Key technology network of BioMEMS through patent analysis

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The growth of an ageing population and demand for telemedicine have rendered, biomicroelectromechanical systems (BioMEMS) as one of the internationally recognized prospective research areas. Previous studies have mostly emphasized on specific BioMEMS technology or the market application of such technology. However, these studies have not actively identified the key technology of BioMEMS and have not determined the technology development trend in recent years. In the present study, BioMEMS patents were used as a basis of analysis to build a technology network and conduct network analysis. The results showed that key BioMEMS technologies mainly comprised chemical containers, measurements, printed circuits and medical diagnoses. Therefore, BioMEMS technology is applicable to not only one technical field, but multiple technical fields. However, recent technological development has mainly emphasized medical diagnostic measuring technology rather than mature technologies such as chemical containers or printed circuits. An analysis of patent holders reveals that institutions which have developed BioMEMS technology for a relatively long period of time are public or semi-public agencies, indicating that government funding and support are necessary in the early phase of BioMEMS development. This study constructed a model of a patent technology network to investigate the development trend of BioMEMS technology.

Keywords: Biomicroelectromechanical system, key technology, network analysis, patent network.

IN realizing future medical services, biomicroelectromechanical systems (BioMEMS) play an increasingly crucial role. Integrating technology such as medical biotechnology, nanomaterials, and microelectromechanical systems (MEMS), BioMEMS apply MEMS technology to the field of life sciences. In addition, the growth of an ageing population and demand for telemedicine have rendered BioMEMS as one of the internationally recognized prospective research areas and one of the most influential industries in the twenty-first century. A research report by the market research institution Yole Développement indicates that because of the growth of in-home physiological monitoring, mobile healthcare and implantable medical applications, the global market value of BioMEMS is expected to surge to USD 6.6 billion by 2018, approximately three times that in 2012 (ref. 1). In fact, several studies have been focused on the development of this technology[2–4].

Most previous studies have emphasized specific BioMEMS technology[3–5] or market application of such technology[6,7]. However, these studies have not identified the key technology that actively drove the development of BioMEMS. In particular, BioMEMS microstructures are increasing rapidly as sophisticated functions, such as chemical reactions and analyses, bioassays, high-throughput screens and sensors, which are being integrated into a single BioMEMS device[8]. Because BioMEMS generate strong future business opportunities, determining the key technology is necessary. Government agencies, research universities and businesses are all eager to identify optimal resource distribution, that is, to identify the fields of technology that merit investments in the form of funding and research manpower. This has been investigated in the present study. Through network analysis, this study illustrates the current condition and position of specific technology in the technology network, thereby identifying the key technology.

In this study, a model of a BioMEMS technology network was constructed through patent analysis. Patents serve as direct proof of innovative production and can be employed as an indicator for observing technological development trends[9–11]. Therefore, patents have been adopted to evaluate technological cooperation results[12–14] and technology transfer studies[15,16]. Patents can be applied as a direct evaluation indicator of technological development. Therefore, in this study, patent data were adopted as a basis for observing BioMEMS technological development trends and key technological fields.

In summary, distinct from previous BioMEMS-related studies that have focused on technological or market application of BioMEMS, the present study mainly investigated the key BioMEMS technology, specifically emphasizing the construction of a technology network model and identification of technological development trends. The results are expected to serve as references for government agencies, scholars and professional industries.

According to market trend analysis, the next step for MEMS development is portable healthcare device and microfluidics chip product technology[17,18]. Portable healthcare devices facilitate obtaining real time physiological data on human body, including technology for determining exercise status, body sound, heart rate, blood pressure, body temperature, and electroencephalogram readings, rapid medical emergency notification mechanisms, smart health management, daily examination and drug delivery technology. Portable healthcare devices that can be worn conveniently are expected to become one of the key products on the MEMS market.

Microfluidics chip technology combines MEMS with biomedical technology. Silicon chips, glass or plastic are

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adopted as substrates. Tiny fluid channels and biomedical sensing elements are manufactured on the surface of these substrates. Therefore, chips exhibit a smaller size, faster functioning speed and parallel processing capacity. Hence, multiple biochemical medical tests on solution samples can be conducted in a small area. Regarding the application of microfluidics chips in medicine, the main focus of development worldwide is point-of-care technology[19]. In ordinary hospitals, after patient specimens (e.g. blood, urine and feces) are collected, they are generally transferred to testing centres for analysis and examination. Transportation consumes considerable time and resources. Moreover, emergency medical treatments or under tight time constraints are likely to be delayed. The major contribution of microfluidics chips is that they enable testing centres to perform immediate analysis of specimens collected. Consequently, physicians can make quick and correct clinical judgments before recommending appropriate treatment required for patients.

