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A bibliometric and social network analysis perspective of X-ray phase-contrast imaging in medical imaging

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Abstract

Introduction: Phase-contrast imaging (PCI) is a novel technology that can visualise variations in X-ray refraction (phase contrast) in addition to differences in X-ray attenuation (absorption contrast). Compared to radiography using conventional methods (i.e. absorption-based imaging), PCI techniques can potentially produce images with higher contrast-to-noise ratio and superior spatial resolution at the same or lower radiation doses. This has led PCI to be explored for implementation in medical imaging. While interest in this research field is increasing, the whole body of PCI research in medical imaging has been under-investigated. This paper provides an overview of PCI literature and then focusses on evaluating its development within the scope of medical imaging. **Methods:** Bibliographic data between 1995 and 2018 were used to visualise collaboration networks between countries, institutions and authors. Social network analysis techniques were implemented to measure these networks in terms of centrality and cohesion. These techniques also assisted in the exploration of underlying research paradigms of clinical X-ray PCI investigations. **Results:** Forty-one countries, 592 institutions and 2073 authors contributed 796 investigations towards clinical PCI research. The most influential contributors and network collaboration characteristics were identified. Italy was the most influential country, with the European Synchrotron Radiation Facility being the most influential institution. At an author level, F. Pfeiffer was found to be the most influential researcher. Among various PCI techniques, grating interferometry was the most investigated, while computed tomography was the most frequently examined modality. **Conclusions:** By gaining an understanding of collaborations and trends within clinical X-ray PCI research, the links between existing collaborators were identified, which can aid future collaborations between emerging and established collaborators. Moreover, exploring the paradigm of past investigations can shape future research – well-researched PCI techniques may be studied to bring X-ray PCI closer to clinical implementation, or the potential of seldom-investigated techniques may be explored.

Introduction

In conventional X-ray radiography, the differences in density and atomic number of adjacent tissues result in differential absorption of X-ray, producing contrast variations in the resulting image.[1] This is known as attenuation contrast and has been the fundamental principle of X-ray imaging since the Roentgen's discovery in 1895. However, the interaction between incident X-ray and electrons also results in X-ray refraction (changes in X-ray phase patterns). Phase-contrast imaging (PCI) is referred to the techniques that are capable of visualising both attenuation contrast and refraction contrast of the transmitted X-ray beam. PCI techniques have been shown to produce significantly higher contrast-to-noise

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ratio than absorption-based imaging, under the following two conditions, when a hard X-ray beam (where X-ray photon energies are greater than 10 keV) is used, and when the object being imaged is soft tissue, composed of low atomic numbers.[2,3] Conventionally, decreasing peak kilovoltage increases image contrast; however, PCI techniques can achieve an image of sufficient contrast that answers the clinical question at higher peak kilovoltages. This reduces the incidence of X-ray attenuation in tissues therefore decreasing patient dose.[3] Additionally, images can be generated at lower exposure factors with greater spatial resolution and are less affected by noise.[2-4] These are desirable properties in medical imaging and can be achieved using a range of PCI techniques.

Forms of PCI have been suggested to exist since the fifth century; however, developments in optics led Frits Zernike to discover, and coin the term, 'phase-contrast imaging' in 1932.[5-7] Before its application to X-ray imaging, the earliest use of PCI was in microscopy, to image transparent microorganisms. Its subsequent applications involved imaging inorganic objects in material science using X-rays.[5-7] Investigations into the biomedical applications of X-ray PCI, however, have only been published over the past two decades.[8]

The most established PCI techniques are propagation-based imaging (PBI), diffraction-enhanced imaging (DEI), crystal interferometry, grating interferometry (GI) and edge illumination.[8,9] Figure 1 shows the schematic set up of these five phase-contrast imaging techniques. PBI, also known as in-line phase-contrast imaging, has the simplest set up. PBI requires a spatially coherent X-ray beam and a large object-to-detector distance.[3] DEI, also known as analyser-based imaging, requires a monochromator positioned between the X-ray source and the object, and an analyser crystal positioned between the object and detector.[9,10] Crystal interferometry uses a monochromator and three parallel beam splitters. The first splitter creates two identical beams. The second splitter converges the beam towards the third splitter, and the object is placed between these two splitters in the path of one of the converging beams. The object creates a phase shift in one of the beams, while the other beam is used as a reference.[9,10] The third splitter recombines both beams, creating an interference pattern that is transmitted to the detector. GI is compatible with both a spatially coherent X-ray beam and a conventional X-ray beam. A spatially coherent beam requires two gratings between the object and the detector. The first grating produces phase shift information, and then, the second grating converts this into information on intensity variation that can be read by the detector. Three gratings, however, are required when using a conventional X-ray beam, where the third grating is placed before the object, close to the source.[5,9] Edge illumination can also use both conventional and spatially coherent X-ray beams. Two aperture systems are required in this technique; one is placed closely before the object to collimate the beam, creating multiple narrow beamlets to pass through the object, and the second is located before the detector. The second aperture system is positioned so that half of each narrow beamlet is detected, while the other half is absorbed by the aperture. Any interactions with the object that produce a change in phase can be detected by how much more, or less, photons are detected.[9]

