19)	HABERER, T (16)	DRENTJE, AG (13)	MATSUFUJI, N (12)	OGAWA, H (11)
KAMADA, T (37)	JAKEL, O (26)	MURAMATSU, M (22)	KATO, H (18)	SCHOLZ, M (16)	OHNO, T (13)	NIKOGHOSYAN, A (12)	SUZUKI, M (11)
KANAI, T (30)	KANDATSU, S (23)	MIZOE, JE (21)	MIZOE, J (18)	ENGHARDT, W (15)	SCHARDT, D (13)	SATO, Y (12)	DURANTE, M (10)
DEBUS, J (28)	KITAGAWA, A (23)	NAKANO, T (19)	YAMAMOTO, N (17)	KRAMER, M (15)	SCHULZ-ERTNER, D (13)	ZHANG, H (12)	FUJISAWA, T (10)

Regarding the Institutions (see table below), the first observation is that universities are predominant in terms of published contributions. A few hospitals (usually linked to universities e.g. MGC linked to Harvard Medical School) and clinics appear to as they contributed to clinical trials importantly.

There is no observation of companies in the top 40 organizations (nor in the top 100) for route 1 research. Differently in route 2, we find one company in the top 10. Accelerator Engineering Corp. is based in Chiba, Japan and was involved in the HIMAC project. Its corporate scientists Noda, Sato and Takada appear in our bibliometric analyses (even in the second one) as important contributors. To be noted that Chiba University is a major contributor to route 2 research. Therefore spatial proximity between scientists seems relevant in this precise case.

Table 4: Top 25 Institutions based on records count in the Science-Citation-Index-Expanded and Conference-Proceedings-Citation-Index-Science

R1: Proton

Top 5	Top 10	Top 15	Top 20	Top 25
HARVARD UNIV (175)	UNIV TSUKUBA (65)	NATL INST RADIOL SCI (33)	INDIANA UNIV (22)	MASSACHUSETTS EYE & EAR INFIRM (19)
MASSACHUSETTS GEN HOSP (146)	IST NAZL FIS NUCL (58)	UNIV FLORIDA (32)	GERMAN CANC RES CTR (21)	UNIV HEIDELBERG (19)
LOMA LINDA UNIV (110)	UNIV CALIF SAN FRANCISCO (48)	KAROLINSKA INST (29)	DEUTSCH KREBSFORSCHUNGSZENTRUM (20)	UNIV WOLLONGONG (19)
PAUL SCHERRER INST (102)	INST CURIE (34)	NATL CANC CTR (28)	UNIV UPPSALA HOSP (20)	UNIV UPPSALA (18)
UNIV TEXAS MD ANDERSON CANC CTR (81)	UNIV TEXAS (34)	UNIV MILAN (23)	FOX CHASE CANC CTR (19)	INST GUSTAVE ROUSSY (17)

R2: Carbon ion

Top 5	Top 10	Top 15	Top 20	Top 25
JAPAN NIRS (164)	GUNMA UNIV (23)	FORSCHUNGSZENTRUM ROSSENDORF EV (8)	UNIV LYON 1 (7)	IST NAZL FIS NUCL (5)
GSI Darmstad (55)	UNIV HEIDELBERG (21)	KYOTO UNIV (8)	KITASATO UNIV (6)	KAROLINSKA INST (5)
CHIBA UNIV (35)	ACCELERATOR ENGN CORP Chiba (13)	KYUSHU UNIV (7)	NARA MED UNIV (6)	NAGOYA UNIV (5)
GERMAN CANC RES CTR (30)	JAPAN ATOM ENERGY AGCY (9)	OSAKA UNIV (7)	RES CTR HOSP CHARGED PARTICLE THERAPY (6)	TECH UNIV DARMSTADT (5)
CHINESE ACAD SCI (23)	TECH UNIV DRESDEN (9)	TOKYO INST TECHNOL (7)	TOYO UNIV (6)	UNIV GRONINGEN (5)

Second analysis: from accelerator science to clinical therapy

During 1970s important developments in accelerators, medical imaging and computing allowed for significant developments of proton therapy. Since the first analysis was centered more on the clinical side (especially radiology and oncology), we started a second data gathering which could be more inclusive of the physics side too. The publication figures (below) show that overall the research contribution from different disciplines to the particle therapy community have been increasing over time and in both routes

We obtained 1634 records for route 1, and 1028 records for route 2. Then we analyzed the evolution of the corresponding co-authorship networks by using 10-year time slices. This is technically semi-statics, and we use it to visualize the evolution and collect network data about scientific collaboration which may be meaningful in a decade. We limited our analysis to the scientific papers authored by the top 250 cited authors in the whole period due to technical limitations from the software used. The table below shows the total number of nodes (authors), and the number of top 250 authors which constitute our sample in each route. For our sample, the number of ties and density of the co-authorship networks is documented by 10-year time slice.

Table 5: R1: Proton route - size, number of ties, and density of the co-authorship network by time slice

Time slices	**Total number of authors**	**Top 250 nodes**	**Ties**	**Density**	**Total number of Organizations**	**Top 250 Organizations**	**Ties**
1965-1974	12	12	25	0.3788	5	5	2
1975-84	516	250	2721	0.0874	42	42	19
1985-1994	1261	250	6056	0.1946	126	126	73
1995-04	2744	250	1496	0.0482	283	250	170
2005-2011	1608	250	6212	0.1996	158	158	108

Note that the last slice includes 7 years instead of 10 due to the data available.

R2: Carbon-ion route – size, number of ties, and density of the co-authorship network by time slice

10-year slices	**Total number of nodes**	**Top 250 nodes**	**Ties**	**Density**	**Total number of Organizations**	**Top 250 Organizations**	**Ties**
1995-2004	1026	250	2466	0.0792	123	123	86
2005-2011	2253	250	5906	0.1898	245	245	183

Note that the last slice includes 7 years instead of 10 due to the data available.

It can be noted that during the last two decades, when route 2 records are picked, the number of nodes increases in route 2 and decreases in route 1. This makes it worth exploring the social networks of scientists for each route during the last two decades more in depth.

Before doing so, we visualize the evolution of the networks per each route (see annexes 1 and 2). This visualization permits to follow the position of nodes in the structure of co-authorship over time, individuals, organizations, and countries.

We focus on proton first. Regarding the interpersonal co-authorship networks, this seems the most complex to understand. For the moment we pointed to Kato and Takeda in route 1 and follow their authorship activity (node size) and position. More analysis is required, by looking at social network analysis measures. Coupling this with interviews can be very helpful in understanding these evolutions.

Regarding the inter-organizational networks of co-authorship, it can be observed that for route 1, Hitachi Ltd is the key company in terms of scientific contributions. It can be observed that it goes from being a big contributor with two ties in slice 1, to being a smaller contributor with a much higher number of ties and a central position in slice 2. In slice 3 the Hitachi component becomes bigger and Ibaraki University becomes the biggest contributor of the component, while Hitachi's contribution is decreased but still significant. A small Japanese company is also present in the network (see red star) and can be still visualized in the last time slice. The nature of the Japanese system may explain this variation in terms of firms' involvement in the scientific community. Indeed, the system is strongly based on collaboration between industry, university and national labs. In any case, this is compatible with the view that technology acquisition by firms requires long term investments in knowledge acquisition. And this long term investment involves firms in co-publishing activities and participation to the scientific community life.

