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Tracing the Evolution of Biomedical 3D Printing Technology Using Ontology-Based Patent Concept Analysis

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ABSTRACT

Three-dimensional (3D) printing enables products to be custom-designed and produced using additive manufacturing processes. This research develops a patent analysis approach to explore biomedical 3D printing technology trends. First, the method searches for related patents. Second, frequently appearing key terms in patents are extracted as a means to identify key concepts of inventions. Third, in order to structure the domain knowledge, the ontology is created by referring to the relevant key terms and literature. The key terms create indexes used to measure similarities for clustering the patents and sub-technologies. Based on the patent context and dynamic patent concept analysis maps, the evolutionary trends of technology development are depicted. Biomedical 3D printing R&D projects are used as case examples to compare against co-occurring patent evolutions. The proposed patent concept analysis is generalisable for critical decision support of R&D planning and evaluation in any market sector.

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Additive manufacturing; biomedical 3D printing; ontology-based patent informatics; formal concept analysis

1. Introduction

3D printing creates 3D objects from digital models by layering cross sections of models using a surface tessellation language. 3D printing processes are categorised into several types including vat photo polymerisation, material jetting, binder jetting, material extrusion, powder bed fusion, sheet lamination, and directed energy deposition (ASTM 2009). As reported by researchers (Gross et al. 2014; Brookes 2015), the highest potential growth in 3D printing applications is in the biomedical domain. The reason for the biomedical domain being viewed as the 'star' and 'cash cow' of 3D printing applications is largely due to the needs for customisation and advanced materials (Brookes 2015). In order to reduce risk, doctors also simulate surgeries (e.g. neurosurgery) using 3D printed models (Klein, Lu, and Wang 2013; Oliveri et al. 2014). After the electronic mock-ups and editing, a patient's digital model is used for 3D printing customised prosthesis or devices (e.g. surgical guides) to improve medical treatment quality and accuracy (He et al. 2006). As identified by Atala (2011), 3D printing is the dominant trend for regenerative medicine including bioprinting and manufacturing auxiliary medical devices. Companies such as Conformis, 3D Biotek, and Organovo have successfully applied 3D printing technologies in their productions. For example, Organovo is promoting commercial 3D organ printing technology (2009). LayerWise uses 3D printing to produce a jaw made from titanium and has successfully completed transplant operations (2012). In order to plan related biomedical 3D printing R&D strategies and maintain competitiveness in the marketplace, the technology trends and the corresponding technology firms should be clearly identified and analysed.

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Some researchers (Rayna and Striukova 2016; Sandström 2016) have reviewed 3D printing development trends from the perspectives of novel manufacturing processes, materials, and applications. In addition to explaining 3D printing from a pure technical standpoint, our research focuses on depicting the patent evolution in the biomedical domain and interprets the innovation trends based on the leading firms or research organisations' patenting activities. The research aims to broaden the strategic technology insights for decision support for R&D development considering commercialisation and business models (Salvador et al. 2014; Ford, Mortara, and Minshall 2016).

In this research, dynamic patent analysis uses extracted key terms to build an ontology schema. Afterward, a clustering algorithm is used to group patents, within the ontology domain, to differentiate segments of the rapidly evolving technologies. Finally, the trends of sub-technology segments and evolution, and the leading assignees' positions are visually traced using a dynamic patent lattice. This research focuses on analysing 3D printing innovations extracted from the US patent database. The goal is to analyse the global trends of biomedical 3D printing, to provide enterprises or research organisations with concisely summarised and useful information for formulating R&D strategies, and to better enable research teams to identify fast-moving technology life cycles.

2. Literature review

The literature related to patent analysis, ontology, knowledge discovery, and formal concept analysis (FCA) are reviewed in this section.

2.1. Patent analysis

Patents analyses are often used by governments and companies to assess their patent portfolios as intellectual assets. Patent portfolios and analytical maps have been acknowledged as a reliable indication of global competitiveness for countries or enterprises (Lacasa, Grupp, and Schmoch 2003). Patents are of multiple values to companies, for example, for improving global reputation and facilitating strategic negotiations with partner companies (Blind et al. 2006). As emphasised by the research literature, patent macro-level statistic and micro-level context analyses are critical to interpret technology trends and sustainable competitiveness. Since patent documents reveal extensive knowledge for recreating the inventions, patent analysis is widely used by companies to formulate R&D strategies and to avoid infringing upon prior-art patent assignees (Shiue and Chang 2010). Most international patent offices (e.g. United States Patent and Trademark Office (USPTO) and European Patent Office (EPO)) provide open access to search and collect data from their patent databases. When patent searches in a particular country are restricted by language or provide only abstracts, third-party private compilations may be purchased from companies such as Thomson Innovation (TI) (2015).