Over the past few years, there has been significant progress in demonstrating the radiographic applications of PCI techniques in areas such as angiography, musculoskeletal imaging, lung imaging, brain imaging, oncology and mammography.[3,8] These investigations produced promising results, supporting the viability of PCI techniques as a method of medical imaging, moving it from pre-clinical applications towards future implementation in a health setting.

Although there have been reviews into the clinical applicability of PCI techniques,[3,8] there is a paucity of studies quantifying the extent and development of this research field. Furthermore, PCI literature, in terms of the collaboration networks between researchers, has been seldom-investigated. In developing research fields, for example towards clinical X-ray PCI, there exists the possibility that activities between different research groups, and the impacts those activities have on the area of investigation are relatively unknown – bibliometric and network analysis methods can assist with understanding recent developments and effects of research strategies and practices on a macro-scale.[11] In particular, social network analysis (SNA) can visualise and quantitatively measure connections among social structures, including research collaboration networks.[12] Such analysis can inform the direction of future research, strengthen collaborations between existing researchers who are working in this area independently and help to establish new links between emerging and existing researchers.

In response to the current gap in the literature, the main objectives of this study were (1) identification of PCI literature; (2) analysis of relationships between individual researchers, institutions and countries investigating the clinical applications of X-ray PCI; and (3) examination of research paradigms in X-ray PCI literature in medical imaging, in terms of techniques and modalities investigated.

Material and Methods

Data collection

Bibliographic data were extracted from the Web of Science Core Collections database.[13] We developed a

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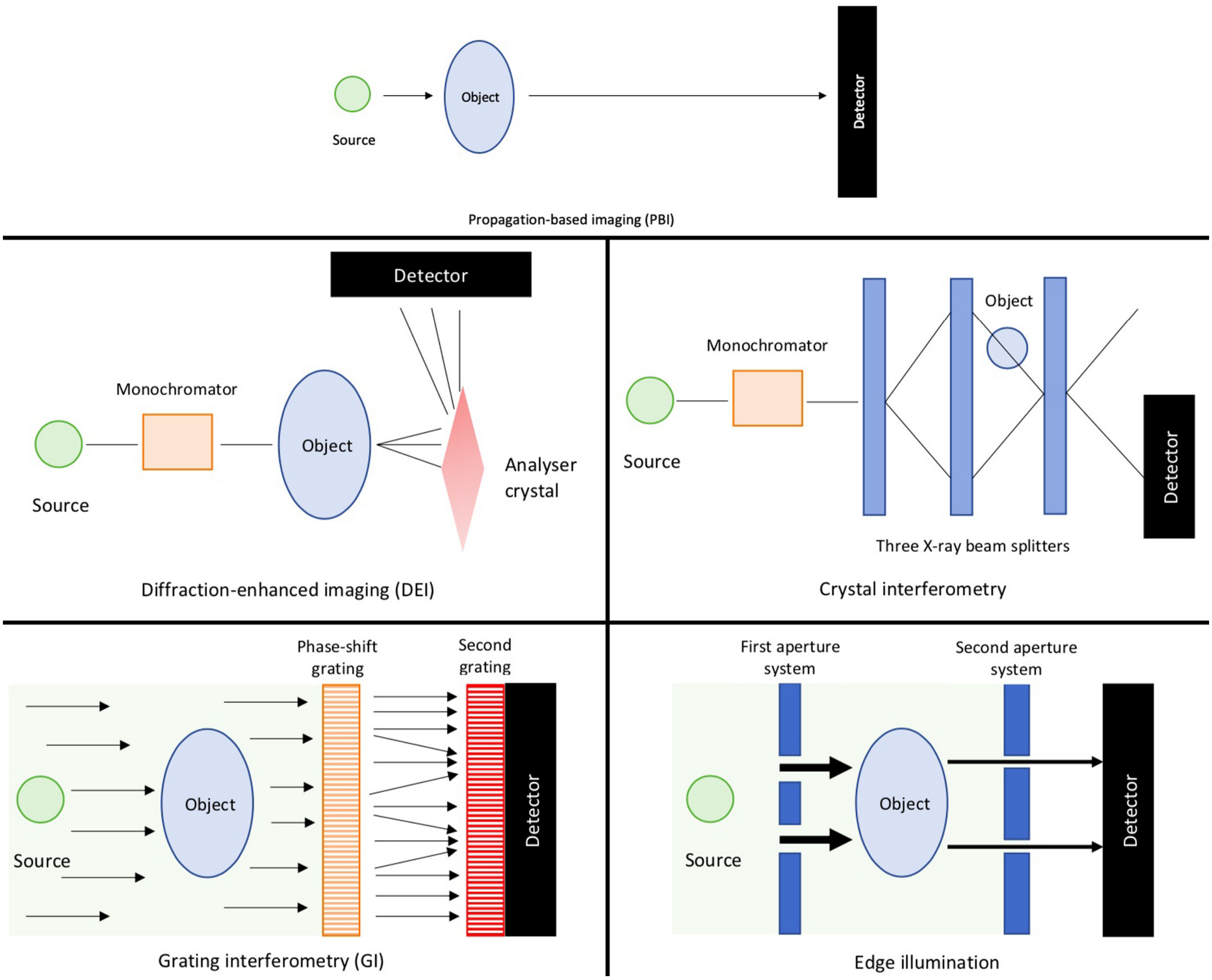