CERN (Ch) and Trium(Canada) are they key government labs appearing in the visualizations, with CERN's component growing bigger. In the 1990s Loma Linda University appears in the network giving a significant initial contribution, as expected from the interviews. In the next decade it continues contributing but not collaborating that more. Yet we know that there are at least two key people behind Loma Linda's contribution, Doctors Slater JM and JD.

By looking at the organizations which appear in the visualizations, it seems that there is an overlap between organizations in proton and carbon ion, compared to the first analysis. The interview data makes us think that while clinical contributions are more on one route or the other, contributions regarding instrumentalities such as imaging and accelerators can show an overlap across both routes. It seems interesting to check this further. One way of looking at it is to analyze the overlap between co-authorship networks in both routes at both the inter-personal and inter-organizational level.

Regarding countries, these visualizations may be considered a simple way of looking at how national systems of innovation are featured by international collaborations and how this affects their outcomes in terms of research contribution. Japan stands as having less or no co-authorship ties, and yet the highest scientific contributions in both routes. As some interviewees stressed, Japan exhibits high coordination in research collaboration between industry, universities and national laboratories. As renown, these may be linked to the 'kairetsu' culture, and be the result of its industrial and research policies.

Findings from semi-structured interviews

*Particle therapy paradigm and the community***.** Mainly through our interviews, but also paper analysis, we learned that the particle therapy paradigm lies in the unique physical and radiobiological properties of protons and carbon ions, compared to X rays.

Yet protons and carbon ions are also distinguished based on their different physical and biological properties. "I am sure there will be evidence that Carbon-ions are better than Protons because I know well their physical and biological properties: Carbon-ions allow you to go through water very well, and our body contains water" (physicist). Scientists have scientific justifications to believe in one particle over the other. Companies bear the risks, invest and specialize in one particle only (e.g. Varian in proton, Siemens in Carbon), with some exceptions for the most recent carbon-ion facilities being able to use protons too[6]. An international coordination initiative (Enlight) and conferences bring both streams together. This entails communication structures to: a) share scientific advances with the community; and b) achieve standards of carrying out clinical trials and evidence collection. "Enlight" network was created in 2002 at CERN in order to bring together clinicians, physicists, biologists and engineers with an interest in particle therapy. A couple of specialized

[6] Carbon-ion therapy facilities are recent and factor 3 more expensive than Proton facilities. Yet carbon ion therapy is young and lacks of clinical trials and toxicology data. It takes decades to collect such evidence. Therefore, constructing carbon ion facilities which can also use protons reduces the sunk costs to be faced in the case the evidence on carbon ion does not allow for its conventional clinical use.

international conferences reunite nowadays the world's community/ies of scientists, industrials, and practitioners interested in particle therapy.

RTD for both technologies has involved the work of physicists, clinicians, biologists and engineers. While these people previously belonged in their respective disciplinary communities they have formed the nucleus of a new scientific community of particle therapy. They currently maintain multiple affiliations in pre-existing and emerging communities of scientific and technological practices. This is especially true for medical doctors (e.g. radiologists, radiation oncologists). The presence of "scientific instrumentalities" (e.g. new accelerators, PET imaging) is binding this new community by making new research options available. This allowed for testing different designs and using different particles and doses for different types of tumors.

Avenues of science-technology overlap. We find overlap between the scientific and technological communities across the triple helix. As shown in the previous section this overlap occurs via co-authorship; our findings are different from Murray's (2002) and similar to Henderson and Cockburn's (1994), Arora and Gambardella 1994, and Liebeskind et al. (1996). In times in which a technological paradigm shift is associated to one in science, firm's publishing is key for a successful transition to the new technological paradigm.

Zucker and Darby (1998) found that most productive "star" bio-scientists played a central role in where and when new bio-tech firms were formed. Murray (2002) found that scientists played a role in firm founding for commercialization of intellectual property. Instead we do not find extensive evidence of company founding. This seems to be due mainly to the high investment size necessary to purchase particle therapy facilities –investment which could only be provided by government and big companies. However, "star scientists" played an important role in: a) where and when new clinical facilities were built for further clinical trials; b) attracting necessary funding from governments and firms for the construction of clinical facilities; c) fostering collaboration with industry for transfer of expertise, construction and development of clinical facilities; d) creating a community of scientists and practitioners around particle therapy.

The nature of user needs. Baba et al. (2009) argue that a "two-way" (both U-I and I-U) interaction model between universities and industry seems to be the most appropriate one to study the innovation dynamics in the advanced materials industry. Scientific knowledge can be expected to flow from universities to firms, while the knowledge of the market and demand by companies to the former one. Firms shall have knowledge about user needs in order to carry out RTD work (Maine&Garnsey 2006). Yet, in our study the use of particle therapy devices requires the interaction of technicians, radiologists and other medical doctors, thus making user needs a complex topic.

Bridging different worlds. There seems to be a discrepancy between the physicists–who consider the technology as ready–and the medical doctors who consider the technology as not yet ready for standard clinical practice. Yet, in the end, what makes the difference for companies are the needs of medical doctors, statistical evidence included. Firms that did not invest in these technologies had two main motives: a) their development requires big investments (both private and public); and more importantly, b) clinicians do not consider the technologies to be ready, and technology acceptance for standard clinical practice depends on the results that statistical evidence will show. This is a process which takes decades, as in drug testing, but with higher complexity (combinations of treatments, type of cancers and their body location have to be tested). Thus, the inclusion of such technologies into their business portfolio has high risk profile. While in bio-tech and some related pharma fields universities develop new ideas which are captured rapidly by industry (Cohen et al. 2002), in our study this process is slower and the role of public research is fundamental.

Conclusions, implications and future research directions

We find overlap between the scientific and technological communities across the triple helix and internationally: more across the triple helix (but less internationally) for Japan, vis-à-vis the US and Europe. This overlap occurs via co-authorship of scientific papers, consulting, patenting, informal advice, circulation of scientists and proximity to star scientists. We do not find extensive evidence of company founding, but we found that star scientists played a key role in getting new clinical facilities and research-based facilities built. Even if science and technology overlap at an international level, the old view of scientific progress based on communities still explains the changes in relationships and structure of scientific collaboration over time. We find this view still holds but further research shall address if the timing (speed) of scientific and technological development is affected and how. The role of government lab and university helices is central in terms of scientific knowledge production as well as development of applications (especially for their home-made IS systems). Government plays an important role in terms of funding research and construction of new facilities, and approving the clinical use of such therapies with major impacts in terms of if the research stream develops or not. Industry plays an important role in terms of risk-taking and investing heavily on the development of cutting edge technologies.

This research may develop further in order to: a) advance a typology of scientists from a social network analysis viewpoint; b) identify both “hidden stars” and “rising stars”; c) link these roles and the evolution of scientific knowledge; and d) the central role of specific institutions in the evolving triple helix of particle therapy worldwide.

