Research Article

Technological development trajectory of chromatography: main path analysis based on patent citation network

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Abstract
After new technology is developed in a certain field, the technology was soon reflected in the patent. Historical, descriptive analysis of patent is often used to analyze the technological development trajectory. Analytical systems plays an important role in the development of every science, including chemistry, life sciences and physics and is a collection of modern sciences and technologies reflecting the advanced achievements of chemistry, physics, materials science, biology, precision instrumentation and control, communications and informatics. Therefore, the level of analytical system development and manufacturing is becoming an important indicator of the comprehensive level of the company's science and technology, so more and more companies are participating in the competition to develop analytical systems. In this paper, the technological trajectory of patents published between 1970 and 2018 were monitored by using the main path identification method based on the calculation of the search path link node (SPLC) value of each patent citation link, proposed by Von Wartburg et al. (Res Policy 34:1591–1607, 2005. https://doi.org/10.1016/j.respol.2005.08.001) and the technological development process was considered. As a result, the chromatographic technology development path consists of four stages: the key point of the 1st period is for the system development related to stable sample injection and mobile phase flow control; in the 2nd period, main development area is to further develop the stabilization system of the sample and the mobile phase developed in the 1st one and in the liquid chromatography, accomplish the fully automatic control of the system and increase the analytical accuracy and precision with combining computer; for the 3rd period is to increase the separation speed and separation efficiency in the chromatography column; in the last period, the main research objects are HPLC or UPLC, and the main area is to increase the stability, reliability and separation speed of the chromatographic system.

Keywords Chromatography · Main path analysis · Patent citation network · Technological trajectory

1 Introduction

Patents are the largest technical information resource in the world, which including more than 90% of technical information of R&D worldwide [2]. Patent metrology is an important research area of scientific metrology, and many scholars are researching on its theory, methods, and applications [3–5]. The retrieval and analysis of the patent's information can reveal the rules of development and evolution, which make important and practically significant step in raising the starting point of indigenous innovation, avoiding industrial low-level, redundant research and development.

After Dosi et al. [6] proposed the concept of technological trajectory, it attracted the attention of scholars, and since then many scholars have explored how to obtain

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technological trajectory. Hummon et al. [7] have put forward three generating methods of main paths, including depth first search, exhaustive search, and traversal counts. Mina et al. [8] make a citation network with individual patents as nodes and citation relation between the patents as arcs. They attempted to obtain the trajectory by deleting nodes that do not have a significant effect on technological evolution from citation network because the citation network becomes more complicated as the number of patents increases. Von Wartburg et al. [1] proposed the search path link code (SPLC) and the search path node pair (SPNP) to determine the network, confirmed the key route of the network using these methods. Both types of methods are based on calculating the SPLC or SPNP value of the citation node, and the elimination of other non-important nodes were eliminated. The results of the two methods are basically identical. Liu et al. [9] recommended that it is more appropriate to use SPLC in searching the technological trajectory according to the patents. Since then, several scholars have confirmed the technological trajectory of different industrial technology developments, such as fuel cell [10], mobile network technology [11], communication exchange technology [12] and aero-engine technology [13], and have confirmed the possibility of searching for technology trajectories from the patent citation network.

Chromatography is a laboratory technique for the separation of a mixture. When the mixture is dissolved in a fluid called the mobile phase, and carries it through a structure holding another material called the stationary phase, the various constituents of the mixture travel at different speeds in the stationary phase, causing them to separate in result [14]. Chromatography can analyze almost all organic compounds, including gases and liquids, and have the advantages of relatively simple operation, high precision, fast analysis speed and low reagent consumption, so this technology caught the attention of many scholars as soon as it emerged and developed rapidly compared to other analytical techniques [15, 16].

Chromatograph, first used by Italian-born scientist Mikhail Tsvet in the 1900s to separate plant pigments such as chlorophyll, carotene and xanthophyll [17], was widely used in the material separation process in the 1930s and 1940s [18]. In 1952, Archer John Porter Martin and Richard Laurence Millington Synge received the Nobel Prize in Chemistry for their completion of basic chromatographic techniques. Since then, paper chromatography, gas chromatography and liquid chromatography have been developed sequentially and used for scientific research and production.

In 1959, the GC–MS combined gas chromatography and mass spectrometer was developed [19–21] and in the 1970s, the LC–MS combined liquid chromatography and mass spectrometer was developed [22]. Since then, chromatography became one of the inevitable analysis systems in the field of several sciences including chemistry, life science, materials science, environment science with not only separation function, comprehensive quantitative and qualitative analysis functions but also structure analysis function [23, 24].

To date, technological trajectory analyzes in various fields such as information, communication, biotechnology, and nanotechnology have been performed, but no examples have been reported for the analytical system. In order to take the superior position in this creation competition using less cost within a short period, it is important to understand the history of development on the world-wide scale and comprehend future progress in time as well as grasping the specifications of analysis system to establish the research strategy thereto. In this paper, we performed patent bibliography analysis on patent data related to the chromatography reported in Derwent Patent Data Base from 1970 to 2018, and tried to interpret the technological development path of chromatography technology.