Figure 1. Schematic set up of the most established phase-contrast imaging techniques.

search strategy to produce results relevant to the objectives. We used various search terms, which included PCI techniques and specific areas of medical imaging. From this search strategy, we conducted two searches for the three objectives.

To identify PCI literature: Using Web of Science, the following title search was performed to evaluate the general development of PCI research; "phase-contrast" OR "propagation-based" OR ("analyser-based" OR "diffraction-enhanced") OR "crystal interferometry" OR "grating interferometry" OR "edge illumination". There were publication year and document type restrictions in the search strategy. Publications were included from the first available publication (1933) to the end of 2018. Only journal articles, proceedings papers and book chapters were the included document types, to focus on new, contributory knowledge in the research field. Language restrictions were not placed on this search to determine the overall progress of PCI investigations regardless of where the research was conducted/published. Publication quality was not paramount for this search, as the aim of this search was to provide a brief overview of PCI literature.

To analyse relationships and to explore research paradigms: A second search was performed, using the following: ("phase-contrast" OR "propagation-based" OR ("analyser-based" OR "diffraction-enhanced") OR "crystal interferometry" OR "grating interferometry" OR "edge illumination") AND ("xray" AND ((clinical (applica* OR implement* OR practice)) OR (breast OR mammo* OR lung OR chest OR pulmonary OR joint OR bone OR cartilage OR vascul* OR angio* OR brain) OR ("medical imag*" OR radiolog* OR radiograph*)). This search explored collaboration networks and examined the research paradigm of clinical X-ray PCI literature. This second search used similar parameters as the first search

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– further refinements included to contain studies published only in English to facilitate data analysis.

Publications from the second search were screened to determine their eligibility for inclusion. Studies that were eligible included theoretical, clinical or experimental investigations into the clinical applicability of X-ray PCI techniques. Bibliographic data of the included studies were prepared for analysis by way of data cleaning; removing errors, unifying inconsistencies and completing missing fields. Moreover, missing author affiliations were taken from institutional webpages and/or the author's research profile pages (i.e. ResearchGate and Google Scholar). Misspelt author names were also verified in this manner.

Data analysis

In the context of this study, each researcher, institution or country is represented by a node, and then, their collaborations, or 'ties', are quantitatively examined using measures of centrality and cohesion.[14,15]

Centrality measures include degree centrality, closeness centrality and betweenness centrality. Degree centrality refers to the extent to which a node directly associates with other nodes. Closeness centrality is an indicator of the rate of information flow to the node in the network and measures the proximity of a given node to all other nodes.[14-17] Betweenness centrality measures the number of times a node appears to connect other nodes together and demonstrates the power a node has to control information distribution in a network.[14,15,18] To enable comparison of different nodes, we also used 'Comparative Influence' which is defined as the average of the three centrality measures, expressed as a percentage.

Cohesion measures are network attributes (rather than node attributes) that illustrate the connectivity and density of a network as a whole. Two cohesion measures were used: component ratio and connectedness. A component is formed when two nodes or more are tied, and the component ratio describes the distribution of ties within the network. Connectedness refers to the strength of connections within a component.[19,20]

Quantitative description of SNA measures used in this study are provided in the Supporting Information - Appendix S1.