Understanding the triple helix of emerging technologies from a network evolution viewpoint may be relevant to inform public funding and private investments in emerging technologies. This may be a potentially complementary approach to cost-effectiveness. The aspect of gatekeepers spanning boundaries (organizational and disciplinary in this case) deserves further research based on our available data. A better understanding of bridging may inform industrial and research policy-making as well as company strategies in order to: foster ties between industry and open science, and support the role of key scientists and the different institutions in the triple helix. By “fleshing out the bones” of the proposed framework is necessary for making it interesting for this research, for researchers in different streams mentioned by the framework, and for the discourse on indicators of science and technology.

Aknowledgements

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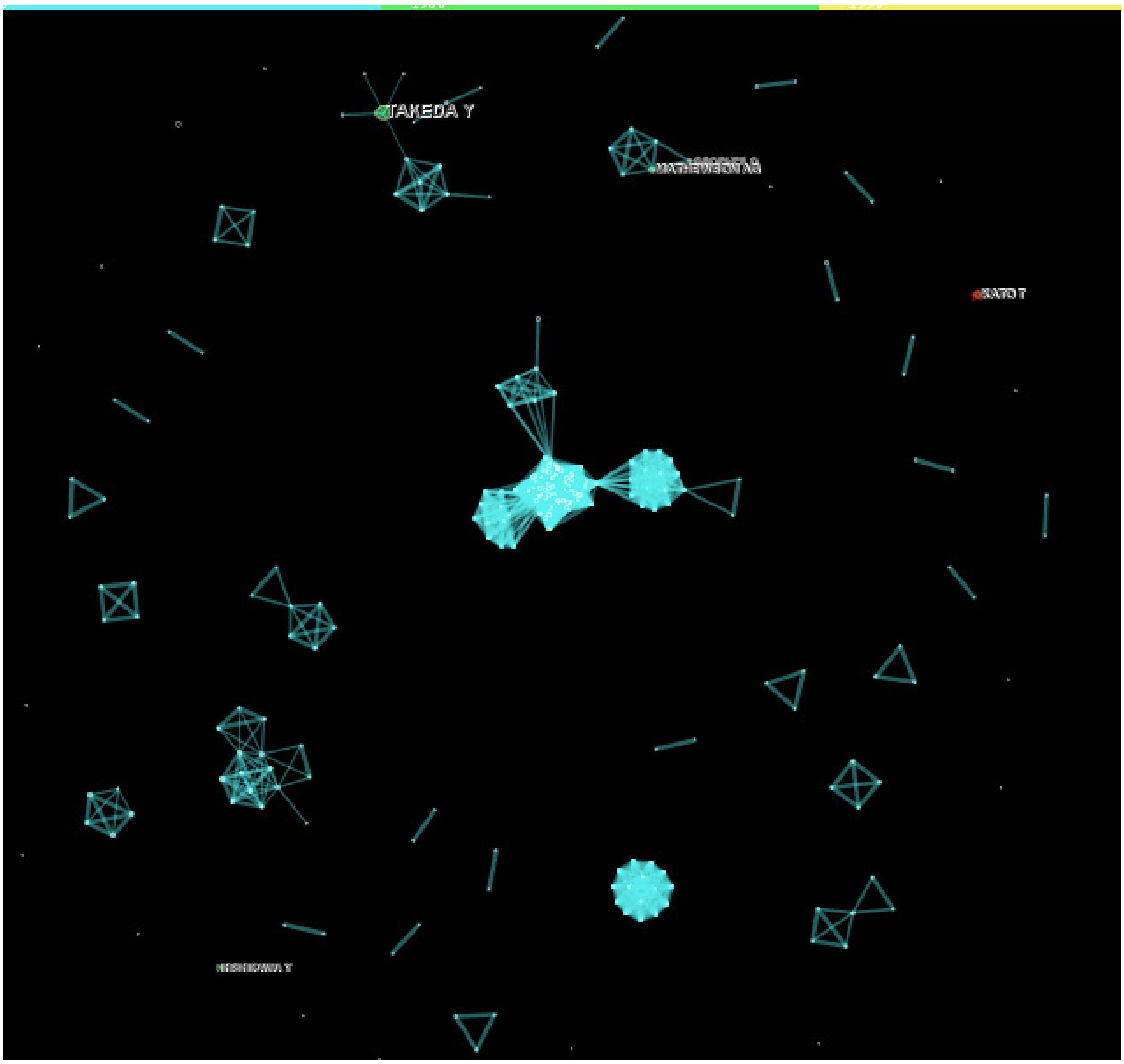
Annex 1: The evolution of scientific collaboration - Proton route (R1)