This paper is organized into four sections. Section 1.1 describes the principles of technological trajectory identification based on SPLC value calculations, and Sect. 2 provides data collection and research methodology. Section 3 consists of the results of data analysis and technology path analysis, and Sect. 4 contains the conclusions, limitations and further study.

1.1 The principle of main path analysis based on SPLC value calculation

Every patent can be considered as knowledge or innovation idea. When a new technology is developed in certain field that technology soon reflected in the patent. The technology development is a continuous innovation process, so that it is used by the other patent in technology development, after all the patents make a citation network by themselves. Generally, the number of citations of a patent increases according to the scientific, technical and application value of the patent. Patent with a large number of citations have reasonable references at the stage of technical development. However, in the first stage of technology development, the purpose and direction of development is different from each other and the technical conditions are also different. After all it is proceeded in various ways. After a certain period of time, some technologies were continuously developed and some technologies were stopped. Regardless of the number of citations, patents belonging to the stopped technology lose their value over the time, therefore, patent in the continuous way of development has a greater reference values than the patent with large citations. To find out the major path with the largest referential value among the continuous developments is the purpose of the main path analysis. The most important thing is to identify key link in a patent citation network. And then optimizing the others makes the complex network simple. The importance of each link is determined by the traversal weight that calculated by the number of times of traversed from start nodes to the end nodes [7]. Von Wartburg found that deciding whether a node is major or not depends on the importance of the individual node and the connectivity of the overall structure [1]. According to this consideration, the SPLC (the search path link code) was used as an index to identify the main path of the network. There are starting patents, ending patents, intermediate patents and isolated patents in the network. A starting patent refers to patent only with citing patent but not cited patent. In this study, the patents from 1970 to 2018 in the Derwent innovation index (DII) database were analyzed, and the starting patents are defined as the first cited patents after the 1970s. An ending patent refers to that patent only with cited patent but not citing patent; intermediate patent is with both cited and citing patent; isolated patent is neither with cited nor with citing patent. In the case of using the SPLC, it needs to analyze all the paths from starting patent to ending patent first, and then calculate the sum of the occurrences of the directed edges in all paths. The SPLC value of the isolated patent is zero. Finally, the largest path for SPLC is chosen as the main path.

Figure 1 is shown to simulate the way of computing. In Fig. 1, the node "O" represents an individual patent and the arrow "→" represents a citation relationship. For example A → C shows that Patent A was cited by Patent C. There are 15 patents in Fig. 1, three of them (A, B and D) are the starting patents, four (G, I, M, N) are endings, two (O, K) are independents, and the last six remainders (C, E, F, H, J, L) are for intermediates. There are 13 connected paths in the Fig. 1. The SPLC value of each connected path is the iteration weight of the paths from the starting patent to the ending patent. Take the A → C connected path as an example, this path lied in the path A → C→E → F→G, A → C→E → H→I, A → C→E → H→J → L→M and A → C→E → H→J → L→N, so the SPLC value of path A → C is 4. Since the path B → C differs only starting point from the path A → C, and the other paths are the same, the SPLC value of path B → C is also 4. Since the path C → E is on all paths beginning with A and B, the SPLC value of this path is 8. In this way, the SPLC values of the all connected paths were calculated and the results are shown in Fig. 1. In citation network, the path with the largest sum of the SPLC values is selected as the main path. In Fig. 1, A → C→E → H→J → L→M, A → C→E → H→J → L→N, B → C→E → H→J → L→M, B → C→E → H→J → L→N are selected as the main path. Since the total SPLC value is 39, which is the highest. The result is shown in Fig. 2.

2 Method

2.1 Data collection

The chromatography patents reported in the period from 1970 to 2018 were searched and downloaded according to the search formula given below from Derwent Innovations Index (DII) database. Under the discussion with experts, the search formula was constructed as follows, taking into account the technical characteristics of the chromatography and the history of its development. The search formula contains the types of chromatography and the major components of the chromatography.

TI = ("*chromatograph*" OR "LC–MS*" OR "GC–MS*" OR "head space sample*" OR "capillary electrophore-

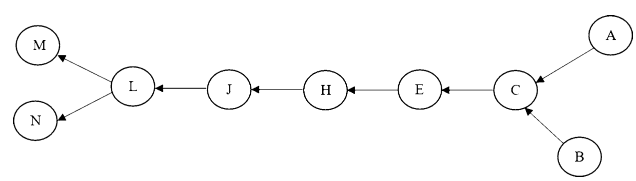
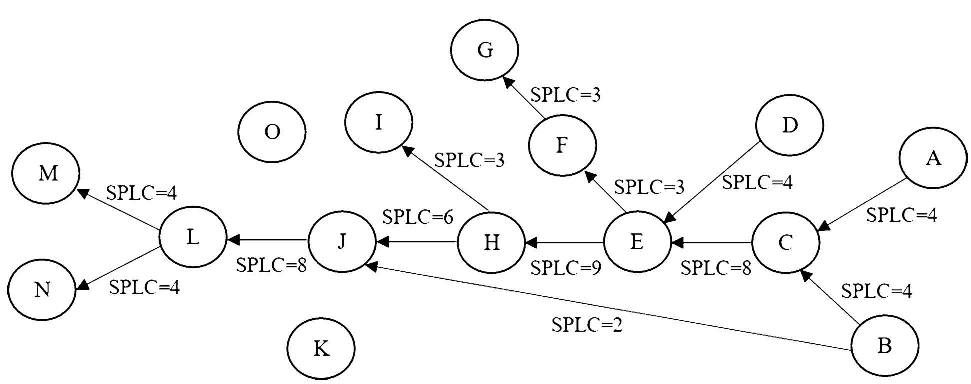