In order to examine research paradigms of X-ray PCI in radiography, we created a keyword visualisation and assessed keyword frequency. The keyword visualisation displays tie strengths between keywords, where the line thicknesses of the ties are proportional to how common the keywords were investigated with each other.

UCINET[21] and CiteSpace[22,23] software programs were used in this study to analyse the bibliographic data, conduct the SNA and visualise author, institution, country and keyword networks.

Results

Worldwide trends

PCI literature has spanned across many decades and has been applied to a diverse range of research fields and categories. This study found that over the course of 85 years (1933 to 2018), a total of 4746 original investigations into PCI were published (Figure 2). The overall trend of investigations into PCI has seen a steady increase since 1990, with a peak number of investigations ($N = 323$) occurring in 2014. The peak in 2014 is presumably related to lots of numerical research published that year around the world on new/improved phase retrieval algorithms and quantitative evaluation of PCI techniques.

In terms of research fields, there were over 160 areas that PCI research was conducted in. While PCI started as an optic phenomenon, Figure 3 shows that overall, PCI was most investigated in its applications to radiology – 1323 investigations out of 4746 were applicable to radiography.

Exploring collaboration in clinical X-ray PCI literature

Our search of X-ray PCI within the field of medical imaging resulted in retrieving 843 papers, which, after removing irrelevant papers, yielded 796 papers for analysis, with a 23-year publication range, from 1995 to 2018. In total, 41 countries, 592 institutions and 2,073 authors contributed to the publications investigating the clinical applications of X-ray PCI.

Centrality analysis

Out of 41 countries investigating the clinical applications of X-ray PCI, Italy consistently ranked highly across all three centrality measures. Italy had the highest betweenness and closeness centrality measures, and the second-largest degree centrality value, resulting in a high Comparative Influence value (Table 1). There is a notable difference in Comparative Influence between Italy and the subsequently ranked countries (i.e. Germany, USA, France, Australia etc.).

At an institution level (Table 1), the European Synchrotron Radiation Facility (ESRF) had the highest Comparative Influence out of all institutions investigating clinical X-ray PCI. It is of note that the Chinese Academy of Sciences (CAS), while having a low degree centrality,

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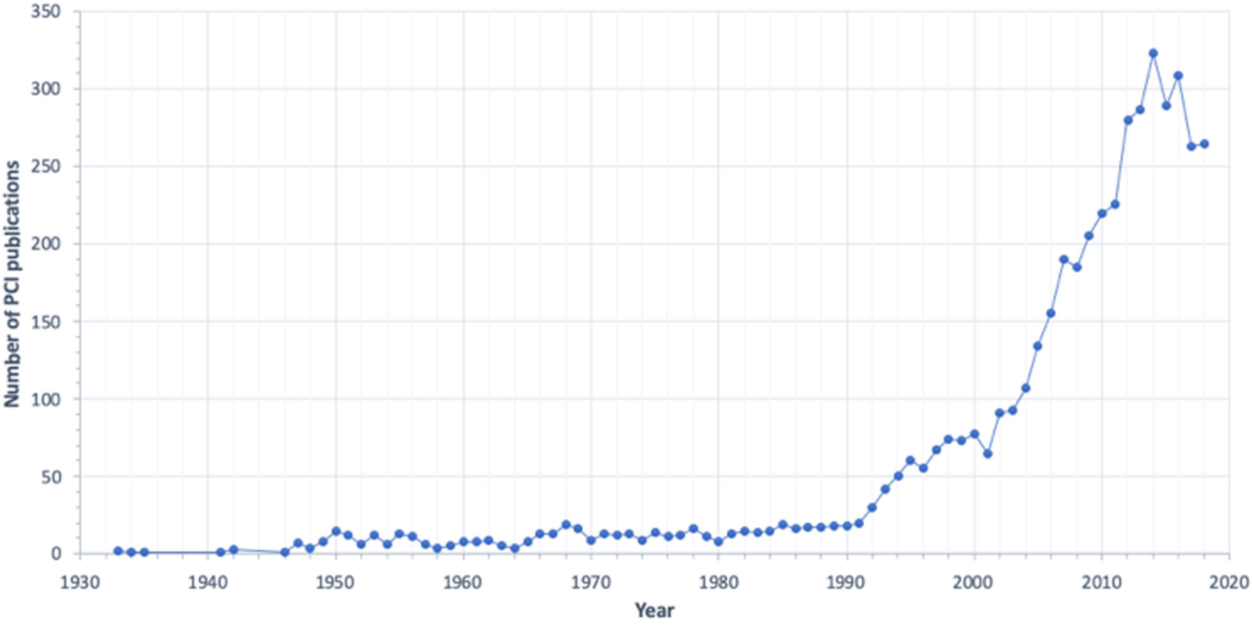

Figure 2. Phase-contrast imaging (PCI) publications per year.

