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Tracing the system transformations and innovation pathways of an emerging technology: Solid lipid nanoparticles

Xiao Zhou[a], Lu Huang[b,*], Alan Porter[c,d], Jose M. Vicente-Gomila[e]

[a] School of Economics and Management, Xidian University, 266 Xinglong Section of Xifeng Road, Xi'an, Shaanxi 710126, China
[b] School of Management and Economics, Beijing Institute of Technology, No. 5 Zhongguancun South Street, Haidian District, Beijing 100081, China
[c] Search Technology, Inc., 6025 The Corners Pkwy, Norcross, GA 30092, USA
[d] Technology Policy and Assessment Center, Georgia Tech, 6025 The Corners Pkwy, Norcross, GA 30092, USA
[e] Universitat Politècnica de València, camino de Vera s/n, 46022, Valencia, Spain

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ABSTRACT

Accurately evaluating opportunities in new and emerging science and technologies is a growing concern. This study proposes an integrated framework for identifying a range of potential innovation pathways and commercial applications for solid lipid nanoparticles – one particularly promising contender within the field of nano-enabled drug delivery. Several text mining techniques – term clumping, SAO technique, and net effect analysis – as well as technology roadmapping, are combined with expert judgment to identify the main areas of R&D in this field, and to track their evolution over time. Through analysis, data from multiple sources, including research publications, patents, and commercial press, reveal possible future applications and commercialization opportunities for this emerging technology. We find that research is moving away from materials and delivery outcomes toward clinical applications. The most promising markets are pharmaceuticals and cosmetics; however, the "time-to-market" is much shorter for cosmetics than it is for pharmaceuticals.

The most significant contributions of this paper have been highlighted as follows. One innovation is extracting the intelligence from three kinds of data sources after in-depth considering their characteristics and matching with the features of different technology development stages to identify innovative research topics. The second one is combining SAO technique with net effect analysis to identify what the evolutionary links between research topics are, and then to use TRM to visualize the evolution of the main areas of R&D over time.

1. Introduction

New and emerging science and technology has attracted great attention among scholars because of its tremendous potential to improve society and stimulate economic development. However, the threats and opportunities inherent in such technologies can cause developers to proceed with caution. On the one hand, the existing competitive advantages inherent in current technological competencies offer stability, and new technology may threaten these advantages or even eliminate entire markets. On the other hand, early analysis of new technical areas may present opportunities to take the lead before other competitors become entrenched (Guo et al., 2015). Therefore, developing ways to assess the current research focus and future development directions of new and emerging science and technologies is a compelling issue.

Technology opportunity analysis (Porter et al., 1994), which applies data mining and text mining tools to ST&I resources to detect technological innovation (Ma et al., 2014 and Ma et al., 2016) offers one possible solution to this problem. The process allows analysts to explore opportunities for transforming new technologies into new products and, thus, provides decision support to researchers, R&D planners and managers, and science policy-makers (Lee et al., 2015). A number of technology opportunity studies that rely on text mining technologies have been conducted to help derive information for competitive technical intelligence analysis, technology development trend analysis (Ma and Porter, 2015), and forecasting (Ailem et al., 2016; Song et al., 2017).

However, such studies have shown limited success at forecasting future developments. Despite advancements in this area through some novel approaches, such as forecasting innovation pathways (FIP) (Huang et al., 2014; Robinson et al., 2013), morphological analysis (Yoon et al., 2014), and subject–action–object (SAO)-based semantic patent analysis (Wang et al., 2015, 2017), it is still difficult to delve into technological details, such as subsystem roles and the entire R&D landscape. And it is still hard to track the relationships among evolving

* Corresponding author.
E-mail addresses: huanglu628@163.com (L. Huang), alan.porter@isye.gatech.edu (A. Porter).

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technologies and markets over time. Further, the potential applications of new technologies are nebulous, making their future innovation pathways highly uncertain. Technology opportunity analysis for new and emerging science and technology still poses notable challenges, and its efficiency needs further improvement.

As part of the ongoing advance of nanotechnology, nano-enabled drug delivery systems are rapidly becoming serious contenders in addressing pharmaceutical challenges, such as solubility, cost reduction, disease targeting, and lifecycle extension (Zhou et al., 2014). Solid lipid nanoparticles (SLNs) have become promising contenders within nano-enabled drug delivery because of some of their unique properties, such as their small size and large surface area, which offer improved delivery performance of pharmaceuticals, nutraceuticals, genes, and vitamins (Lingayat et al., 2017; Nair et al., 2012). Consequently, in time, gathering technical intelligence and exploring the potential innovation pathways SLNs may take in its early stages could provide valuable support for researchers and R&D administrators when making decisions.