Fig. 2 Main path obtained

Fig. 1 SPLC value of individual node



sis*" OR "amino acid anal*" OR "autosampler*" OR "auto sampler*" OR "field flow separate*" OR "evaporative light detect*" OR "column thermostat*" OR "post column derivate*" OR "fraction collect*" OR "thermal cracker*" OR "hydrogen flame ion detect*")

The date of data searching and downloading is February 27, 2020. From 1970 to 2018, there were 36,134 patents in the subject category = "INSTRUMENTS INSTRUMENTATION".

Since the purpose of this study is to identify the trajectory of chromatography instrument development, the patent related to analysis methods and sample preparations are not suitable for this study. These patents not only complicate the citation network, but also prevent us from getting the required technological trajectory. Therefore, the patents in subject categories such as biotechnology, food, polymers, metallurgy, materials, agriculture, construction, and sports science have been deleted from the patent download process. The DII database provides English index information of all patents, so there is no language and country restrictions for data download.

Finally, 18,381 chromatography instrument related patents were downloaded and used for the study.

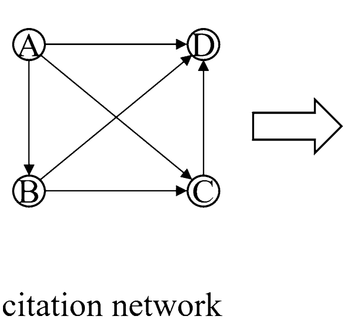
2.2 Data processing

In the main path analysis using patents, the first step is to make a citation matrix between patents. Figure 3 shows the principle of the citation matrix. In the citation network, the direction of the arrow indicates the patent citing the patent. A → B means B cite A. In citation matrix, the row element indicates the cite patent, and the column element indicates the cited patent. The matrix element is 1 if there is a citation between patents and 0 if it is not. Patent have no self-cite, so the diagonal element is 0.

To do this, we wrote a Delphi program that extracts citations from a database downloaded in DII and generates a matrix representing the mutual citations between them. Each patents downloaded from the DII data base have patent family. A patent family is a set of patents taken in various countries to protect a single invention (when a first application in a country—the priority—is then extended to other offices). In other words, a patent family is the same invention disclosed by a common inventor (s) and patented in more than one country [25]. So, when constructing a matrix, the patent numbers of the cited patent family member are replaced with the patent number of fundamental patent. In other words, if patent A cites one of the family patents of fundamental patent B, it is considered that A cites fundamental patent B and constructs a citation matrix. Also, isolated patents that do not have both citing and cited are removed from the matrix.

As a result, out of 18,381 patents, 7372 patents have mutually cited relations, so 7372 * 7372 citation matrix was formed for 7372 patents. The matrix was obtained as a text file considering the number of data and the writing speed.

This citation matrix was imported into Ucinet program developed by Stephen Borgatti [26] to obtain *.##h visual files and then visualized with the Netdraw program. Visualization results were stored as *.net files that the Pajek program [27] could read, and the files were imported from the Pajek program and analyzed using the technical path analysis using the SPLC value calculation algorithm.



	A	B	C	D
A	0	1	1	1
B	0	0	1	1
C	0	0	0	1
D	0	0	0	0

citation matrix

Fig. 3 Principle of obtaining a citation matrix from a citation network

3 Results and discussions

3.1 The analysis of technology development period

The patent publication quantity curve according to the year is shown in Fig. 4.

According to the change in the number of patents related to the chromatography for each year, the period from 1970 to 2018 can be divided into four periods. The 1st period is from 1970 to 1983, number of patents per year was less than 200, which tends to increase at a non-annual rate. In the 2nd period (1984–1993), the number of patents in the first half of the year increased relatively rapidly (the highest point: 303 in 1988), and then gradually decreased since 1989. In 1993, the last year of the 2nd period, the number of patents decreased to 150. In the 3rd period (1994–2007), the number of patents increased again, but the rate of increase was very small, by 2007, it had reached 330 cases in 1988. The 4th stage is seen as a high-speed growth staircase, and the number of patents has grown rapidly each year, and in 2018, the number of patents reached 1567 patents per year.