Evolution of the inter-personal network of co-authorship

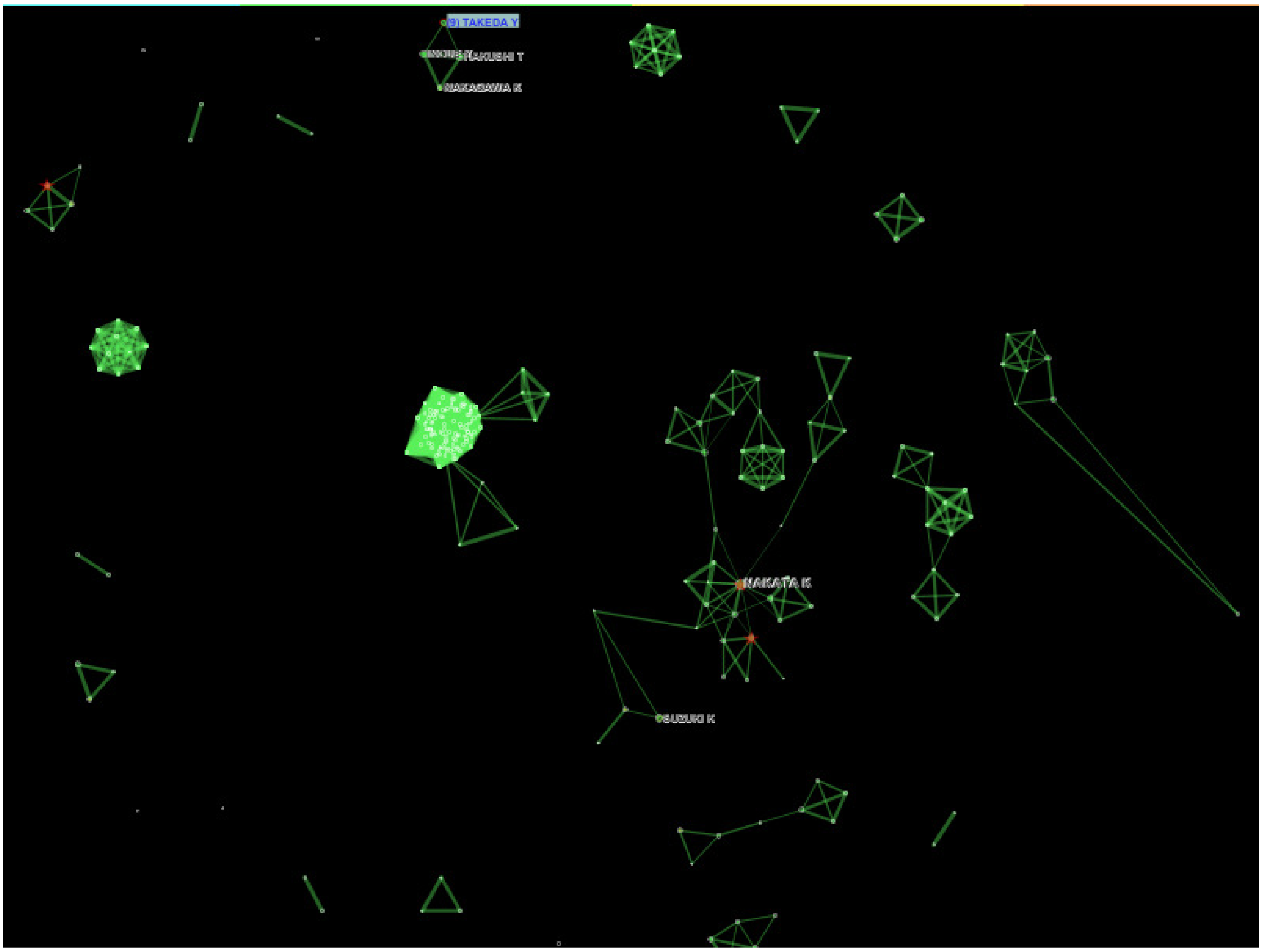
1965-1974

- Ties: co-authorship
- Nodes size: scientific contribution by author
- Ties size: frequency of co-authorship