Patent analysis estimates technological trends that impact market advantages and profitability and enables the comparison of innovations across countries. A typical patent analysis includes patent searches, patent document segmentation, abstracting, clustering, visualisation of trends, and interpretation of patent quality (Tseng, Lin, and Lin 2007). Statistical analysis is often used to create visual displays called patent maps (Chen 2009). Patent documents can also be abstracted into compressed, yet accurate, short summaries for quick references (Trappey and Trappey 2008; Trappey, Trappey, and Wu 2009). Domain patents may be clustered and classified into meaningful subgroups based on criteria such as sub-technologies (Trappey, Trappey, and Wu 2010), international patent classifications (Trappey et al. 2006), or ratings of patent quality (Trappey et al. 2012).

2.2. Ontology

Ontology is applied in knowledge engineering, artificial intelligence, and computer information management to express and describe the body of knowledge in given domains using formalised

language. Ontology is explicit specifications consisting of a set of concepts, relations, objects, and functions (Gruber 1993). Further, Huhns and Stephens (1999) say that ontology represents a portion of a real-world knowledge domain. The ontological set of objects and the relationships are frequently depicted as formal graphs to represent the domain knowledge and its common vocabulary (Chandrasekaran, Josephson, and Benjamins 1999). Three general methods are used for building ontology schemas and include the bottom-up, top-down, and middle-out approaches. Bottom-up is from specification to generalisation of a given knowledge domain. Top-down is from generalisation to specification, while middle-out starts the knowledge map from significant concepts towards generalised and specific elements of knowledge definition (Uschold and Grüninger 1996)

2.3. Knowledge discovery

Knowledge discovery extracts implicit, undiscovered, and potentially useful information from large data sets (Fayyad, Piatetsky-Shapiro, and Smyth 1996). In the past, knowledge discovery required human interpretation of data, which was time consuming and subjective. Modern approaches use algorithmic and quantitative modelling. In addition to data mining, text mining is applied for discovering knowledge in text documents (Sánchez et al. 2008).

Text mining technologies utilise text data (or documents) and combine statistical methods to trace word, key phrase, or term frequencies. Both data and text mining are applied to patent analysis since the documents consist of structured (patent numbers, assignees, and issue dates) and unstructured text (claims, abstracts, and descriptions). The problem becomes complicated in the field of electronics, biology, and chemistry where the means and methods of description vary internationally, as innovations occur, and when language translation is necessary.

2.4. Formal concept analysis

Wille (1982) developed FCA based on the lattice theory of Birkhoff (1973) which is a mathematical approach for analysing the relations among objects with shared attributes. The algorithm is used to create a hierarchy of cases that can be graphical analysed as meaningful diagrams depicting the interrelationships of data (Jiang et al. 2003).

The basic notions of FCA are formal contexts and concepts. Formal contexts are represented as a set of triplets {O, A, R}, where O is a set of objects, A is a set of attributes for O, and R represents relations between O and A. If an object o_i has attributes a_j, the relationship is marked with 'X' in Table 1's context matrix. The matrix of the relations is converted into a hierarchical conceptual structure called the concept lattice. Given a subset of objects $O_S \subseteq O$ with a set of common attributes $A_S \subseteq A$, then every object in O_S has all attributes in A_S. The formal concept for the context (O, A, R) is defined as a pair (O_S, A_S). O_S is the extent and A_S is the intent of the formal concept (O_S, A_S). The extent covers all objects belonging to the formal concept, while the intent models attributes shared by those objects (Tam 2004).

A concept lattice is built using formal contexts. First, the super-concept is defined with the sub-concepts of each concept. Suppose that an object $O1 \subseteq O2$ with the common attribute $A1 \subseteq A2$. Then the concept ($O1$, $A1$) is a sub-concept of the concept ($O2$, $A2$), while the concept ($O2$, $A2$) is a

Table 1. Example formal context matrix.

		Attributes			
		a_1	a_2	a_3	a_4
Objects	o_1	X			X
	o_2		X		
	o_3	X		X	
	o_4	X		X	X
	o_5		X	X	X

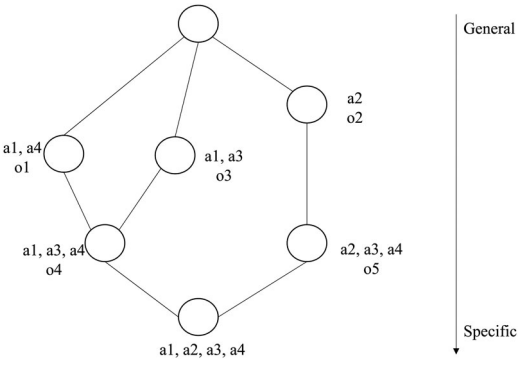

Figure 1. The concept lattice.

super-concept of the concept ($O1$, $A1$). The concept lattice is a top-down graph from general to specific concepts. Figure 1 illustrates the concepts and the relationships between sub-concepts and super-concepts defined in Table 1.

The FCA and its graphical concept lattice have been applied for applications in web resource searching and web page ranking (De Maio et al. 2012; Du and Hai 2013) and in a wider context for digital media knowledge e-discovery (Poelmans et al. 2013; Valerde-Albacete et al. 2016). FCA algorithms have been modified for various applications with special features. For example, De Maio et al. (2012) have developed fuzzy FCA for hierarchical web retrieval. Lee, Jeon, and Park (2011) have modified formal concept analysis (MFCA) by adding time sequence for evolution analysis. Trappey, Chen, and Trappey (2015) have developed a computer-supported FCA linking patents and litigations in multilayered concept lattices to interpret the relationship between technology patents and related litigation activities.