Fig. 4 The chromatography system patent numbers in order of application year

3.2 Core patentee and core research field

The chromatography patents were applied as much as 1801 cases during the 1st period of 1970–1983, 2253 ones during the 2nd period of 1984–1993, 3314 ones during the 3rd period of 1994–2007 and 10,915 ones during the 4th period of 2008–2018. The 10 core patentees in each period are given in Table 1.

The company that released the most patents during the 1st period from 1970 to 1983 was the Phillips Company, which announced 45 cases accounted for 2.5% of the total patent volume. The number of patents announced by the previous 10 units was 271, which was 15% of the total number of patents during this period. Shimadzu Corporation was the company that made the most patents in the 2nd period from 1984 to 1993, with a total of 297 cases, 13.2% of the total number. Hitachi Corporation also published 170 patents during this period. The Phillips Company, which published the most patents in the 1st period, published only 8 patents in the 2nd period, and the number of patents announced by the previous 10 units were 722, representing 32.0% of the total number of patents announced during this period. During the 3rd period (1994–2007), 3314 patents were published, and Shimadzu Company alone published 712 patents, representing 21.5% of the total number of patents. Hitachi (220) is followed by former. In addition, Agilent and Waters, one of the world's leading chromatography manufacturers, were also in top ranking. The previous top 10 companies published 1290, which represents 38.9% of the total number of patents announced during this period. During the 4th period (2008–2018), the amount of patent presentation surged, reached to whopping 10,915 patents. The largest number of patented units is still Shimadzu Company, but their contribution swelled to 6%, significantly lower than in previous periods. The total number of patents of the previous 10 companies was 1528, and the contribution share of the total number of published patents fell to 14.0%. This is the result of more companies and research units competing for technology development during this

Table 1 Major patentee for period

Period 1		Period 2		Period 3		Period 4	
Patentee	fq	Patentee	fq	Patentee	fq	Patentee	fq
PHILLIPS	45	SHIMADZU	297	SHIMADZU	712	SHIMADZU	658
VARIAN	39	HITACHI	170	HITACHI	220	STATE GRID CORP CHINA	150
GAS CHROMA TOGRAPHY	33	NIPPON ELECTRON	38	AGILENT	100	HITACHI	148
PERKIN ELMER	32	YOKOGAWA	47	HEWLETT	61	WATERS	136
HITACHI	28	CHROMATOGRAPHY RES	42	WATERS	46	AGILENT	98
SIEMENS	25	KURITA WATER	33	TOSOH	37	UNIV ZHEJIANG	85
PETROCHEM	20	HEWLETT	32	SEKISUI	34	ZHENGZHOU TOBACCO	67
SHIMADZU	17	PERKIN ELMER	24	GL SCI KK	28	GE HEALTHCARE	66
TOPCHIEV PETROCHEM	16	DOW CHEM	22	YAMATAKE	27	WUZHOU INST FOOD DRUG	61
ZELINSKII ORG CHEM INST	16	TOSOH	17	HORIBA	25	TOSOH	59

*fq: frequency

period. It is notable that the Chinese company STATE GRID CORP CHINA has published more patents than HITACHI, took the second place. Three Chinese companies and one Chinese university were in the rankings of the top 10 units. Distinguished from the previous phases, universities have published many patents during this period, with 1845 announcements, equivalent to 16.9% of the total number of patents. Their contributions at period 1, 2, and 3 were 1.9%, 4% and 6.1%, respectively. This is evidence that universities are increasingly participating in technology development activities of companies during this period.

Table 2 shows the Derwent Class (DC) code and their number included in applied from the 1st period to the 4th period. As shown in Table 2, the first and second DC in periods 1–4 are S03 (Scientific Instrumentation) and J04 (Chemical/physical processes/apparatus), with the highest frequency. However, the 3rd, 4th and 5th ranks are variants on these periods. In the 1st period, J01 (Separation), S02 (Engineering Instrumentation), T06 (Process and Machine Control); in the 2nd period, V05 (Valves, Discharge Tubes and CRTs), J01 and E19 (Other organic compounds general); in the 3rd period, V05, T01 (Digital Computers) and J01; in the 4th period, T01, J01, and E13 (Heterocyclic) are in the 3rd, 4th, and 5th positions respectively.

3.3 The analysis of technical trajectories

The citation matrix of patents in the 1970–2018 periods was composed and one type of technical path analysis, Standard global main path method [20], was carried out for the chromatography technological trajectory analysis. Standard global main path method is widely used across scientific disciplines. In project planning, for example, it is called Critical Path Method (CPM) too. Standard global main path is the path from source to sink vertices with the overall highest sum of traversal weights on the path. The weight of each node was calculated using the SPLC algorithm and the analysis was carried out using the Pajek program.

The technological trajectory obtained in this way is shown in Fig. 5. All of the 48 patents were included in this main route, and the materials were given to Table 3.