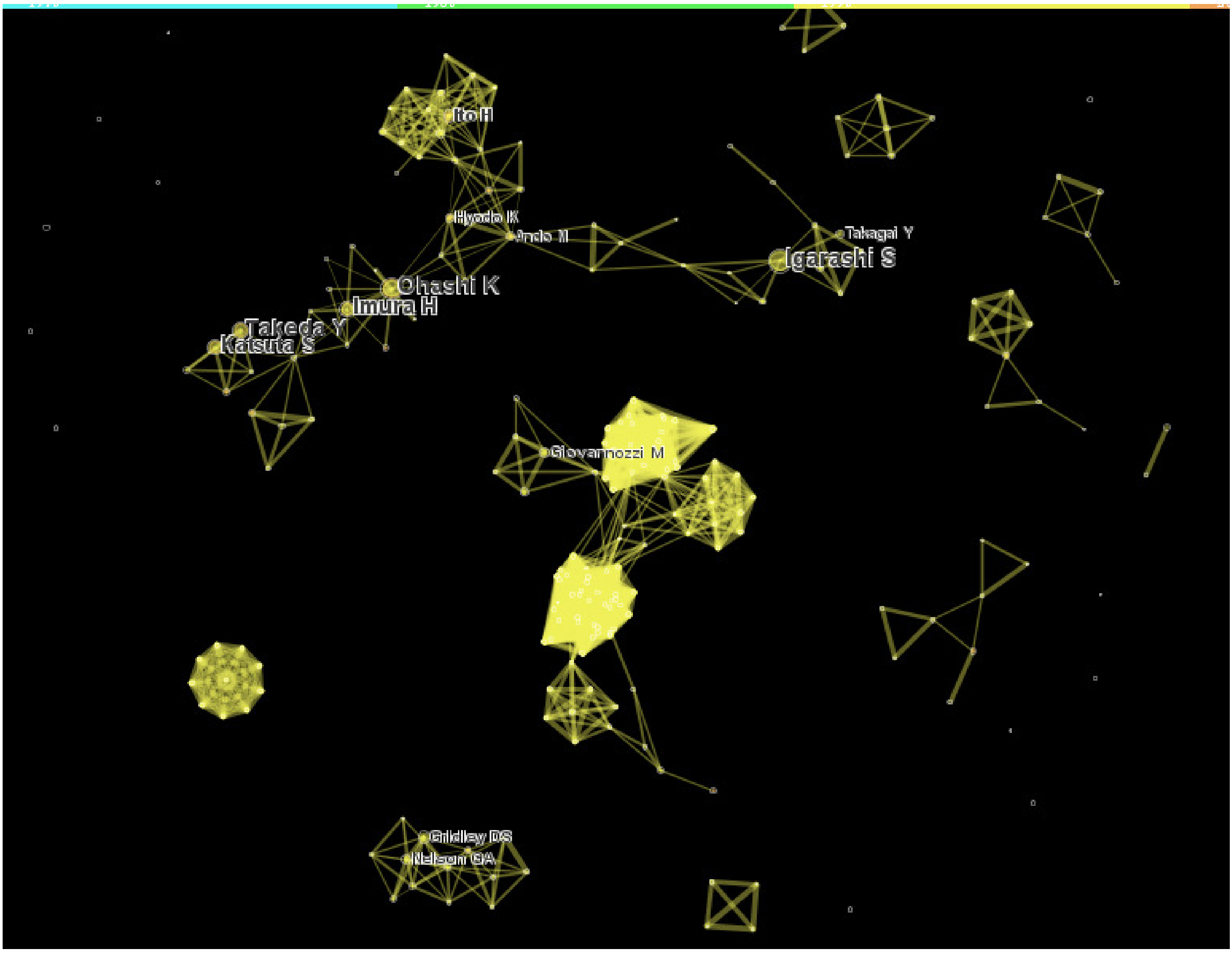
1975-1984



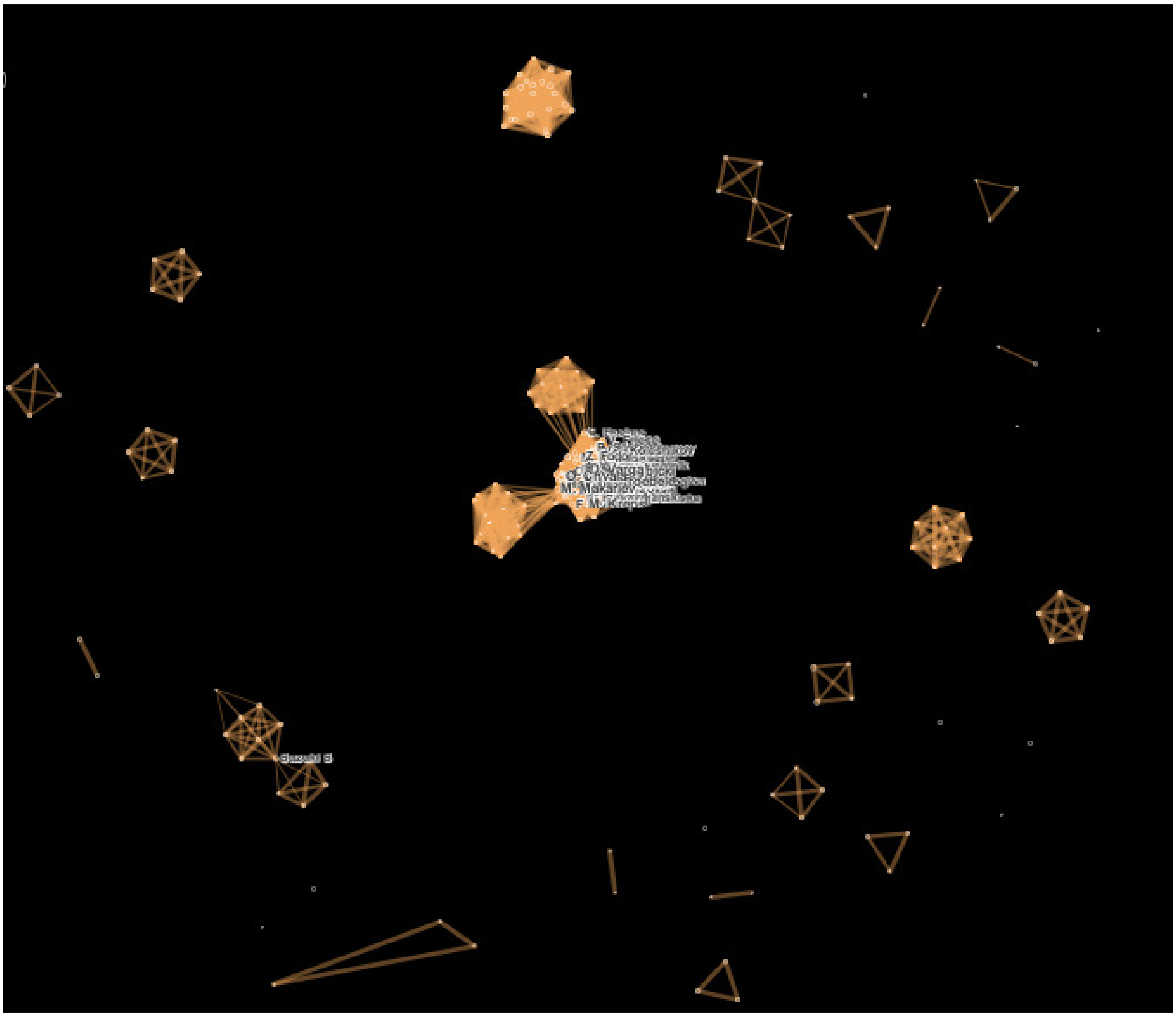
1985-1994



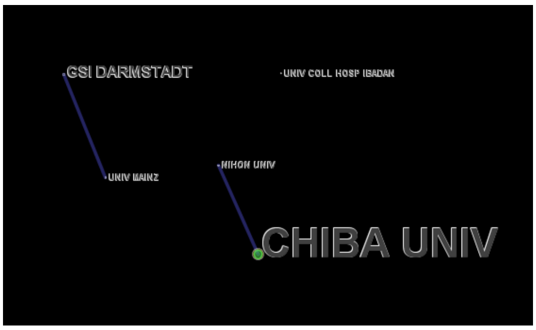
1995-2004


Ito H
Hyodo K
Ando M
Takagai Y
Igarashi S
Ohashi K
Imura H
Takeda Y
Katsuta S
Giovannozzi M
Gridley DS
Nelson GA

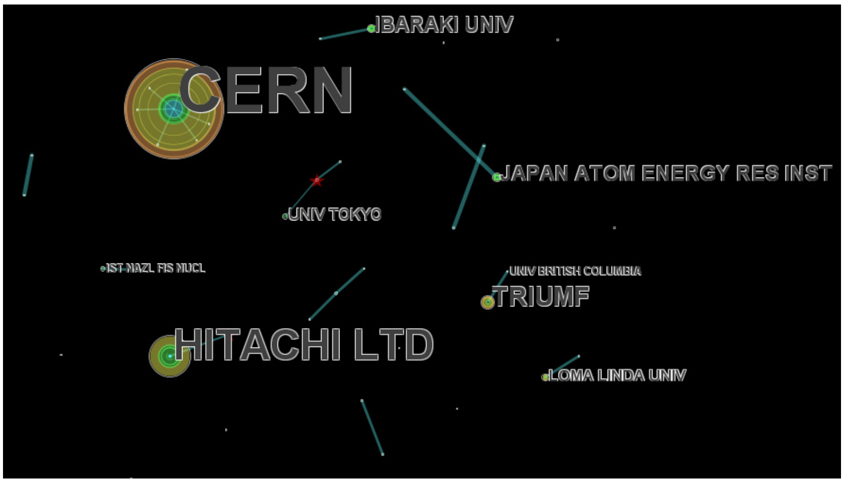
2005-2011



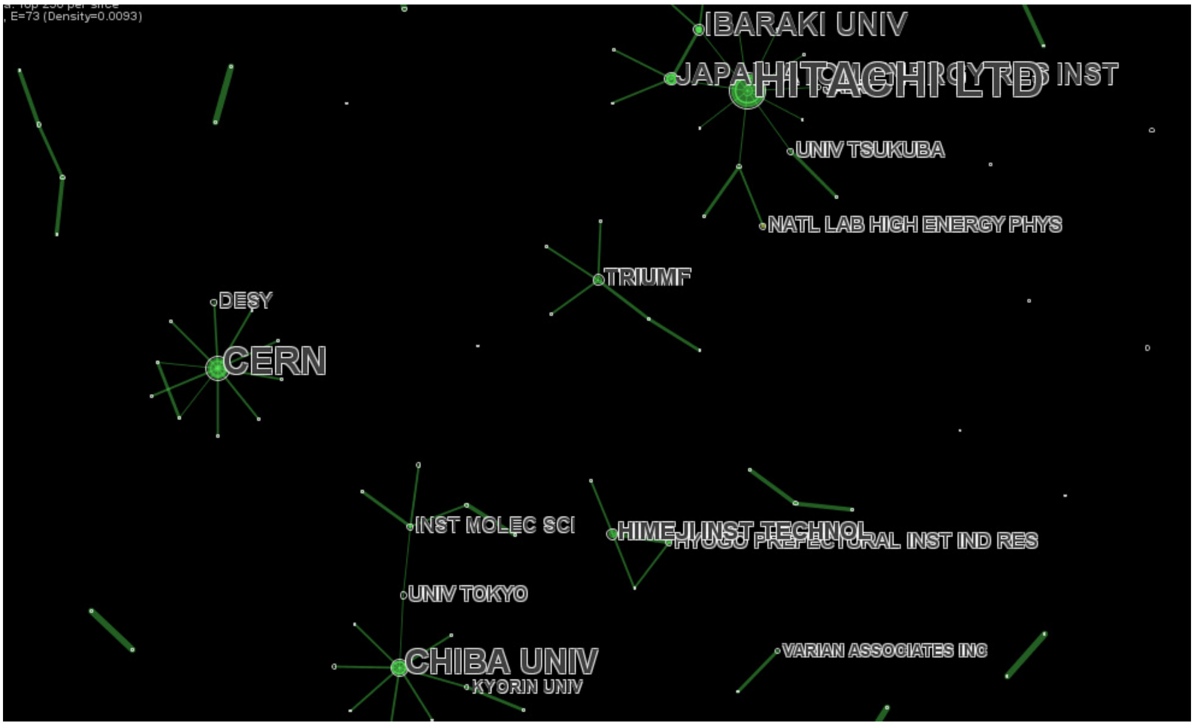
Evolution of the inter-organizational network (co-authorship)