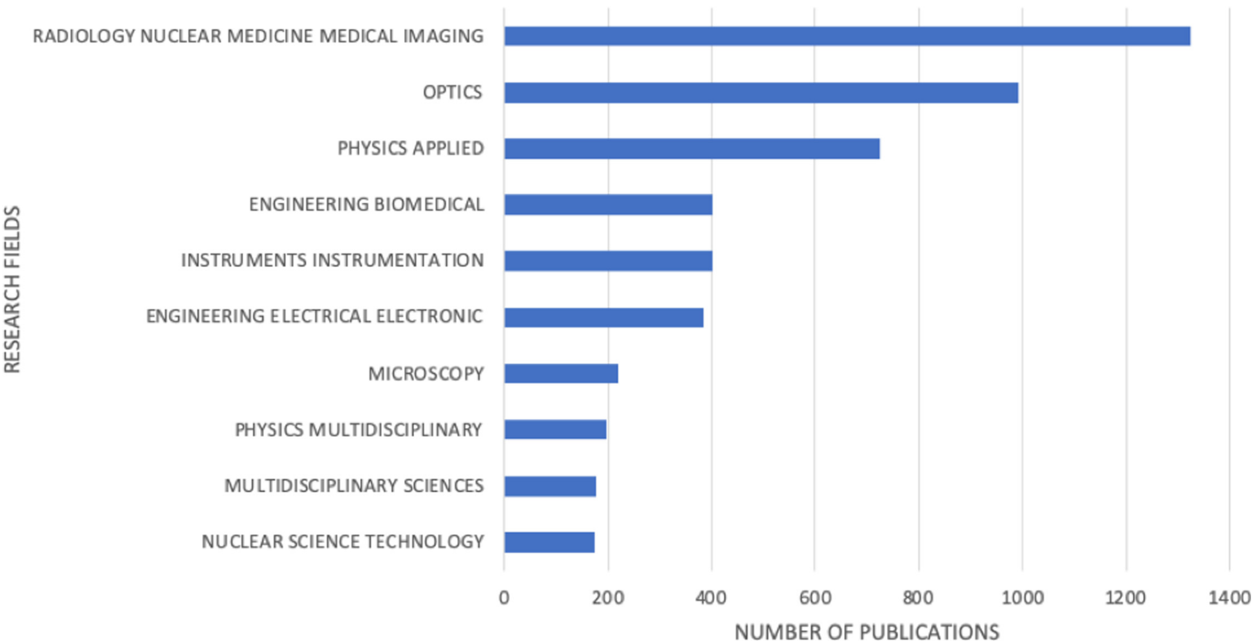

Figure 3. Top 10 research fields in phase-contrast imaging (PCI) publications.

had the second-highest betweenness centrality and relatively high closeness centrality.

In terms of Comparative Influence at author level (Table 1), F. Pfeiffer, a German physicist at Technical University Munich (TUM), was the most influential researcher in this research field. He is renowned for his contributions to the development of X-ray PCI and its applications in medical imaging. A. Bravin, from ESRF, was also a highly influential author, having a higher closeness centrality but lower degree and betweenness centrality than F. Pfeiffer. The third-most influential researcher investigating clinical X-ray PCI was G. Tromba from Elettra Sincrotrone Trieste, Italy.

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Table 1. Top 10 countries, institutions and authors with highest Comparative Influence and their normalised centrality values in phase-contrast imaging (PCI) publications.