In the future, BioMEMS are expected to be applied to multiple fields, including the following: (i) pharmaceutical: drug discovery and commercialization; (ii) *in vitro* diagnostics: biological test development and commercialization; (iii) medical devices: Medical equipment development and commercialization; (iv) medical home care: prescribed medical devices and services for home care[20]. The healthcare sector is estimated to excel in its future output value. Global BioMEMS and microsystem market in the healthcare sector is expected to grow at a CAGR of 25.1% over the period 2014–2019 (ref. 21). Consequently, governments worldwide should acknowledge the development potential of BioMEMS and facilitate their technological development by allocating appropriate resources to BioMEMS-related industries. In the present study, BioMEMS were used as the main subject of analysis to determine their key technology through patent analysis. This key technology was subsequently investigated through network analysis.

In recent years, several studies have adopted network analysis to investigate the technology development paths of specific industries[22–24], to determine the knowledge map of the technological development of specific countries[23,25], or to explore the framework and scope of knowledge fields through patent analysis[26,27]. Through network analysis, the technology evolution mode and data transmission path can be displayed precisely. In particular, objective and practical data can be obtained through analysis of patent statistics, including patent code, year of approval and classification of technology[28]. Therefore, analysing the development of specific technology through patent statistics is useful. Patents constitute the source of technological and commercial knowledge. The interdependence and connection between technologies can be identified through network analysis; the results can serve as a useful tool in managing research and development activities[23,28]. Therefore, in this study, technology network analysis was adopted to investigate the key players in BioMEMS-related patents and discuss the connection between multiple technology groups.

The United States is the largest commercial transaction market in the world. Its development of systems and data can be traced to as far back as 1975. Moreover, the US system exhibits universal representability in the analysis of international technology. When inventors apply for patents in other countries, they tend to apply in the United States as well[29]. Consequently, in this study, the US Patent Database was selected as the data for patent analysis. This study collected patents from the United States Patent and Trademark Office (USPTO) patent database which were approved and announced between 1976 and 2015. The search conditions were set as follows: (TTL/Biomems) or (ABST/Biomems) or (ACLM/Biomems) or (SPEC/Biomems). A total of 282 patents were retrieved. In addition, to classify technology in the technology network, the USPTO and the European Patent Office implemented cooperative patent classification (CPC) at the beginning of 2013. Therefore, in this study, CPC was adopted as a framework for analysis.

Previous studies have determined key players within a network through network analysis to differentiate gatekeepers from stars[30,31]. However, recent studies have adopted the network-centric analytic approach[32,33] to identify key players within a network. In the present study, the latter method was also used to identify the key technology in patent technology network.

Closeness centrality refers to the total shortest distance between one node and other nodes. When a node is closer to other nodes, it possesses higher closeness. In a technology network, closeness centrality enables evaluating the global centrality of a given type of technology, according to which the network reach of this technology to other technologies can be determined.

$$C_{\mathrm{C}}(n_i) = \left[\sum_{j=1}^{g} d(n_i, n_j)\right]^{-1},$$

$d(n_i, n_j)$ refers to the distance between nodes n_i and node n_j.

Betweenness centrality indicates that a few nodes in a network cannot be connected to other nodes without passing through a specific node (broker). Nodes with higher degrees of betweenness centrality occupy crucial positions in the network structure; the connection and communication between other technical nodes must rely on this technical node.

$$C_{\mathrm{B}}(n_i) = \sum_{j<k} g_{jk}(n_i)/g_{jk},$$

g_{jk} represents the number of shortest paths from nodes j to k, and $g_{jk}(n_i)$ refers to the number of shortest paths from nodes j to k that must pass node i.