3. Methodology

The methodology is divided into five steps including patent search strategy, key-terms extraction, ontology creation, patent clustering, and dynamic patent lattice. They are described in the following subsections.

3.1. Patent collection and key-terms extraction

The first step collects related patents that are used to define the key phrases. The key terms in these phrases must appear in the titles, abstracts, and claims of the selected patents as shown in the search strategy (Table 2). The patents related to 3D biomedical printing applications are collected from the TI portal and the patent country of first issue is the USA. The patent search time frame is set from 1980 to August 2014.

Since the patent analysis centres on 3D printing for biomedical applications, the search query screens patents related to these phrases. After the search results are recovered, a domain expert reviews the patents obtained from the initial query and selects those that are directly related to the technology. The second step is extracting key terms using text mining techniques. The key

Table 2. Patent search query.

Search year	Country
August 2014	US Granted; US Applications
Patent search query	All = ((((additive ADJ manufactur*) or (3d or three ADJ dimension) NEAR (print* or fabricat* or manufactur*))) and (Biomedical or (Bionic ADJ scaffold))) AND DP> = (19800101)

terms are ranked according to the normalised term frequency (NTF) value which is used to aggregate common key terms among the patents. The value increases proportionally to the number of times a word appears in the document. In order to avoid the length of the document impacting the importance of key terms, the term frequencies are normalised for the key-term ranking (Salton and Buckley 1988; Sedding and Kazakov 2004; Trappey, Trappey, and Wu 2010).

3.2. Patent technology ontology

The related literature and extracted key terms are used to construct the ontology. Key terms that follow the generally accepted meaning are placed into the first stage ontology. The research refers to technical applications from several articles (Hoy 2013; Klein, Lu, and Wang 2013; Gross et al. 2014). The categories include mature 3D printing techniques for prosthesis, orthopaedics, and surgical models, as well as the newer technologies for bioprinting (e.g. soft tissues and body parts using scaffolds). Figure 2 depicts the first stage knowledge ontology for biomedical 3D printing medical applications. 3D printing is currently focusing on artificial bone manufacturing since it is economically viable and technically feasible. Customised prosthesis and medical aid equipment are part of the growing 3D printing market (Gross et al. 2014). 3D printing is also moving towards the manufacturing of organs, which is explored in this article. Bioprinting of organs requires a scaffold as the support structure for cells to form tissues (Hoy 2013).

3.3. Patent clustering

Patents contain sufficient technology descriptions so that a person familiar with the field can duplicate the invention. Of course, the owner of the patent has a monopoly over production and licensing, but the knowledge behind the invention is open to the public to read and study. Patent clustering enables researchers to divide patents into given domains to represent technology trends, research directions, and development opportunities. Sub-technologies that result from clustering help refine the ontological map of the relationships and interconnections.

This section clusters patents based on the NTF values of the key terms using the K-means algorithm. The algorithm is divided into four steps. The first step is to select K random documents as a start-up cluster. Next, all documents are assigned to its nearest cluster centre. Then, the cluster centres are recalculated. Finally, a confirmation test determines whether the iteration is the best clustering result. The process repeats until the members within the clusters do not change. The *R*-Squared (RS) and Root Mean Square Standard Deviation (RMSSD) are used as the statistical indicators to determine the best number of clusters. RS calculates the difference between each cluster and RMSSD calculates the homogeneity within clusters. The research sets the best number of clusters with the smallest value of RMSSD × (1/RS) (Hsu 2006).

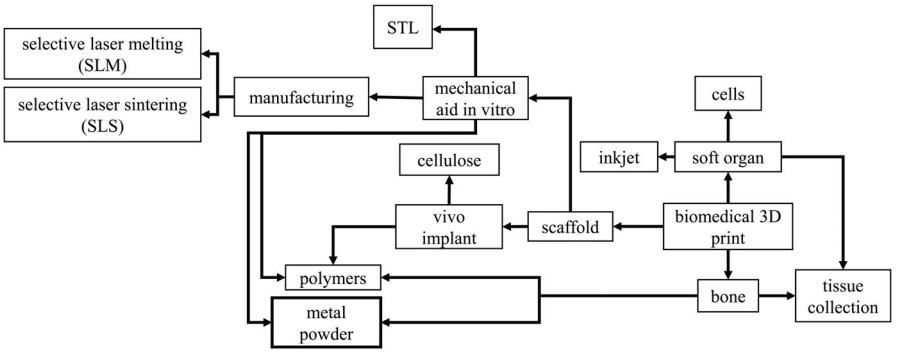

Figure 2. Basic biomedical 3D printing knowledge ontology.

3.4. Dynamic patent lattice

Dynamic patent lattice analysis is used to analyse patent evolution. The conventional patent analysis approach does not consider time and changes in attributes which are necessary to analyse technology evolution. MFCA is an extension of lattice analysis which accounts for time periods and changes in attributes (Lee, Jeon, and Park 2011). MFCA follows a process flow to create dynamic patent lattices. First, the key-terms matrix is mapped to the patent context based on threshold values. Second, a keyword vector of patents is used to calculate the similarity between patents using the cosine similarity theorem. Finally, the patent context is used to generate patent nodes and links between related patents.