This study proposes an integrated framework for capturing a variety of potential innovation pathways and commercialization options for SLNs. Our analysis stretches from raw data to technological intelligence, and our method includes text cleaning, term clumping, context-relevant insights, and pathway visualization. Our data are derived from multiple sources including research publications, patents, and commercial press.

2. Related work

2.1. Core technologies within novel technology opportunity analysis

We have combined several different approaches to accomplish our novel technology opportunity analysis framework for new and emerging science and technology. This section provides an overview of the term clumping, subject-action-object (SAO) technique, and technology roadmapping (TRM) techniques incorporated into our framework.

2.1.1. Term clumping

Clustering of terms is a powerful aid in detecting topics and their relationships in a collection. Term clumping concerns text objects (individual terms or phrases) and their adjacent properties and can be used to clean and combine terms to enhance topic coverage (Kostoff and Block, 2005). Trivial words and phrases are usually removed before the clustering process to improve overall accuracy.

The notion of term clumping was proposed by Bookstein's group (Bookstein et al., 1998). Their research focused on the clumping properties of content-bearing words and also measured clumping strength to address similarities among terms. They believed that the term with the largest deviation from a Poisson distribution might have the greatest content-bearing value (Bookstein et al., 2003). Later, Trumbach and Payne (2007) proposed a “concept-clumping algorithm” with the potential to improve the technical specificity of term clusters. Their method generates a list of technically relevant noun phrases and calculates synonymous terms through a rule-based algorithm. The most significant contribution of this algorithm is that it improves the precision of clumping groups of different term lengths. In 2014, Zhang and Porter proposed a suite of term-clumping steps to produce a final list of cleaned and consolidated terms and phrases. First, less informative terms, such as stopwords, general terms, academic terms, general scientific terms, are removed by applying several thesauri. Then, fuzzy-matching routines are used to consolidate similar terms, combine term networks, and prune and screen the lists. This approach reduces the term set substantially and greatly improves the quality of the terms that can be used to generate more meaningful core clusters (topics) (Zhang et al., 2014).

Later, this refined process was combined with principal components analysis (PCA), which has been widely accepted by researchers as a way of generating a more balanced factor set, with examples done in the dye-sensitized solar cell and biotech domains (Wang et al., 2014; Zhou et al., 2014). One noteworthy point of this process is that the most frequent terms are excluded since it is believed that these terms are too general to reflect specific areas. However, in our research, we find that high-frequency terms can show areas of major research, which may help to identify research foci within the overall SLN domain. Considering our research aims, this analysis process was useful after making some revisions. Selected high-frequency terms were retained, once common terms and fuzzy-matched (similar) terms had been removed during data preparation.

2.1.2. Subject-action-object (SAO) technique

To identify the innovation pathways for technology, most research focuses on the content of the innovation, meaning the new technology or its application. Term clumping and clustering algorithms, such as PCA or factor analysis, can be applied to extract these “innovative contents.” However, another issue in gauging the pathway of an innovation is the lack of a credible method that is widely accepted by academia. Faced with this situation, some researchers have turned to the SAO technique with moderate success. In this technique, the subject (S) is the noun or phrase that reflects the new technology or solution. The action (A) is the verb or verb phrase that demonstrates how to solve the problem. And the object (O) is the noun or phrase that represents the old technology or the problem that has been solved. In this way, an SAO structure emphasizes two technologies and the semantic relationship between them, thus enabling researchers to glean a more complete understanding of how a technology is evolving.

In recent years, text mining combined with an SAO technique has been used to gauge technology innovation pathways. Yoon et al. (2013) extracted SAO structures from a patent dataset and calculated the semantic similarities between “S” and “O” to effectively predict technology development trends. Through deeply mining the meaning of SAOs, Zhang et al. (2014) identified innovation processes of dye-sensitized solar cells and illustrated the process with an informative mapping technique. Later, Guo et al. (2016) combined extracted SAOs from patent information with morphology analysis to depict the technical evolution pathways of dye-sensitized solar cells.

Although the SAO technique has had a great effect on identifying the specific innovation processes in an evolving technology area, it also has obvious drawbacks in relationship identification and data source selection which we will discuss in some detail in Section 2.1.3.