In addition to betweenness centrality, a structural hole can be applied to evaluate the capability of technology to serve as mediator. A structural hole refers to a node that occupies the key message communication passage in the network and the effect is called the hole effect[34]. When vacant space exists between clusters, connections can be established by bridging the nodes. If a type of technology serves as a bridge, that is, it connects two previously separate technology clusters, then this bridging technology acquires a positional advantage in the technology network. Technical items less affected by the structural hole encounter fewer constraints and are less likely to be obstructed by other technical items. Burt[34] indicated that the structural hole effect can be assessed according to the network constraint index. Within a range of 0–1, a node that exhibits a higher structural constraint index value is less independent and has a weaker structural hole effect.

$$C_{ij} = \left(P_{ij} + \sum_k P_{jk}\ P_{kj} \right)^2,$$

where C_{ij} is the scores of node i that are constrained by node j, P_{ij} the proportion of node i's relation links that are connected to node j to all the relation links of node i, P_{jk} the proportion of the relation links of node j to those of all nodes, P_{kj} is the proportion of the relation links of all nodes to those of node j. In this equation, the total constraint of node i in the network is the total distance of node i's links that pass node j. In other words, $C_i = \sum_j C_{ij}$.

Before technology network analysis was conducted, patent search result analysis was performed to obtain an overview of technological development. Table 1 displays the number of top ten four-stratum cooperative patent classification (CPC) codes.

Table 1 shows that the BioMEMS technology is mostly classified under the A61B5, A61N1, H01L2924, G01N33 and B01J2219 codes. According to the CPC international patent classification definition, A61B5 covers detecting, measuring or recording instruments, implements and processes for diagnostic purposes; A61N1 includes electrotherapy and circuits for these purposes; H01L2924 covers indexing schemes for arrangements or methods for connecting or disconnecting semiconductor or solid-state bodies; G01N33 includes investigating or analysing materials through specific methods; and B01J2219 covers chemical, physical, or physicochemical processes in general and their relevant apparatus.

Table 1. Frequency distribution of top 10 four-stratum cooperative patent classification (CPC) codes

Rank	CPC code	Frequency of occurrence	Percentage
1	A61B5	146	7.48
2	A61N1	118	6.05
3	H01L2924	99	5.07
4	G01N33	83	4.25
5	B01J2219	68	3.48
6	A61F2002	63	3.23
7	B01L2300	52	2.66
8	H01L2224	44	2.25
9	B01L3	42	2.15
10	A61F2	37	1.90

The aforementioned analysis illustrates that the focus of BioMEMS technology is mainly diagnozing and analysing biological materials, measuring biological current, and semiconductors. In addition, Table 2 shows an analysis of the top 10 patent holders. The National Institutes of Health, Boston Scientific Scimed, Inc. and the National Science Foundation possess the longest patent duration, indicating that these institutions have developed patents over a long period of time and are among the first to develop BioMEMS-related technology and patents.

To determine the key BioMEMS technology, four strata were adopted to investigate 240 CPC codes. Figure 1 shows the network model of key technology. Table 3 presents various key CPC codes.

Table 3 illustrates that B01L3, G01N33, H05K3 and A61B5 are the top five technical fields for closeness centrality, betweenness centrality and the hole effect. This result indicates that key BioMEMS technology is mostly concentrated on containers or dishes for laboratory use, e.g. laboratory glassware (B01L3), investigating or analysing materials by specific methods (G01N33), apparatus or processes for manufacturing printed circuits (H05K3) and detecting, measuring or recording for diagnostic purposes (A61B5). The aforementioned discussion reveals that the key BioMEMS technologies mainly comprise chemical containers, measurements, electrical science and medicine. In other words, BioMEMS cannot be developed without interdisciplinary studies in these fields.

The variation of patents that have been related to key technology (i.e. B01L3, G01N33, H05K3 and A61B5) over the years was further analysed in this study to identify the BioMEMS technology trend. Figure 2 displays the analysis result and indicates that in recent years, technology related to A61B5, namely measuring instruments for diagnostic purposes, has received increasing attention. However, other key technologies are relatively mature in development and thus generated fewer patents during the last year.

By using network analysis according to empirical data, this study found that the key BioMEMS technologies mainly cover chemical containers, measurements, electrical science and medicine. The fact that the key technologies are not limited to one specific field indicates that BioMEMS require interdisciplinary collaboration. In

Table 2. Patent approvals by the top 10 patent holders

Rank	Patent holders	Patent code	Percentage	Average patent age
1	Celera Corporation	14	4.96	4
2	Applied Biosystems, LLC	11	3.90	5
3	National Institutes of Health, U.S. DEPT. of Health and Human Services (DHHS), US Government	10	3.55	6
4	Fernandez Dennis S.	10	3.55	2
5	Vanderbilt University	9	3.19	4
6	The Invention Science Fund I, LLC	8	2.84	1
7	Boston Scientific Scimed, INC.	8	2.84	6
8	National Science Foundation	7	2.48	6
9	Depuy Spine, INC.	6	2.13	5
10	California Institute of Technology	5	1.77	1