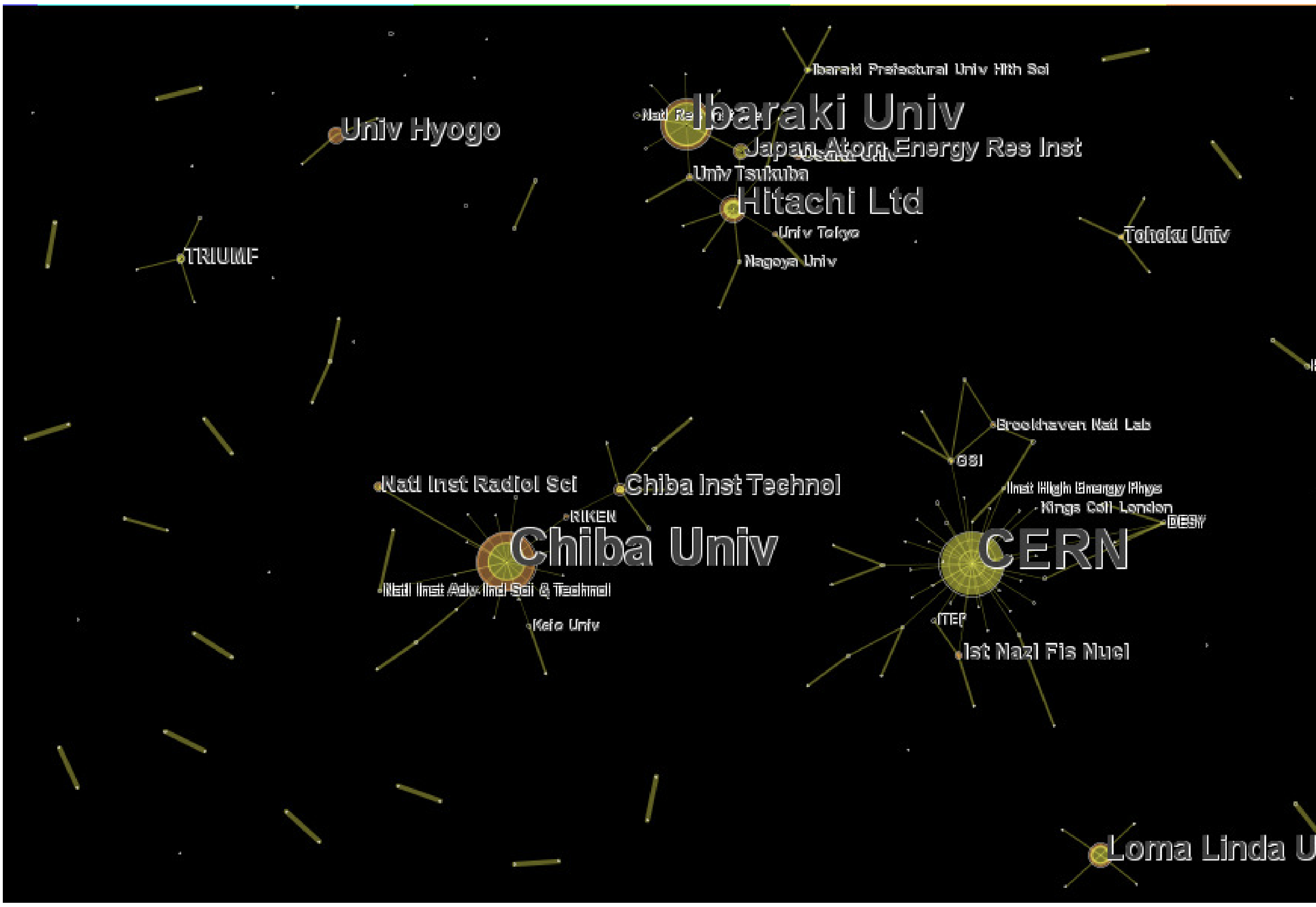
1965-1974



1975-1984

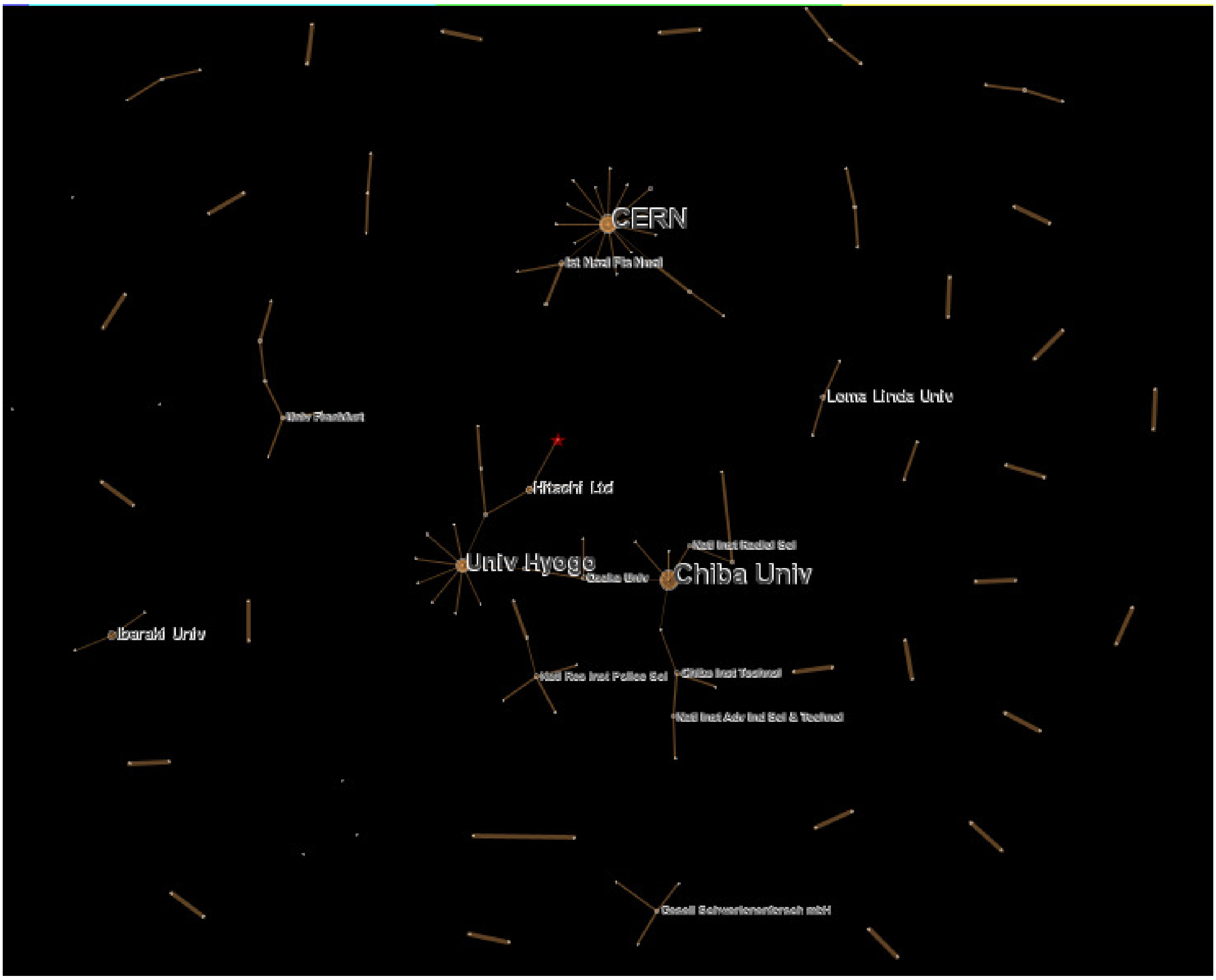


1985-1994



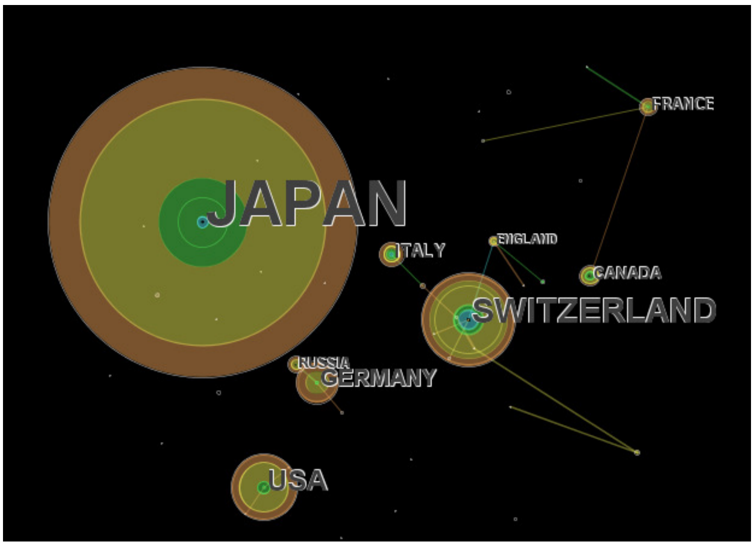
Ibaraki Prefectural Univ Hlth Sci
Ibaraki Univ
Univ Hyogo
Japan Atom Energy Res Inst
Univ Tsukuba
Hitachi Ltd
Univ Tokyo
Nagoya Univ
Tohoku Univ
TRIUMF
Brookhaven Natl Lab
GSI
Inst High Energy Phys
Kings Coll London
DESY
Natl Inst Radiol Sci
Chiba Inst Technol
RIKEN
Chiba Univ
CERN
Natl Inst Adv Ind Sci & Technol