First, MFCA is used for the construction of the patent context. The context includes year of issue, patent number, and the key-terms vector. The year of issue is added to the original key-term matrix to account for the timing of patent trends. The NTF values are transformed into a binary value (0–1) based on predefined thresholds. The value one means that the patent is related to the key term, while zero denotes the lack of a strong relationship (Table 3).

The second process uses the cosine similarity index to calculate the similarity between patent documents and is defined as:

$$\text{similarity } (i, j) = \frac{X_i \cdot X_j}{|X_i||X_j|} = \frac{\sum_{k=1}^{n} X_{ik} \times X_{jk}}{\sqrt{\sum_{k=1}^{n} (X_{ik})^2} \times \sqrt{\sum_{k=1}^{n} (X_{jk})^2}},$$

where

similarity (i, j): the similarity between patent i and patent j;

X_{ik}: the value (1 or 0) of key term k as patent i context.

The MFCA algorithm is an iterative process and generates the dynamic patent lattice based on the year issued. The process of building the lattice is described as follows. First, a patent which contains unique key terms that have no relation with the common key terms of other patents is assigned a similarity value of zero. This value indicates that the patent is a unique technology concept and generates a patent node without linkage. Second, the key terms of patents that include new key terms are included in the subset of key terms of other patents and are assigned a value $0 < \text{similarity} < 1$. This ranking means the technology concept of the patent has evolved from other patents. A new patent node is generated and linked to the related patent node. The standard of linkage is that the similarity exceeds the predefined threshold. Finally, the key terms of patents that are the same as an existing patent with the same issue date are assigned a similarity value of one. A patent that does not generate a new patent node is merged into the existing patent node.

There are additional aspects to consider when using MFCA. Only patents issued earlier than the target patent are taken into account when constructing the lattice. Two different patents having the same key terms and year of issue are represented as two concept nodes. The relations among concept nodes are derived using the cosine similarity index and the patent linkage is divided into two types. A solid line shows that the similarity is greater than 0.3 and all of the patents on the branch have common key terms. A dotted line shows that the similarity is greater than 0.3, but all of the patents on a branch do not necessarily have common key terms. Using the rules defined

Table 3. An example of patent context represented by key terms.

		Key terms				
Issued year	Patent number	K1	K2	K3	K4	K5
2009	P1	1	1	0	0	0
2010	P2	0	1	0	0	0
	P3	1	0	0	0	0
2012	P4	0	0	1	1	0
	P5	0	0	1	1	0
	P6	0	1	1	1	0

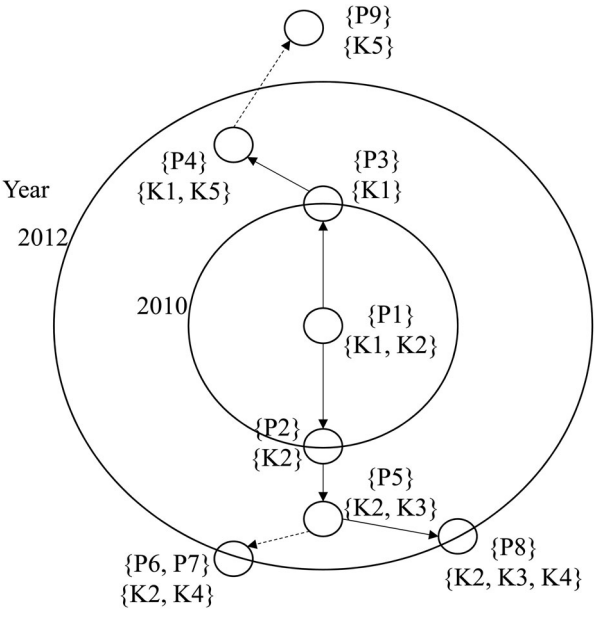

Figure 3. A radial dynamic patent lattice graph.

above, the dynamic patent lattice is constructed (Figure 3). The horizontal time axis is divided into concentric rings so that the time and space relationships may be used to distinguish changes in key terms over time.

4. Case study

The patent analytic method is applied to the biomedical 3D printing domain. The patent evolutions and the leading firms are highlighted and used for benchmarking domestic assignees' patents in technical clusters.

4.1. 3D biomedical printing applications for patent collections

As indicated in Table 2, the patent search strategy is to identify patents relevant to biomedical 3D printing technologies and novel applications. A total of 446 patents were collected for the initial search and archived. Some example patents found in the USPTO database are shown in Table 4.

The patent list was uploaded for text mining and key-term extraction. The preliminary extraction of key terms required expert verification. The key terms which poorly express the technical characteristics were removed and some synonymous key terms were merged. The key terms listed in Table 5 describe the refined knowledge context of biomedical 3D printing extracted from related patent documents.