	Rank	Country	nDegree	nCloseness	nBetweenness	Comparative influence (CI) (%)
Country	1	Italy	0.078	0.775	0.268	95.88
	2	Germany	0.089	0.725	0.110	78.17
	3	USA	0.047	0.746	0.219	76.87
	4	France	0.047	0.717	0.137	65.44
	5	Australia	0.054	0.613	0.041	51.68
	6	England	0.021	0.638	0.054	42.04
	7	Switzerland	0.024	0.625	0.031	39.78
	8	Japan	0.014	0.604	0.062	38.94
	9	Sweden	0.010	0.596	0.055	36.25
	10	Peoples R China	0.010	0.592	0.032	33.13
Institution	1	European Synchrotron Radiation Facility	0.012	0.489	0.217	90.20
	2	Technical University of Munich	0.017	0.443	0.131	83.67
	3	University of Trieste	0.013	0.451	0.070	66.97
	4	Elettra Sincrotrone Trieste	0.010	0.457	0.091	64.75
	5	Monash University	0.012	0.409	0.054	59.67
	6	Chinese Academy of Science	0.006	0.404	0.132	59.49
	7	Ist Nazl Fis Nucl	0.008	0.442	0.067	56.07
	8	Brookhaven National Lab	0.007	0.406	0.074	52.73
	9	Paul Scherrer Institute	0.009	0.400	0.048	52.28
	10	University College London	0.004	0.413	0.070	46.79
Author	1	Pfeiffer, F	0.009	0.356	0.11129	99.45
	2	Bravin, A	0.006	0.362	0.10834	88.01
	3	Tromba, G	0.005	0.347	0.09045	77.56
	4	Stampanoni, M	0.004	0.324	0.08845	71.14
	5	Zhong, Z	0.004	0.315	0.06800	64.19
	6	Olivo, A	0.004	0.339	0.05695	63.09
	7	Rigon, L	0.004	0.338	0.03643	56.85
	8	Arfelli, F	0.004	0.339	0.03360	56.09
	9	Coan, P	0.004	0.327	0.03178	54.44
	10	Yuasa, T	0.002	0.291	0.05689	51.24

Network cohesion analysis

Country, institution and author networks were also evaluated using cohesion network measures (Table 2). The results show that the component ratio was very low (close to zero) for all three country, institution and author networks. At country level (Figure 4), ties between countries were well distributed, with the network being almost one component, where only Czech Republic was not connected to that main component. At institution level, however, the component ratio was slightly higher than the country and author-level values.

The proportion of node pairs that had a direct way (of any distance) to each other, measured by connectedness, was also very high in all three networks, particularly at country level.

Research paradigms in clinically oriented X-ray PCI literature

For X-ray PCI literature concerning medical imaging, definitive research paradigms in terms of the PCI techniques and modalities investigated were discovered (Table 3). X-ray PCI was investigated as a technique most frequently with computed tomography and mammography as modality. GI was most investigated with medical imaging, followed by DEI and PBI.

Table 2. Network cohesion measures in phase-contrast imaging (PCI) publications.

Network measure	Country level	Institution level	Author level
Component ratio	0.025	0.076	0.022
Connectedness	0.951	0.789	0.721

One of the earliest clinically oriented investigations of PCI was in mammography, with PBI and DEI being commonly researched techniques.

Links between keywords were also explored. There were strong links between GI and the keywords “clinical”, “preclinical” and “set-up”. GI was also commonly investigated with the keyword “human”, which may suggest substantial research into the implementation of GI in clinical settings.

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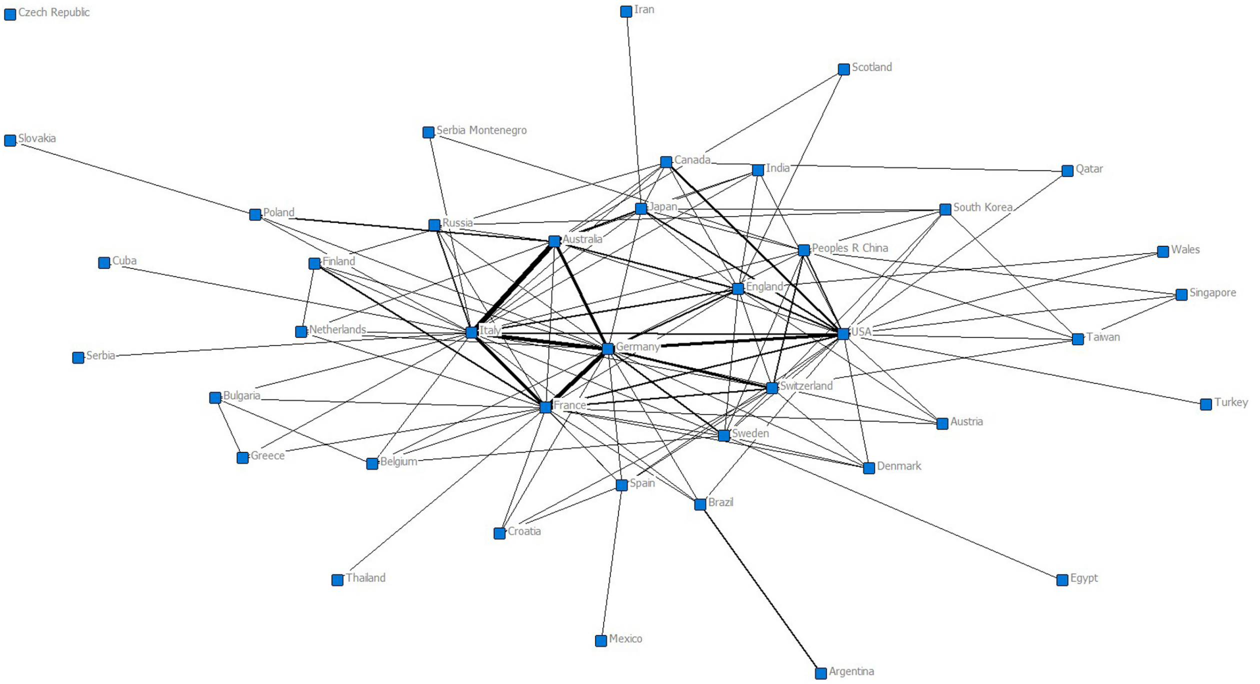