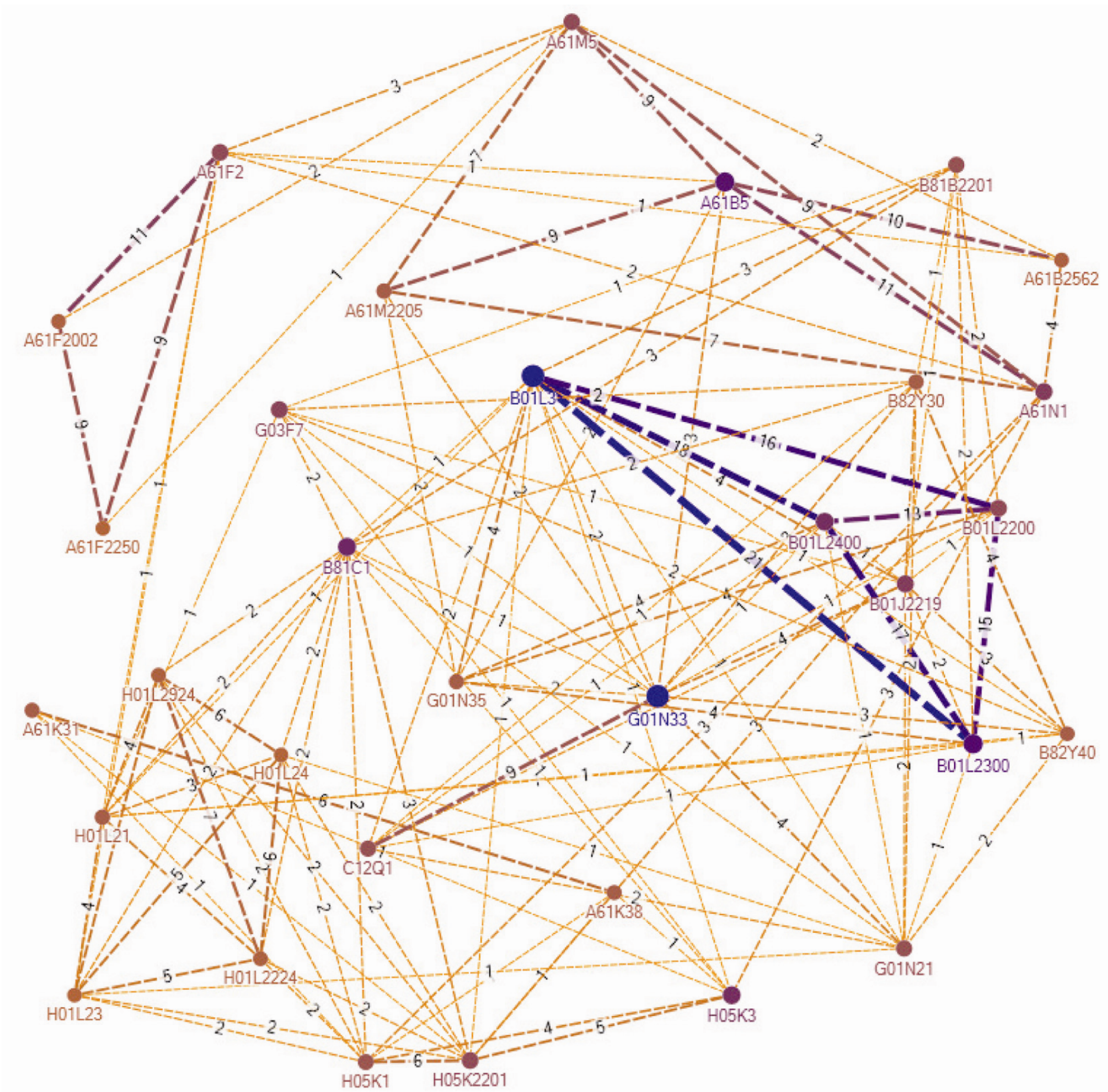

Figure 1. BioMEMS network arranged by the four CPC strata. The size of a node indicates the number of nodes it connects, and the thickness of an arc signifies the strength of the connection. Only nodes that connect more than 15 nodes are retained.