Keio Univ
ITEP
Ist Nazl Fis Nucl
Loma Linda U

1995-2004



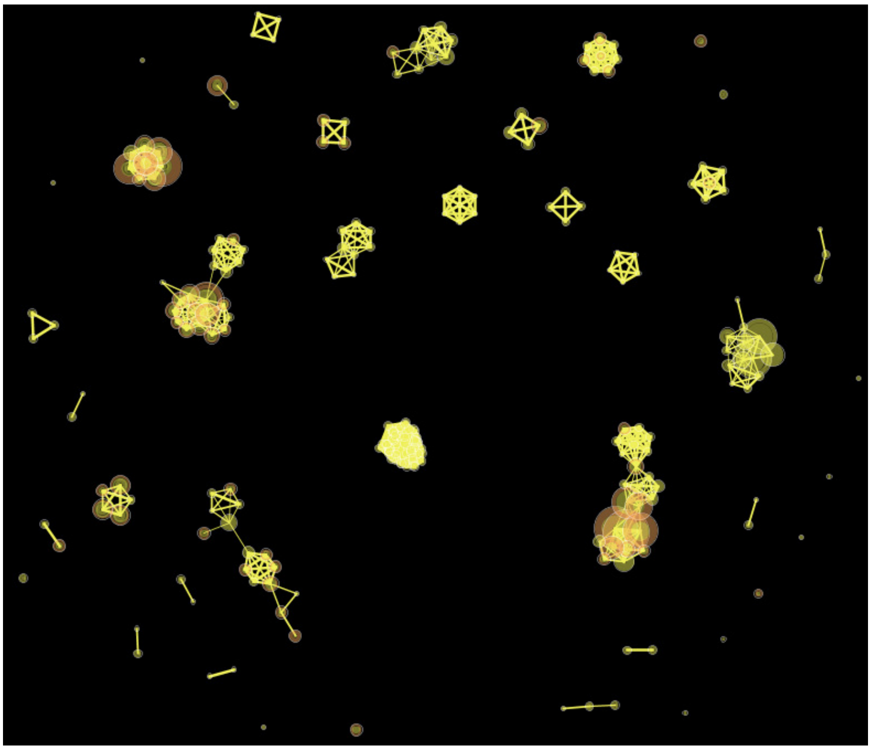
2005-2011

Overall contribution by country (each circle is one decade; e.g. a tree section)



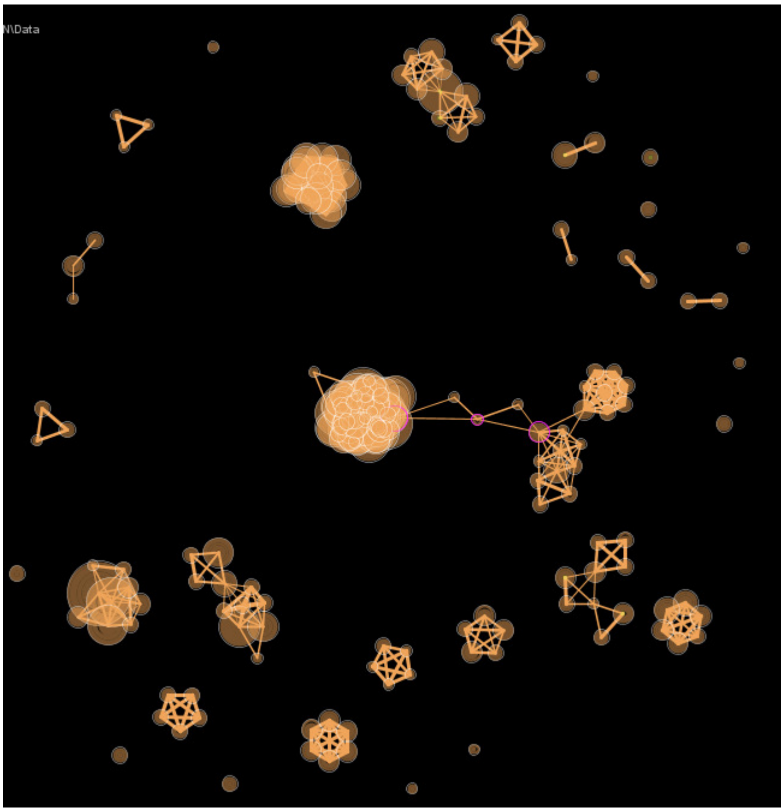
Annex 2: The evolution of scientific collaboration – Carbon ion (R2)

Evolution of the inter-personal network of co-authorship



- Ties: co-authorship
- Nodes size: scientific contribution by author
- Ties size: frequency of co-authorship