4.2. Biomedical 3D printing application patent clustering

K-means is used for patent clustering and 33 patents, selected from the patent search results as a case study, are divided into four clusters (Table 6). The key terms in each cluster are ranked and selected based on the NTF values. The selected key terms used represent the technology characteristics and the sub-technologies of each cluster. The details of the key terms in each cluster are identified. Cluster 1 has terms that are related to scaffolding, cluster 2's key terms describe prosthesis construction for bone implants, cluster 3 has key terms related to soft organ bioprinting technologies, and cluster 4 describes printing approaches used for creating tissues and collections of cells.

Table 4. Sample biomedical 3D printing patents.

No.	Patent number	Title
1	US7198641	Scaffolds for tissue engineered hair
2	US7217853	Composition for cushions, wound dressings, and other skin-contacting products
3	US7316748	Apparatus and method of dispensing small-scale powders
4	US7456331	Composition for cushions, wounds dressings, and other skin-contacting products
5	US8105380	Cellular scaffold
6	US8252303	Injectable depot compositions and uses thereof
7	US8323348	Bone implants
8	US8352056	Surgical implant guide and method of manufacturing the same
9	US8463418	Methods and apparatus for fabricating porous 3D cell culture construct for cell culture and other biomedical applications
10	US8465582	Process for producing inorganic interconnected 3D open cell bone substitutes
11	US20130203146	Microfabricated scaffold structures
12	US8529630	Patient selectable joint arthroplasty devices and surgical tools
13	US8551099	Surgical tools for arthroplasty
14	US8585708	Patient selectable joint arthroplasty devices and surgical tools
15	US20130345794	Multilayered vascular tubes

Table 5. The key terms extracted from biomedical 3D printing patents.

Key terms	No.	Key terms	No.
adipose tissue	K1	hydrogel	K30
adipose-derived	K2	hydrophilic	K31
alginate	K3	hydrophobic	K32
arthroplasty	K4	hydroxypropylcellulose	K33
bacteria	K5	hydroxypropylmethylcellulose	K34
bioabsorbable	K6	implant	K35
biodegradable	K7	injectable depot	K36
bioinert	K8	knee	K37
biopolymer	K9	laser	K38
bioprinter cartridge	K10	muscle	K39
bioprinting	K11	pore	K40
blood placenta	K12	porosity	K41
bone implant	K13	powder	K42
bone marrow mesenchymal	K14	prosthetic	K43
capillary	K15	protein	K44
cartilage	K16	regenerative	K45
cellulose	K17	rubber	K46
centrifuge	K18	scaffold	K47
concentration	K19	semi-solid aggregates	K48
construct	K20	skin-contacting	K49
cord blood	K21	sodium carboxymethylcellulose	K50
Drug	K22	subchondral bone	K51
ectodermal	K23	sulphate beta-hemihydrate	K52
elastomeric plasticiser	K24	tissue construct	K53
fibres	K25	tissue collection	K54
fibroblasts	K26	UV cross-linkable	K55
Gap	K27	vascular	K56
hair follicle	K28	vitro	K57
hot melt	K29		

4.3. Mapping biomedical 3D printing applications to the patent ontology

The extracted and refined key terms are mapped onto the original knowledge ontology (Figure 2) using the meanings and relationships. The key terms in the technology ontology are distinguished according to the results of patent clustering. Figure 4 depicts the refined biomedical 3D printing ontology. Scaffolds, which provide a growth environment and nutrients to the cells, are an important part of cultivating tissues or organs. Manufacturing organs and tissues using 3D printing technology requires scaffolds to grow a particular organ. The scaffold contains many pores in which cells are planted. Cells attach to the surface of the scaffold and absorb nutrients from the pores. After the

Table 6. Biomedical 3D printing patent clusters.

Cluster	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Patent	US20130344601, US20130203146, US20130174287, US20130056910, US20130190210, US7198641, US7217853, US7316748, US7456331, US8105380, US8352056, US8463418, US8691974, US8709081, US8911762	US20140259629, US20110262486, US8323348, US8465582, US8529630, US8551099, US8585708, US8623026, US8657827	US20140093932, US20140099709, US20130345794, US8252303, US8691274, US8931880	US20140193900, US20130060338, US7595043

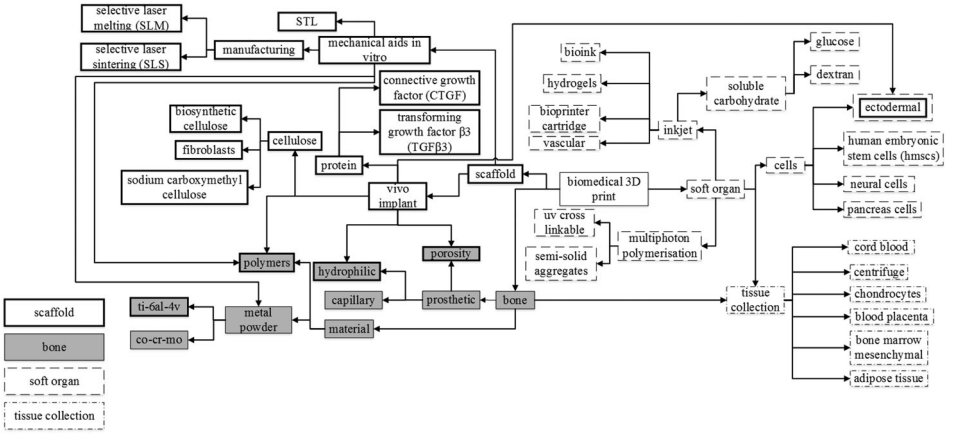

Figure 4. A refined ontology for biomedical 3D printing technology.