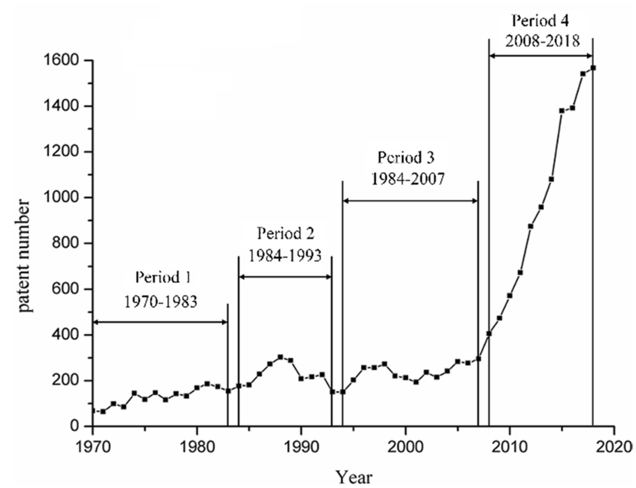


Fig. 5 Development trajectory of chromatography technology (1970–2018)

- The 1st Period (1970–1983)

This period contains 22 patents, its sources, in other words, the first starting point of the patents are US3487678-A, US3934456-A, US3518874-A, US3683701-A and US3847507-A.

US3487678-A is a patent relating to device design for injecting a sample into a chromatography column and ensuring its transport. This technology was also continued to DE1598223-B, a patent related to the design of valves to ensure continuous flow of mobile phase in the chromatography, this is again cited by DE2454046, a technical patent for mixing samples and mobile phases under high pressure conditions and sending them to the separation column. DE2454046 is connected with US4059009 A. This is a patent for the technique of preventing the pressure change and loss of samples during the flow of sample and mobile phase into the chromatography separation column using by-pass rotary valve, following after EP73913-A which embodied the control technique of chromatograph systems to stabilize the flow in single-stroke, syringe-type high pressure pump.

US3934456-A describes a technique that reduces pulsation of sample flow and promotes a solvent gradient

Table 2 Main DC code for four periods

Period 1		Period 2		Period 3		Period 4	
DC	Frequency	DC	Frequency	DC	Frequency	DC	Frequency
S03	1637	S03	2167	S03	3165	S03	10,492
J04	1038	J04	1590	J04	2539	J04	9249
J01	416	V05	189	V05	289	T01	1359
S02	92	J01	175	T01	225	J01	1014
T06	70	E19	65	J01	207	E13	411

Table 3 Patents included in the chromatography technological development path

Period	PN	Title	Granted author	Apply time	Granted time
Period 1 (1970–1983)	US3487678-A	Sample loading apparatus for chromatography column	UK ATOMIC ENERGY AUTHORTI	01 Apr 1968	Jan 1970
	US3518874-A	Analysis of mixtures of substances in one or—more chromatographic columns	CESKOSLOVENSKA AKADEMIE	26 May 1964	Jul 1970
	US3683701-A	Multiport sampling valve	STAUFFER CHEM CO	25 Aug 1970	Sep 1972
	DE1598223-B	Chromatograph charging device	CZESKOSLOVENSKA AKADEMIE	26 May 1965	Feb 1973
	US3847507-A	Pump for liquid chromatograph system	TOYO SODA MFG CO LTD	17 May 1972	12 Nov 1974
	DE2454046-A	Injection of samples into a carrier gas—for chromatography	WATERS ASSOCIATES INC	14 Nov 1974	15 May 1975
	DE2508572-A	Pumping system for liquid phase chromatograph	MICROMERITICS INSTR CORP	27 Feb 1975	18 Dec 1975
	US3934456-A	Solvent gradient generator for liquid column chromatography	VARIAN ASSOC INC	22 Jul 1974	27 Jan 1976
	US3985019-A	Liquid chromatography solvent proportioning	BOEHME D R	10 Nov 1975	12 Oct 1976
	US3985021-A	Liquid chromatography pump drive	VARIAN ASSOC INC	10 Nov 1975	12 Oct 1976
	DE2649593-A	Pump for high pressure liquid chromatograph	VARIAN ASSOC INC	29 Oct 1976	12 May 1977
	DE2719317-A	Elution liquid stream for liquid chromatography	NIHON BUNKO KOGYO KK	29 Apr 1977	17 Nov 1977
	US4059009-A	Fixed volume liquid sample feed to chromatographic columns	MICROMERITICS INSTR CORP	10 Sep 1976	22 Nov 1977
	US4063077-A	Solvent programmer	WRIGHT J R	15 Feb 1977	13 Dec 1977
	US4137011-A	Liquid chromatography system with motor driven pump	SPECTRA PHYSICS INC	14 Jun 1977	30 Jan 1979
	DE2922689-A	Piston pump for liquid chromatography	MAGNUSSEN H T	02 Jun 1979	13 Dec 1979
	US4233156-A	Dual pump for liquid chromatography apparatus	HITACHI LTD	07 Mar 1979	198,048
	DE2931017-A	Liquid chromatograph pressure intensifying system	MAGNUSSEN H T	31 Jul 1979	198,028
	US4225290-A	Pumping control for e.g. chromatographic system	INSTRUMENTATION SPE	22 Feb 1979	30 Sep 1980
	EP41793-A	Chromatographic column flow rate monitor	BECKMAN INSTR INC	26 May 1981	16 Dec 1981
	US4311586-A	Solvent mixing apparatus for liq. chromatograph	TRACOR INC	22 Apr 1980	19 Jan 1982
	EP73913-A	Control system for chromatographic apparatus	ISCO INC	19 Jul 1982	16 Mar 1983