Figure 4. Country collaboration network in phase-contrast imaging (PCI) publications; where each node depicts a country and ties represent collaboration between countries.

Table 3. Keywords with over 100 frequency in phase-contrast imaging (PCI) publications.

Rank	Keyword	Frequency
1	Computed tomography	417
2	Synchrotron radiation	321
3	Mammography	242
4	Grating interferometry	200
5	Tissue	176
6	Diffraction-enhanced imaging	159
7	Resolution	140
8	Phase retrieval	134
9	Animal	123
10	Cancer	109
11	Propagation-based imaging	109

DEI was investigated with the term “clinical”; however, it was not explored at the same magnitude as with GI. DEI was strongly associated with imaging specimens and less associated with the keyword “human”. The term “cancer”, which was the 10th most frequent keyword, had the strongest connection to DEI as a technique, compared to all other X-ray PCI techniques. PBI had strong ties with the keywords “preclinical”, and “mammography” and was often investigated with the term “synchrotron radiation”.

There were not enough results or links from previous research to establish any firm conclusions for the clinical use of edge illumination; however, it has been investigated with mammography. Crystal interferometry was the least investigated.

Discussion

Investigations into PCI have been increasing, especially in its applications to radiology. The first investigation into the clinical applicability of X-ray PCI was conducted in 1995, by Davis et al.[24] They examined the effectiveness of X-ray PCI on objects with low subject contrast (i.e. soft tissue), which had implications for radiography and materials science.[24] Such implications have garnered interest in investigating the value of PCI to radiology, particularly its enhanced image quality, and patient dose reductions with the use of particular X-ray PCI techniques.[2-4] PCI may also reduce the need for further imaging and provide more accurate diagnoses with improved sensitivity and specificity.[25]

Based on the results, it can be argued that Italy possesses a breadth of connections, can obtain new knowledge gathered by other countries in the network rapidly and can best control the flow of information to other countries in the network. And while Germany, USA and France also had high Comparative Influence and notable betweenness centrality values, their overall influence is not as strong as Italy. Many of these

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influential countries are from the European region or are economic powerhouses. This seems to suggest that the influential countries may have greater access to resources; such resources may include physical resources (i.e. European Synchrotron Radiation Facility), financial resources (i.e. funding, research grants etc.) and human resources (i.e. researchers). For example, the world-first and only patient trial of two-dimensional (2D) PCI mammography has been conducted in Italy (at Elettra Sincrotrone Trieste).

Many influential institutions were also located within the European region including TUM (Germany), University of Trieste (Italy) and Elettra Sincrotrone Trieste (Italy). Monash University (Australia) possessed high degree centrality, showing that it was well-connected within the network, but did not have network control (betweenness centrality) or rapid information flow (closeness centrality) as other nodes. CAS is also very well positioned in the network; although they do not have a high number of collaborations, their ties are very effective in terms of controlling information flow and receiving new information rapidly. In addition, these institutions are well known in the PCI research community, and influential researchers are also associated with these institutions.

For authors renowned in this field, they are more desirable to work with. They can control the information in the network, have a sheer volume of publications while also possessing a breadth of connections to other authors. The influence and expertise that they have can attract new and established authors to collaborate with them. The most influential researchers we identified were from institutions located in the European region.

In terms of analysing the networks themselves, all three networks (i.e. country, institution and author networks) had a low component ratio. This conveys that the number of isolated nodes in each network was limited and that a majority of nodes were linked. However, as the component ratio for the institution network was higher than the other two networks, it suggests that there were more isolated institutions than there were isolated countries or authors. This may be as a result of researchers collaborating with other scholars within their own institutions, as opposed to those external to their institutions. This shows that there is potential to create new ties between contributing institutions, especially for isolated institutions and isolated groups of contributors. In addition, judging by the connectedness of the networks, the clinical X-ray PCI research field is cohesive within its network components.