growth of the organ, the scaffolds are removed so the material must be biodegradable. There are two categories of materials used, including polymers and cellulose. Polymers include polycaprolactone and polylactic acid, and cellulose contains sodium carboxymethyl cellulose, biosynthetic cellulose, and nano-cellulose. Two human proteins are used including the connective growth factor and the transformative growth factor β3, which are injected into the scaffold to attract stem cells and stimulate the formation of tissue.

The most important aspect of organ printing depends on the ability to plant stem cells having the characteristics of regeneration and differentiation. Stem cells are collected from cord blood, placental blood, bone marrow mesenchyma, or adipose tissue. 3D inkjet technology is used to spray stem cells on the scaffold and these cells are attached using hydrogels. After the cells form tissues or organs, the scaffold dissolves. Additionally, organ printing includes the construction of vascular organs to supply nutrients and oxygen to support the growth and survival of the tissues and organs. The process of manufacturing vascular organs is described as follows. First, soluble materials such as glucose or dextran are used to create a support structure. Then, the ectodermal and endothelial cells are coated on the structure. Finally, the soluble support structure is washed away, leaving the vascular structure. There is another manufacturing method for creating vascular structures which uses a multiphoton polymerisation technology.

The process of bone regeneration and organ printing are similar. The stem cells are collected and bone structure is created using inkjet technology. Additional metal powders (such as Ti-6Al-4V and Co-Cr-Mo) or polymers are the materials used for printing bone implants. The manufacturing techniques commonly used are selective laser sintering and selective laser melting.

Table 7. Key-term matrix for cluster 2 context.

		Key terms																	
Year	*No*	K4	K8	K9	K12	K13	K14	K16	K17	K19	K20	K21	K35	K37	K42	K44	K51	K54	K56
2011	6	0	0	1	1	1	1	0	0	1	1	1	1	0	0	1	0	1	1
2012	9	0	1	1	0	1	0	0	0	0	0	0	1	0	1	0	1	0	0
2013	14	0	0	0	0	1	0	0	1	0	0	0	1	0	1	0	1	0	0
2013	18	1	0	0	0	0	0	1	0	0	0	0	1	1	0	0	0	0	0
2013	19	1	0	0	0	1	0	1	0	0	0	0	1	1	0	0	0	0	0
2013	20	0	1	0	0	1	0	1	0	0	0	0	1	1	0	0	1	0	0
2014	23	1	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0
2014	24	1	0	0	0	1	0	1	0	0	0	0	0	1	0	0	1	0	0
2014	31	1	0	1	0	1	0	1	0	0	1	0	1	0	0	0	1	0	0

4.4. Biomedical 3D printing patent evolution analysis

The key-terms matrix and patent clustering results are used to construct a dynamic patent lattice for exploring the development trends of biomedical 3D printing. The clustered key terms and patents are to ensure that there is uniformity within each cluster. The patent context matrix is constructed using the key-term NTF transformed binary values based on a predefined threshold. As shown in Table 7, the binary key-term NTF values represent cluster-2 patent context.

The similarity of key-term vectors of each patent and the patent context are calculated using the cosine similarity theorem. The similarity values between patent pairs in a given cluster are then used for patent evolution analysis. The threshold value of similarity for forming a linkage between two nodes is defined as 0.3. If a newer patent has common key terms with all older patents in the branch, a solid line is used to link the new patent. Otherwise, a dotted line is used for linking the node. Following the MFCA algorithm described in Section 3.4, the dynamic patent lattice is constructed (Figure 5). Table 8 presents the sample relationships between patent nodes in cluster 1. In Table 8, the evolving concepts and the linkages between patents are derived based on the common key terms (boxed) of similar patents.

The dynamic patent lattice identifies four clusters as the biomedical 3D printing key technology fields. Cluster 1 covers scaffold technologies. Patent US7198641 (2007) claims a new scaffold technology for hair follicle growth. The key terms include hair follicles, fibres, implant, and scaffold. The patent