1995-2004

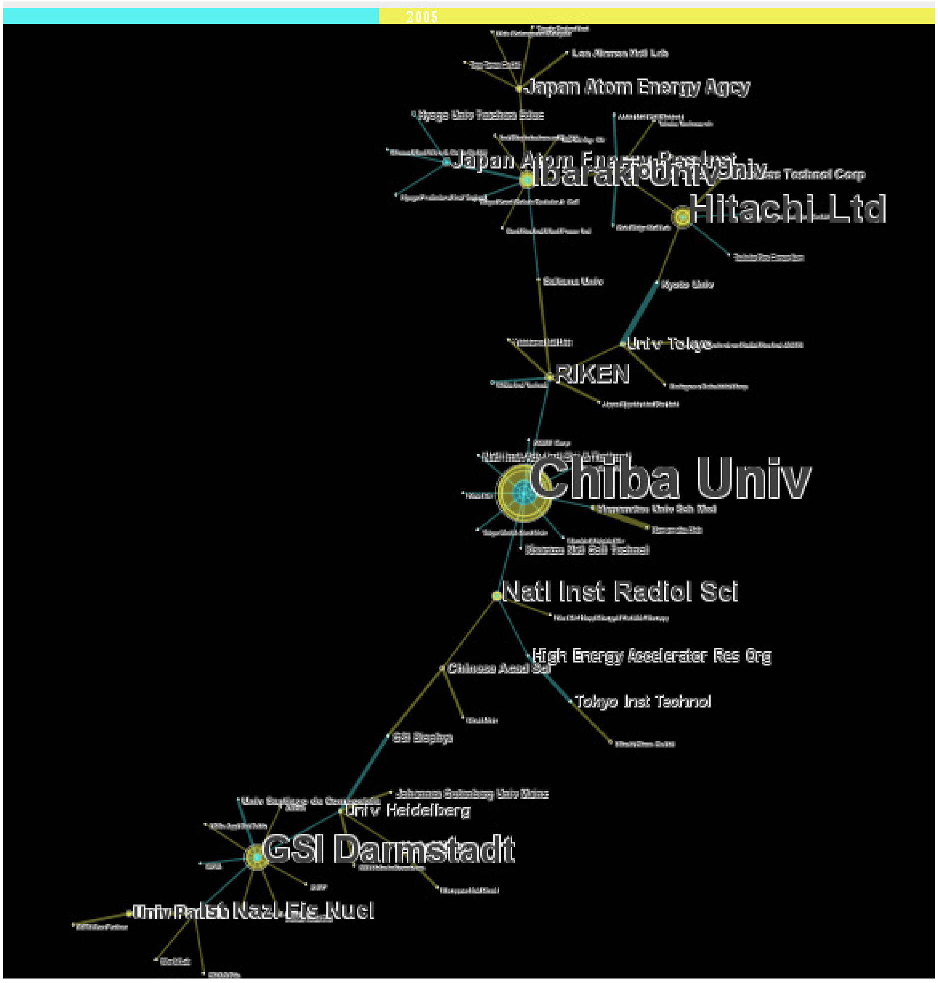


2005-2011

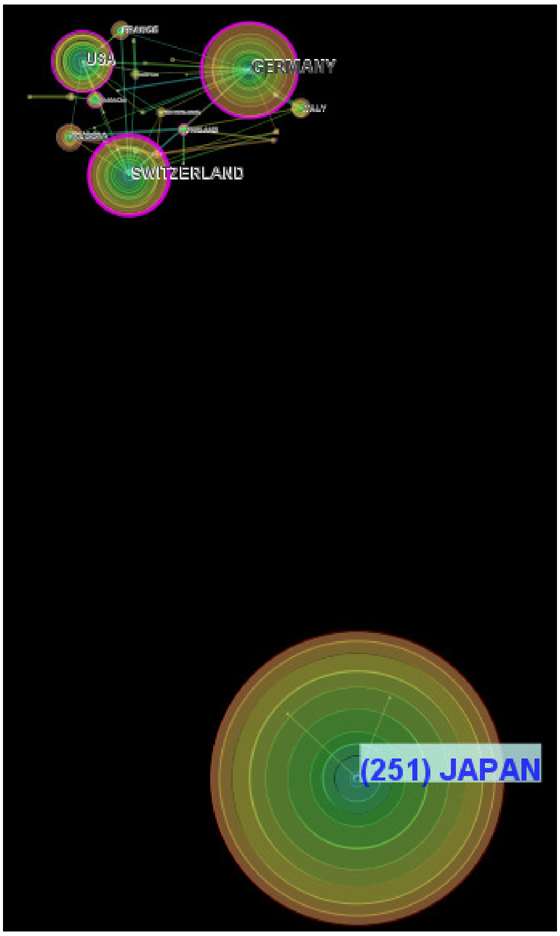
Evolution of the inter-organizational network (co-authorship)

Merged (see colors for each decade) * There may be a bug in the colors visualization

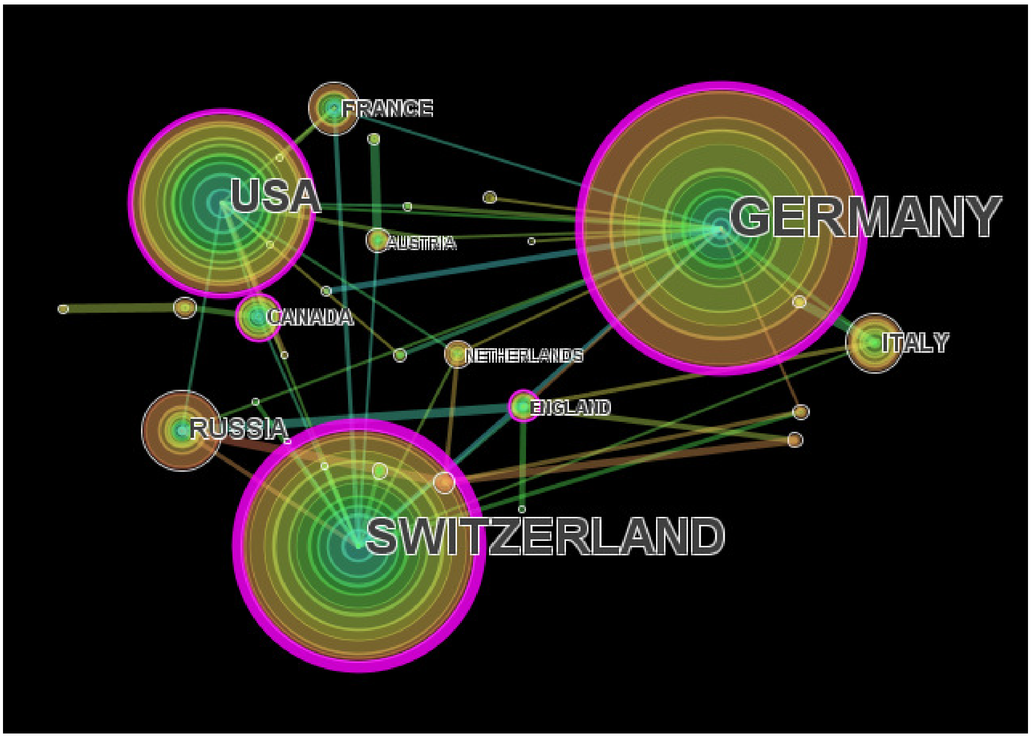
1995-2004 2005-2011



Overall contribution by country (each circle is one decade; e.g. a tree section)



Focus on the collaborations



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