Table 3 (continued)

Period	PN	Title	Granted author	Apply time	Granted time
Period 2 (1984–1993)	EP106009-A	Solvent supply system for liquid chromatography column	SHIMADZU CORP	01 Mar 1983	25 Apr 1984
	FR2533456-A	Automatic liquid chromatography apparatus	PHARMUKA LABS	28 Sep 1982	30 Mar 1984
	EP175925-A	Apparatus optimizing liquid chromatographic separation of unknown sample	PERKIN-ELMER CORP	21 Aug 1985	02 Apr 1986
	US4595496-A	Liquid chromatography system	MILLIPORE CORP	08 Aug 1985	17 Jun 1986
	DE3608227-A	Liquid chromatography system	APFEL H	12 Mar 1986	17 Sep 1987
	US4762617-A	Measuring macromolecular solute interaction in chromatographic column	US DEPT ENERGY	15 Jan 1987	09 Aug 1988
	US4767279-A	Composition and volumetric delivery control for liquid chromatography	MILLIPORE CORP	02 Jun 1987	30 Aug 1988
	US4824446-A	Gas chromatography simulation predicting separation	APPL AUTOMATION INC	23 May 1988	25 Apr 1989
	EP355546-A	Controlling gas chromatograph functions	ERBA STRUMENTAZIONE SPA	07 Aug 1989	28 Feb 1990
	US5108466-A	System to control operation of a chromatographic detector	HEWLETT-PACKARD CO	21 Dec 1990	28 Apr 1992
	EP570707-A2	Automatic configuration of gas chromatograph operating parameters	HEWLETT-PACKARD CO	21 Apr 1993	24 Nov 1993
Period 3 (1994–2007)	US5431712-A	Chromatographic separation of a sample	HEWLETT-PACKARD CO	31 May 1994	11 Jul 1995
	US5467635-A	Gas chromatograph with pressure regulator and sensor	SHIMADZU CORP	12 Dec 1994	21 Nov 1995
	US5545252-A	Gas chromatographic system operation	PERKIN-ELMER CORP	01 Mar 1995	13 Aug 1996
	JP9033502-A	Gas chromatograph device	SHIMADZU CORP	18 Jul 1995	07 Feb 1997
	JP11014612-A	Sample guide process for gas chromatograph	SHIMADZU CORP;	23 Jun 1997	23 Jun 1997
	EP959351-A2	Direct on-column injection of large volumes in a gas chromatography analysis apparatus	THERMOQUEST ITAL SPA	17 May 1999	24 Nov 1999
	GB2368031-A	Gas chromatograph comprises multiple layers each including pre-column and main column with stationary phase	AGILENT TECHNOLOGIES INC	22 Aug 2001	24 Apr 2002
	US2003150806-A1	Pressure-driven planar liquid chromatography device	NANOSTREAM INC	13 Feb 2003	14 Aug 2003
	US6663697-B1	Miniaturized chromatographic column for performing gas chromatography for analyzing chemical samples	SANDIA CORP	06 Jun 2002	16 Dec 2003
	WO2007092798-A2	Device to perform chromatographic separations	WATERS CORP	05 Feb 2007	16 Aug 2007
	WO2007109157-A2	Forming gradient used in liquid chromatography system	WATERS CORP	16 Mar 2007	27 Sep 2007

Table 3 (continued)

Period	PN	Title	Granted author	Apply time	Granted time
Period 4 (2008–2018)	WO2009092345-A1	Sample dispenser for high-performance liquid chromatography system	DIONEX CORP	07 Jan 2009	30 Jul 2009
	US2014069176-A1	System used to generate concentration gradient eluent flow for chromatographic separation	DIONEX CORP	12 Sep 2012	13 Mar 2014
	DE102014103766-A1	Method for adjusting gradient delay volume of liquid chromatography plant for chromatography running in HPLC	DIONEX CORP	19 Mar 2014	12 Jun 2014
	WO2016160157-A1	Liquid chromatography (LC) system for separating mixture into its constituents	WATERS CORP	17 Feb 2016	06 Oct 2016

by installing multi-compartment vessel between a separation column and the high-pressure pump. This patent is again cited by US3985019-A (with valves under complementary control dividing pump fill cycle technology patent that allows the mobile commercial sale to be accurately placed at the given setting value) and US3985021-A (with control of pump motor rotational speed to ensure reduce pulsations). After that above these two patents are cited in US4063077 and DE2719317, then these are continued to US4311586-A and EP73913-A, finally cited in EP73913-A.