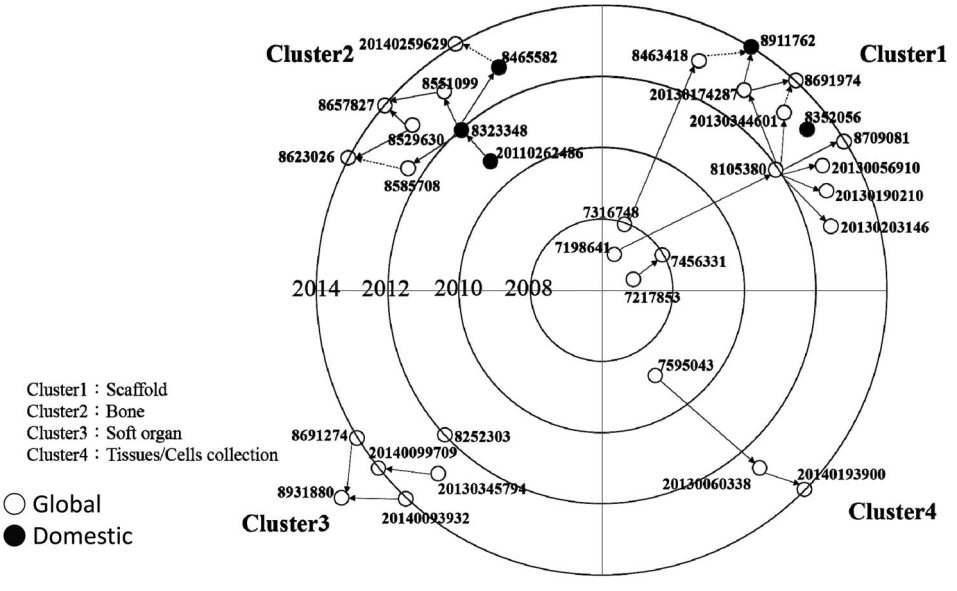

Figure 5. Dynamic patent lattice of biomedical 3D printing sub-technology clusters.

Table 8. The relationships and key terms of patent nodes in cluster 1.

Patent	Linked patent	Key terms
Evolution direction：→		
		Cluster 1: Scaffold
7198641	8105380	K6, **K12**, **K14**, **K21**, **K23**, K25, **K26**, K28, K35, K40, K47, K54, **K57**
7217853	7456331	K9, K17, **K22**, **K24**, **K29**, K31, K32, K33, K34, K46, K49, K50
7316748	8463418	**K7**, **K9**, K15, **K20**, K27, **K29**, K38, **K40**, K42, **K47**
8105380	20130056910	K6, K12, K14, K21, K23, K26, **K38**, K40, K47, K54, **K55**, K57
8105380	20130174287	K6, **K7**, K12, K14, **K20**, K21, K23, **K25**, K26, K40, K47, K54, K57
8105380	20130190210	**K1**, K6, **K11**, K12, K14, **K16**, **K20**, K21, **K22**, K23, K26, **K30**, **K39**, K40, **K44**, K47, **K48**, K54, **K56**, K57
8105380	20130203146	K6, **K7**, K12, K14, **K19**, **K20**, K21, K23, K26, K40, **K44**, K47, **K50**, K54, **K55**, **K56**, K57
8105380	20130344601	K6, **K9**, K12, K14, K21, K23, K26, **K27**, K40, **K41**, K47, K54, K57
8105380	8709081	K6, K12, K14, K21, K23, K26, **K30**, **K31**, K40, **K44**, K47, K54, K57
8463418	8911762	K7, K9, K15, K20, K27, K29, K38, K40, K47, **K52**

Note: *Ki*: key term of original patent; **Kj** (bold font): key term of linked patent; K1 (boxed): common key term of two linked patents.

claims describe that a bioabsorbable material is used to create a porous scaffold to stimulate the growth of hair follicle cells. The technology was further developed by patent US8105380, with claims adding key terms ectodermal, bone marrow mesenchymal, and fibroblasts. The patent uses mesenchymal and ectodermal materials to create cellular scaffolds suitable for *in vivo* and *in vitro* cell culture cell transportation. The patent US8105380 develops different processes and materials to improve the performance of the scaffold. The technology development of patents US8105380 and US20130203146 shows that the manufacturing process has evolved to two-photon polymerisation for biomedical scaffold creation, where biopolymers are used as the material in the patent. The added key terms of US20130203146 include polymer, UV, cross-linkable, and vascular. The evolution from US8105380 to US20130344601 adjusts the pore structure to create a more porous microstructure scaffold, while improving the structural support. The key terms of US20130344601 contain biopolymer, gap, and porosity. Patent US8105380 evolves to US20130174287 which also adjusts the structure for porous scaffold production. The patent claims to control the size of pores between 0.125 to 0.4 mm^3 and uses Polylactide (PLA) and Polybutylene terephthalate (PBT) as materials. The development of technology from US8105380 to US20130056910 shows that the process of manufacturing is changing towards stereolithography with the lasers used from the platform bottom. The material used is polysiloxane. The added key terms of US20130344601 contain laser and UV cross-linkable technology. Patents US20130344601 and US20130174287 focus on the construction of scaffolds and the generation of pores. These two patents are co-evolutionary towards US8691974 that uses biosynthetic cellulose as the scaffold material. The key terms in US8691974 include alginate, bacteria, cellulose, and construction.