2.1.3. Technology roadmapping

The use of TRM traces back to Willyard and Mcclees (1987) and their application of the method in Motorola's developmental planning. From that point on, TRM became widely used by agencies and companies to represent the macro scale development of new technologies. TRM not only indicates the direction of future technological developments, but also potential trends in R&D and its connections to current product development. A search for “technology roadmap*” in Web of Science (WoS) renders a total of 652 publications. Of those, 212 publications have appeared in the last five years.

Generally, retrospective TRM and prospective TRM are the two branches of TRM research. For the prospective TRM research, qualitative analyses, which include literature studies, expert opinion gathering, and delphi-based analyses contribute heavily. Lee et al. (2012) conducted an empirical analysis of TRM on the basis of classical communication theory. They proposed six hypotheses focusing on the factors that improve TRM's credibility. Preisler et al. (2012) gathered information gleaned from workshops and interviews with diverse market players, including manufacturers, business enterprises, building developers, research institutions, and political decision makers, to construct a TRM for solar thermal cooling in Austria. Zhang et al. (2016) employed literature analysis, on-the-spot investigation and expert discussion to set up a six-step analysis method to plan the development

progress of coal mining technology in Shannxi province. These examples showed expert engagement is a very effective way for predicting the future developmental trajectory, especially for macro-level foresight, such as national technology planning, but they are also time-consuming and costly. In addition, these qualitative approaches depend on expert judgment, which may be heavily influenced by personal experience and cannot easily gain consensus among different experts.

Another branch of TRM research is about retrospective analyses. In this domain, data constitute the core ingredient – empirical analyses, rather than expert opinion based. This kind of TRM mainly relies on statistical analyses and data mining techniques, which can provide the detailed information for depicting the development process of a target technology or a product from its beginning to the present. Choi et al. (2013) used the concept of "function" to develop a quantitative TRM. The most significant contribution in their research is the information they provide on the uses and purposes of a technology, not just the keywords. Considering the lack of research on how and which information can be used to construct a TRM, Yoon and Phaal (2013) focused on the characteristics of significant data and presented an approach to structure technological information drawn from raw data through several data mining techniques. Later, Zhang et al. (2015a, 2015b) proposed an approach that constructs TRMs semi-automatically, incorporating multiple sources of ST&I data to gauge innovation patterns for new and emerging science and technologies.

This research merges multiple-sources of intelligence to improve the usability of TRM in real-world commercial applications. The advantage of this kind of TRM is that it uses quantitative methods to distinguish both actual and potential features from objective data. Its disadvantages include: (1) A tendency to focus on ST&I data (e.g., publication and patent data) and to only nominally include other kinds of data sources, like popular, business, and regulatory content. Resulting TRMs did not benefit from the insights one can draw by connecting basic research with applications and commercial endeavors. (2) Not all information can be retrieved from these data sources given the constraints of reasonable access and budgets. (3) Not all publications or patents are equally valuable. (4) ST&I database coverage temporal lags can lead to incomplete data.

Furthermore, since SAO-based TRM is a popular research branch of data-driven TRM, and we will use this combined method to predict the potential innovation pathways in our research, more in-depth comparisons between current research approaches can be noted. In this paper, we zoomed in and compared SAO-based TRM research from the perspectives of data resources, research approaches and research aims & advantages in some depth. We retrieved five years of publications from WoS, yielding 25 records. After reviewing these publications thoroughly, we classified the researchers into three groups in terms of research relevance. From Table 1 we see that they had great contributions on identifying the core topics and tracing the specific relationships/functions among these topics. However, some limitations deserve note. The first is the lack of a broad data source to identify the real research issues. From their research, most of the intelligence was retrieved from patents (Choi et al., 2013; Guo et al., 2016; Wang et al., 2017; Yoon et al., 2013). Although some researchers tried to obtain information from publications (Zhang et al., 2015a, 2015b), they employed publications and patents separately instead of combining them together to solve the same research question such as figuring out the key topics of a continuously evolving domain. A second drawback is that current research in the SAO technique is able to find the relationship between one "point" and another "point" (Wang et al., 2017; Zhang et al., 2014), i.e., a very specific technology, but it cannot identify links between clusters that contain suites of related technologies.