Citation paths beginning with US3518874-A are continued to US3518874-A → DE2649593-A → US4223156-A → EP41973-A → EP73913-A. US3518874-A, this path is for a patent relating to the control of pumps and drawing eluent from first and second primary reservoirs. DE2649593-A (the pump for high pressure liquid chromatograph, which shaft to operate both the pump piston and the inlet valve to permit passage of liquid from the reservoir to the column) is continued to US4223156-A (the patent for dual pump fills and pumps out the liquid mobile phase at a fixed flow rate without any pulsation), continuously after EP41793-A and EP73913-A.

On the same principle, US 3847507-A is cited in EP73913-A throughout the US4137011A, DE2922689-A and US4225290-A. In the same way US3683701-A (multiport sampling valve for supplying corrosive gases or liquids to a chromatography) is finally cited to EP73913-A through DE2508572-A, DE2931017-A and EP106009-A.

Overall, the focus of the chromatography system development in step 1 (the 1st period) is the system development related to stable sample injection and mobile phase flow control.

- The 2nd Period (1984–1993)

The 11 patents are included in the 2nd period.

FR2533456-A describes a technique involving automatic liquid chromatography apparatus, which use eluent collection vessels with automatic valve and pump operation. This is in conjunction with US4595496-A, a patent that describes the liquid chromatography system, which has mobile phase components supply valves switched in set rate to pump cycle, and the patent EP175925-A, which describes apparatus optimizing liquid chromatographic separation of unknown sample.

To take the other example, patent US4595496-A was again cited in US5108466-A via DE3608227-A after being cited by two patents US 4767279-A and US4762617-A. US4767279-A is a patent describing a composition and volumetric delivery control for liquid chromatography that uses flow signal proportional to instantaneous volumetric flow of pump to control pump motor speed; patent US4762617-A relates to measuring macromolecular solute interaction in chromatographic column by comparing sum of profiles of individual solutes with mixture using computer model; DE3608227-A deals with the technique which produce an accurate result of the analysis without any constant volume extraction device by using comparator for actual and desired flow rate applying a correction factor; patent US5108466-A relates to operation system of a chromatographic detector that detector response is optimized and analytical accuracy is improved by modifying the characteristics of carrier and make-up fluids during a chromatographic run.

Between patents EP175925-A and US5108466-A, there are two patents US4824446- A and patent EP355546-A. Patent US4824446-A describes a technique for gas chromatography simulation predicting separation for chemical compounds identified by its experimentally determined elution time, the column characteristics being retrieved from computer data base; EP355546-A describes the technique that controlling gas chromatograph functions depending on advancement stage of analysis by detecting carrier gas data before and after sample injection.

Overall, focus point in the 2nd phase further develops the sample and the mobility stabilization system studied in the 1st phase by combining the liquid chromatography with the computer to realize the fully automatic control of the system and to increase the analysis accuracy by compensating.

- The 3rd Period (1994–2007)

There are 12 patents in the 3rd period.

EP570707-A2 is for a system that calculates the device configuration parameters from the input data of the gas chromatography to proceed the analysis operation automatically according to the parameter. US5431712-A is for chromatographic separation of a sample using chromatographic analysis system that operates in split-splitless injection mode configurations. US5467635-A is one of a technique for achieving high resolution with fast speed on gas chromatographs using pressure regulators and sensors. JP9033502-A is for Gas chromatograph device that comprises sample gasifying chamber, temperature controller, split ratio controller and gasification controller. And the advantage of this is automatic injection of a number of samples is practicable. The other patent JP11014612-A made it sure that allows the analysis of a wide range of compounds, minimizes the amount of solvent used, prevents adsorption of the sample components and decomposition by a filter, prevents damage to the column by maintaining temperature of sample vaporization chamber. Patent EP959351-A2 describes a technique for direct on-column injection of large volumes in gas chromatography with capillary columns. GB2368031-A is for a technique that detect both heavy and light analytes in a short period of time by using multiple layers each including pre-column and main column with stationary phase coating on their inner surfaces, and by using detector in fluid communication with downstream side of main column. US6663697-B1 describes a technique for achieving effective and rapid analytes separation while ensuring desirable thermal characteristics by using retainer with blocking elements that divides long groove into medium-retaining portion and output portion in gas chromatograph. US2003150806-A1 introduces microfluidic separation channels containing packed stationary phase material to liquid chromatographs to allow for higher packing throughout, and facilitates large production volumes a modest capital cost. WO2007092798-A2 proposes controller to control flow rate and formation of concentration gradient at two flow rates and performs gradient elution and chromatographic separations, which allows detectors to receive more samples and generates more data. WO2007109157-A2 proposes a technique that forming a gradient in a liquid chromatography system by introducing venting storage capillary to atmosphere, and running pump at low pressure and higher flow rate to fill storage capillary until gradient is formed in it.

In above patents, the main focus of development in the 3rd period was to increase the separation speed and separation efficiency in the chromatography column. It is noteworthy that the main research object in the 2nd period was the liquid chromatograph system, but the gas chromatograph system in the 3rd period.

- The 4th period (2008–2018)

There are 4 patents here.