Table 3. Top five CPC codes in BioMEMS

CPC code	Closeness centrality	CPC code	Betweenness centrality	CPC code	Hole effect
B01L3	119.683	G01N33	5144.049	G01N33	0.183
G01N33	119.267	B01L3	4357.267	A61B5	0.185
B81C1	109.600	H05K3	3600.489	H05K3	0.190
H05K3	108.150	G03F7	3256.687	B01L3	0.191
A61B5	105.917	A61B5	2547.84	B01J2219	0.200

The hole effect was calculated according to the network constraint index.

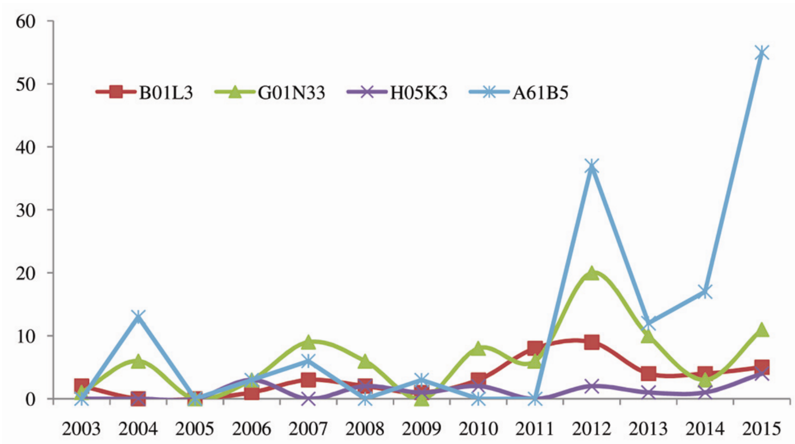

Figure 2. Variation of key BioMEMS technology over the years.

addition, an analysis of the main patent holders indicates that the National Institutes of Health, Boston Scientific Scimed, Inc. and the National Science Foundation have developed patents for the longest period and are also among the first to develop BioMEMS technology and patents. The fact that these institutions are either public or semi-public agencies shows that government funding and support are necessary in the early phase of BioMEMS development.

Regarding technology trends, this study determined that the key technological development of BioMEMS in recent years has focused on A61B5, namely measuring instruments for diagnostic purposes, rather than on relatively mature technologies such as chemical containers or printed circuits. Although chemical containers or printed circuits remain an essential technology in BioMEMS development, in recent years, attention has shifted to patents related to diagnostic measuring technology, indicating that BioMEMS technology development has gradually moved towards portable healthcare devices. This development trend aligns with the previous studies[17,18]. The present results are consistent with the development trends in emerging fields.

With regard to theoretical contributions, most previous studies have emphasized specific BioMEMS technology[3–5] or the market application of such technology[6,7]. However, these studies have not determined the focus of technical fields, technology development trends, or network distribution among technical fields. To bridge this research gap, a new perspective emphasizing the observation of technical fields was adopted in the present study.

This study has provided valuable information, useful to the government, for policy suggestions. In particular, a technology map of BioMEMS was proposed. Through analysing and determining the focus of BioMEMS technology development in the technology network, this study has provided the government with information related to allocating research and development resources and promoting emerging technology. For the current key BioMEMS technology, this study has found that the central key technology type in recent years has been measuring instruments for diagnostic purposes, which are classified as being in the field of medicine instead of electrical science or chemistry. Furthermore, diagnostic measuring is a technical field which requires high-level technology, presents substantial obstacles for investors, but likely produces large profits. Therefore, the government must play a crucial role in developing BioMEMS-related industries, specifically in long-term support and talent cultivation.

In this study, patents were solely adopted as a basis for research on technology development trends. Nonetheless, BioMEMS development is not restricted to patents; other forms of development, such as essays and preliminary studies, personnel exchanges, specific products, or other forms of production, are commonly observed. The fact that other forms of production were not included constitutes a major limitation of this study. In addition, to investigate a large-scale technology network of the entire BioMEMS, only the number of patents was adopted as an empirical basis because of time constraints and research attributes. The uniqueness of individual patents was not evaluated through content analysis. Finally, because of manpower and funding limitations, only the database of the USPTO, the patent and trademark office of the largest commercial transaction market in the world, was used as the source of patent data. Therefore, subsequent researchers should increase the scope of research by including data from other patent offices (e.g. the European Patent Office and Japan Patent Office) in observing and verifying information.

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