To reduce drawbacks thus noted in previous research, we tried to make some improvements in our research. Based on accurately characterizing the technological development stages, this paper aims to predict the innovation directions with most potential. To attain this aim, two efforts should be made. On the one hand, we draw upon the advantages of a TRM based on SAO semantic analysis, as well as further enhance insight by applying net effect analysis to identify real relationships among key research topics, and then trace the development path. We also consider the characteristics of different types of data in our efforts to input multiple data sources into the TRM's construction, which can help us to look through the intelligence from basic research to real commercial practices. On the other hand, we emphasize the value of generating an expert-driven TRM for forecasting the potential innovation pathways, enriched via review by knowledgeable domain professionals.

2.2. Solid lipid nanoparticles

In this paper, we focus on SLNs, which belong to the class of lipid nanoparticles. These special kinds of nanoparticles are able to keep a stable physical state and are therefore able to overcome some limitations other traditional colloidal carriers, such as emulsions and liposomes, cannot. Because of their good release profiles, SLNs' prominent advantages have attracted special interest over the past decade in targeted drug delivery. Currently, SLNs, and a next generation, nanostructured lipid carriers (NLC), are looking forward to applications in cosmetics, drug delivery, and clinical medicine, etc. (Naseri et al., 2015). Unsurprisingly, related industries are paying great attention to R &D and future commercialization opportunities in this field. Therefore, identifying the innovation pathways and forecasting the possible commercial directions in this domain promise significant value for academia and industry.

2.3. Research questions

Upon concluding our deep literature review, it was clear that

Table 1
Comparison of SAO-based TRM studies.

No.	Data	Research approaches	Aims & advantages	Leading authors and related papers
1	Patent	SAO morphology analysis TRM	It is useful to identify the specific relationships between keywords and to forecast technology innovation opportunities.	Guo et al. (2016), Wang et al. (2017)
2	Patent	Patent semantic analysis (SAO) TRM	(1) Aided by patent semantic analysis to identify the R&D topics, core technologies and products, and then treating the uses and purposes of a technology from the perspective of "function." (2) Combine SAO semantic analysis and roadmaps to identify hot spots and R&D overlaps effectively.	Yoon et al. (2013), Choi et al. (2013)
3	Publications Patents	Topic modeling SAO + TRIZ Fuzzy set analysis TRM	(1) Employ topic modeling and fuzzy set analysis to identify core R&D topics by using WoS publications. (2) Gain intelligence from patents and try to combine SAO and TRIZ to figure out the real problem & solutions in one target domain	Zhang et al. (2014, 2015a, 2015b)

finding the best and most reasonable way to evaluate and illustrate the evolving stages of a new and emerging technology was a pressing issue for industry and academia. It is also a prerequisite for governments that want to secure an advantageous position in the fierce competition of future global markets. We, therefore, formulated three key research questions here:

1. How to determine the main innovative research topics within the target domain?
2. How can we find the linkages between topics for a continuous evolving domain?
3. How to visualize the evolution of the main topics over time and predict the most promising pathways?

3. Methodology

Aiming to address those three research questions, the analytical process can be divided into three major stages: (1) figuring out the key research topics and constructing a technical dictionary; (2) identifying the real linkages between topics; and (3) visualizing and forecasting the innovation pathways. This section provides an overview of how text mining techniques and TRM were integrated and combined with expert judgment to chart the evolution of the main areas of R&D in an emerging technology over time. The details of how we practically applied this framework (Fig. 1) are illustrated in Section 4.1.

3.1. Overview of the integrated framework

In the first stage, text mining techniques can be used to depict the key factors of the entire R&D system. Here we generate three steps (steps A to C) to best harness multiple sources of information and build a complete technical dictionary in this stage from Fig. 1. In step A, we retrieved high-quality research reviews to help identify the subsystems within the target technology and, to flesh out more details. Then, term clumping, and PCA, a clustering algorithm, were independently applied to publications, patents, and commercial press items to generate key terms and better topical factors in step B. In step C, aided by semantic similarity analysis, our panel of experts then merged and refined those statistical results to yield a set of the most prominent R&D topics (clusters), and then a dictionary of technical terms was constructed to holistically reflect the R&D concepts in the domain.

Followed the outputs – technical dictionary – gleaned from several text mining steps, the main objective of the second stage is to profile the potential links among key innovation factors. SAO technique, which is an useful text mining tool, can be used here to extract useful intelligence (i.e. the evolving linkages between topics) from news and research material. In step D, we used the key terms from our constructed technical dictionary as the search terms to retrieve SAO structures, aided by IHSM Goldfire Innovator (http://invention-machine.com/factsheet_GoldfireInnovator.html).