WO2009092345-A1 suggested a sample dispenser in a high-performance liquid chromatography system, which injection valve switched to pressure balancing position so that sample conveying device reduces pressure to ambient pressure and allow avoiding the damages of the valve components by high flow speeds. US2014069176-A1 proposes a system used to generate concentration gradient eluent flow for chromatographic separation, which mechanically allows the eluent concentration to be changed relatively quickly without mechanical proportioning devices that are connected to a pump. DE102014103766-A1 describes a technique for automatically adjusting value of gradient delay volume in HPLC. WO2016160157-A1 describes a technique for accommodate particular needs of the chromatographic operation by allowing a user to automatically convert a system mixing volume and a sample dispersion volume in an HPLC or UPLC system.

In the 4th period, the core objects are HPLC or UPLC, and the main research project is to increase the stability, reliability and separation speed of the chromatographic system. In this period, only 4 patents were included in the technology main path, this shows the stabilization of sample and mobile phase flow, and the automation and high speed of the separation process are basically completed ever before.

4 Conclusion, limitation and further study

The major focus of this study lies in mapping the technological trajectories and analyzing the patent citation network. Through this study, we have come to find the citation relationship between each patent. Through the main path, not only the technological changes can be observed in the industry, but also possible for us to understand which area is the current mainstream for chromatography technology.

Through analyzing the patent citation network related to chromatography system from 1970 to 2018 and adopting SPLC values as a statistical index, this study has brought out a technological development route i.e., technological trajectory and introduced the following conclusions.

According to the changes in the number of patent applications per year, the development process of chromatography technology can be divided 4 periods: the 1st is from 1970 to 1983, the 2nd is from 1984 to 1993, and the 3rd is from 1994 to 2007 and last is from 2008 to 2018.

The number of patent applied in the 1st period is 1801. The three companies with the most patent applied during this period were PHILLIPS (45), VARIAN (39), and PERKIN ELMER (33). But the number of applications is less than 50. The major technical fields (DC codes) during this period were S03, J04, J01, S02, and T06. According to the result of the main path analysis, the focus research area of the 1st period of the chromatography technological development is for the system development related to stable sample injection and mobile phase flow control, and the basic research object is the liquid chromatograph. The number of patents applied in the 2nd period is 2253, which did not increase significantly compared to the 1st period. The companies with the largest number of applications during this period were SHIMADZU CORP (297), HITACHI LTD (170) and YOKOGAWA KK (47), all of which were Japanese companies. The number of applications from these three companies is 22.4% of the total number of applications during this period, indicating that Japanese companies value the development of chromatography technology and has begun to master the core technology of chromatography technology. The major technical fields of this period are S03, J04, V05, J01 and E19, which have changed compared with the 1st. The focus area of chromatography development is to further develop the stabilization system of the sample and mobile phase developed in the 1st one, and in the liquid chromatography, accomplish the fully automatic control of the system and increase the analytical accuracy and precision with combining computer, and the basic research object is the liquid chromatograph. The number of patents applied in the 3th period is 3314; increase more than 1000 from 2nd period, but the increase rate is not high. The units that contributed the most to the number of applications were SHIMADZU CORP (712), HITACHI LTD (220), AGILENT INC (100), consisting of 2 Japanese companies and 1 American company. The application number of SHIMADZU CORP is for 21.5% of the total application number during this period, and the application number of the first three companies is for about 1/3 of the total application number, indicating that the field of chromatography technology has gradually formed a technological monopoly. The major technical field is the same as in the 2nd period except that E19 in the 2nd period was changed to T01. The main for the 3rd period is to increase the separation speed and separation efficiency in the chromatography column. Different from the prior two periods, the basic research object in this period was the gas chromatography system. The number of patents applied in the last period was 10,915, increases more than twice that of the 3rd period. The companies with the most applications during this period are Shimadzu Corp, STATE GRID CORP CHINA and HITACHI LTD, two Japanese companies and one Chinese company entered the top 3. Different from the previous three stages, the number of patents applied by universities has increased rapidly, accounting for 16.9% of the total applications, which shows that more universities are participating in technology research and development activities. The basic technical fields of the 4th period are S03, J04, T01, J01 and E13. The main research objects are HPLC or UPLC, and the main area is to increase the stability, reliability and separation speed of the chromatographic system.

Although this study derives the technological development trajectory of chromatography by combining patent bibliographic analysis and main path analysis, there are some limitations. First, it is necessary to conduct an empirical analysis on the influence of the patent of the identified technological trajectory on the development of chromatography technology in sights of historical consideration. Second, chromatographic technology is a collection of many sub-technologies; the citation network will contain the technical development paths for these sub-technologies. However, since this study identified only the most important paths related to separation, the relationship between these sub-technology paths could not be considered. Future research could focus on searching sub-technological trajectories and examining the relationship between main and sub-technological trajectories.

The research method described in the paper will be helpful provide guidance on selection of research and development direction and also on the establishment of technical development strategies in analytical equipment production companies and research units.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate All authors declare that they have no conflict of interest. This article does not contain any studies with human participants or animals performed by any of the authors.

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