Being aware of these network paradigms can help to strengthen the current collaboration networks and provide insights for forming new partnerships, where expertise can be shared, and greater contributions can be made to further develop this research field.

X-ray PCI techniques have been frequently investigated with mammography, due to the limitations of conventional imaging techniques. Breast tissue and lesions have comparable characteristics in terms of X-ray attenuation and therefore appear quite similar using conventional absorption-based imaging.[3,25] However, the difference in phase shift between the breast tissue and breast lesions is distinct, and by using PCI techniques, the sensitivity of mammography can be improved using PCI.[25]

In angiography, DEI, PBI and crystal interferometry techniques were tested with computed tomography (CT) and plain imaging of laboratory animals. Studies have shown these techniques are able to identify smaller vessels and plaque better than conventional, absorption-based imaging.[3,8] DEI has also been used in musculoskeletal imaging, demonstrating increased sensitivity to otherwise undetected, early degenerative changes in animal cartilage. In addition, GI was used to image an ex vivo human hand, producing clearer visualisations of tendons and ligaments.[8] DEI and PBI have been applied to image lung anatomy and physiology using plain imaging and CT. In laboratory animals, interstitial diseases and fluid in the airways were identifiable.[3,8] GI and PBI have been used in brain CT imaging and tested with animal and human ex vivo brain tissue. Clear differentiation between grey and white matter, neoplasms and brainstem structures have been described.[8] In oncology, PCI techniques have been tested with microscopy, conducting histopathological analyses of renal carcinoma specimens. Using PBI, deeper renal structures and typical malignant features were able to be clearly demonstrated and distinguished.[3]

GI may be frequently researched because it is compatible with conventional sources, with minimal modifications; however, high radiation doses are experienced with this technique.[5,9] Dose improvements should form part of further investigations to bring this technique closer to clinical implementation. Further research is required to determine its appropriateness for imaging patients in a clinical setting. Improved patient doses have been reported; however, the current set up often requires a synchrotron.[5] Further research investigating clinical translation is needed.

Edge illumination is compatible with conventional and synchrotron sources and should be considered for further investigation in a clinical setting.[9] Crystal interferometry has been least investigated due to its impracticalities. This technique is sensitive to minor changes in temperature and set up.[9,10] As a result, it may be difficult to maintain

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the crystal interferometry set up in a clinical environment.

It should be noted that some new methods of PCI, or modified forms of the previously established techniques, have been developed over the last couple of years. One of the latest additions to the group is the X-ray speckle-based phase-contrast imaging technique.[26,27] At the time of conducing this review, most publications about X-ray speckle-based imaging were proof of concept studies and thus it was not included in this work along the other five more established techniques. Future studies need to include new emerging X-ray phase-contrast imaging techniques, such as X-ray speckle-based imaging, and their applications in medical imaging, in their examination of PCI techniques.

As easy it is to say that greater collaborations should take place between institutions, and to place a greater focus on seldom-investigated techniques in medical imaging, this may not be entirely feasible. As previously discussed, there are resources that make a country or institution influential, and conversely, the lack of resources may limit a country or institution's influence. This may result in a restricted capacity to partake in greater collaboration. There are also constraints with the techniques themselves (i.e. requiring a synchrotron), which can also lead to difficulty when attempting to apply them in a clinical setting. These may have to be overcome before any major advancement in clinical translation can take place.

Conclusion

Over the past two decades, there has been increasing interest in PCI, and the literature investigating the applications of X-ray PCI in medical imaging is growing. In this study, by evaluating clinical X-ray PCI research at macro-scale using bibliometric and SNA methods, deeper insight was gained about the collaboration of contributors and research paradigms in this field. The European region possesses influential countries, institutions and authors, and while collaborations at a country and author level were quite involved, there were a considerable number of isolated institutions. Because of this, there is great potential for researchers to identify and collaborate beyond their affiliated institution and foster broader connections. In terms of research paradigms, GI and PBI held an advantage over other techniques and are closer to be clinically implemented, with edge illumination and crystal interferometry being seldom-investigated. Computed tomography was the most examined modality in the research field, and breast imaging has drawn particular interest for clinical PCI investigations, particularly with PBI. In effect, this awareness can promote greater collaborative investigation and further inform the direction of applying X-ray PCI with medical imaging.

Conflicts of interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Quantitative description of social network analysis measures.

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