The second branch in cluster 1 is from US7316748, which describes a method of depositing small-scale materials (biological powders). The technology evolves into US8463418, which develops a complete system of 3D printing based on deposition technology from the earlier results of US7316748. Patent US8911762 combines the hot melt composite material in US8463418 and also improves the pore structure technology of US8911762. Biodegradable PLA-calcium is used to manufacture the porous scaffold structure. A small branch is from US7217853, building a scaffold for the repair of skin wounds using material extrusion. The evolution from US7217853 to US7456331 is an improvement of adhesiveness and increases flexibility and delivers drugs to the wound through the scaffold. The added key terms include drug and elastomeric plasticiser. Observing the assignees distribution, the patents are owned by a high mixture of biomedical companies and universities. More than 1/3 of the patents are under review. The cluster evolution trend indicates that the technology life cycle remains in the growth stage and commercialisation has not begun to accelerate.

Cluster 2 describes the construction of bone implants. The development of the technology started with claims from US20110262486. The patent mixes ceramics with collagen as the material used to manufacture bone. Patent US8323348 improves the material in US20110262486 with a bio-inert substrate covered with a ceramic as the substitute bone material. Patent US8323348 extends to two

branches. One branch is US8465582, which is a further improvement to the bone material. The other extends to US8529630 and US8551099 which are owned by Conformis, Inc. for improving bone structure. US8529630 trims the surface of artificial joints to improve the speed and manufacturing success of joint arthroplasty. US8551099 makes a small cut on the artificial joint to align the connecting point of the subchondral bone to increase the accuracy of the surgery. Patents US8529630 and US8551099 co-evolved to US8657827, which is also Conformis patent. US8585708 uses surgical guides in joint arthroplasty to increase the accuracy for placement and positioning. Thus, US8529630 and US8585708 jointly co-evolved into another Conformis patent US8623026. US8623026 adjusts the structure to match surgery guides, improving the outcomes of an invasive joint arthroplasty surgical procedure. Cluster 2 is clearly dominated by Conformis patents. Based on FCA lattice analysis, Conformis-owned technologies have evolved systematically to create competitive products and services in customised knee replacement implants.

Cluster 3 is related to bioprinting technologies of soft organs. US20130345794 provides for the construction of multilayered vascular parts free of preformed scaffolds. US20130345794 contributes to US20140099709, which uses connective tissue cells to create a tissue structure without using a preformed scaffold. The added key terms include bioprinter cartridge, cartilage, and tissue collection. The other branch in this cluster links inkjet printing applied to printing organs. US20140093932 uses UV light to cure the scaffold material. The bio-ink is sprayed on the scaffold to build the tissue structure. US8691274 provides the design for equipment to print organs, including an electrospinning device and an inkjet printing device. US20140093932 and US8691274 are co-evolutionary towards US8931880, which improves the bioprinter cartridge. The support material is extruded and cured by UV to create the scaffold, while bio-ink is sprayed onto it. The key terms in the patent are bioprinter cartridge, hydrogel, laser, and semi-solid aggregates. In Cluster 3, Organovo is well positioned in patenting the bioprinting tissue technologies.

The patent nodes of Taiwan assignees are also marked in 'black dots' in Figure 5. Taiwan patents are mostly located in clusters 1 (scaffolds) and 2 (bones). In cluster 1, patent US8911762 is linked to patents US8463418 and US2013017428, which use biodegradable polylactic acid and calcium (PLA–calcium) to manufacture a porous scaffold. PLA is melted and mixed with sulphate to form the PLA–calcium composite. In cluster 2, patent US20110262486 provides bone manufacturing methods divided into two processes. One process uses a type II collagen coated or mixed with porous bone material combining metals, bioceramics, natural biopolymers, and synthetic polymers. The other process uses type II collagens frozen and dried to create porous bone scaffolds in a container. This patent is linked to patent US8323348, which uses a bio-inert substrate covered with a ceramic as the base material. The patent further evolves into US8465582, which creates mixtures of ceramics and polyelectrolytes to manufacture an inorganic interconnected bone substitute.

5. Conclusion

Patent evolution analysis enables researchers to monitor the development of biomedical 3D printing applications over time. Cluster 1 indicates that global firms are using ectodermal cells, polymers, or biosynthetic cellulose as the base materials for scaffolds (e.g. the Taipei Medical University uses PLA-calcium to create biodegradable scaffolds). In cluster 2, ceramic is combined with other polymers to create stronger structures for bones. Conformis has the technology and dominates patents in this cluster. In cluster 3, Organovo is a global leader of soft organ printing, enabling the construction of organs that are substantially free of preformed scaffolds. Global firms and Taiwan companies are developing materials that are more suitable for humans and are non-perishable. Printing organs requires vascular structures to supply blood to ensure survival. In the future, several key domains are open for further biomedical 3D printing including materials, structural design, the construction of vascular structures, and advanced manufacturing techniques. By studying the case implementations of this research, biotechnology firms can explore emerging opportunities to create competitive advantages in the most promising areas of the evolving technology frontier.

From the patent analytic perspective, this research aims to disclose accurate insights of biomedical 3D printing evolution trends using clustering and FCA patent lattice approaches. The methods can be generalised for patent analytics in other domains. Nonetheless, for predicting R&D spillover to other non-traditional paths for break-through innovations based on past patent data, the approach has limitations. Extrapolating future R&D directions is a great challenge and is a good topic for future research efforts.

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