As previously mentioned, the actions in SAO structures reflect real evolutionary relationships between specific technologies (subjects and objects). Given the focus is on how these technologies evolve, the relationships gleaned from specific SAO structures needed to be appropriately grouped. Aided by the technical dictionary, we were able to determine which research topics the subject and object belonged to for each SAO structure. So in step E, SAO structures with the same subject topic and the same object topic, but with different actions, were then classified into groups. This classification system allowed us to focus on the specific evolutionary actions within each group, and classify them according to the net effect they produce – positive, negative, or utility (usage). Based on the general links between key research topics, we were able to identify the evolution of each research strand, starting from the basic research stage through to applied research up until commercialization.

In the third stage, the main objective is to visualize and project prospective innovation pathways based on the text mining results which we obtained from previous stages and expert intelligence. Since technology roadmapping is a widely accepted tool by combining qualitative and quantitative information together to visualize and predict the macro scale development of new technologies, it is suitable for achieving our goal in this stage. In this stage, two steps were utilized here. In step F, the main consideration is how to layout alternative innovation pathways. Through text analysis, we identified the core research groups and their correlations to assess the potential market opportunities and explored each possible innovation. Following convention, our TRM was plotted on two dimensions with the x-axis representing time, and the y-axis representing the development stage of

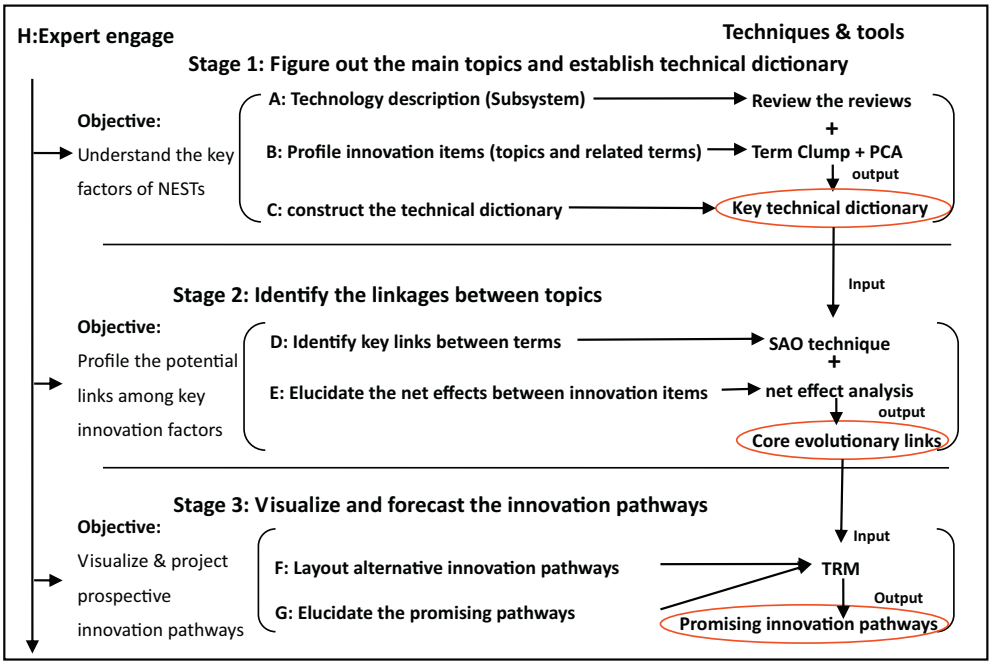

Fig. 1. Analytical framework.

Table 2
The SLN search strategy in WoS.

No.	Search terms	Number of records
1	TS = ((SLN* or NLC* or SLM*) and (carrier* or nanocarrier* or nanoparticle* or nanosphere* or microparticle*));	3116
2	TS = (("Solid* lipid*" or "Nanostruct* lipid*") near/3(carrier* or nanocarrier* or nanoparticle* or nanosphere* or microparticle*))	4060
3	TS = ((lipid* near/3 solid*) and (nanocarrier* or nanoparticle* or nanosphere* or microparticle*))	3707
Total	1# or 2# or 3#	5176

the technology (Groenveld, 2007). To show the details, the step G was applied here. The y-axis was split into three levels: basic R&D, application transfer, and commercialization. The refined SAO structures combined with expert judgment were used to determine the development stage. Here, Subjects and Objects are research topics, not specific technologies. The correlations among the research topics, subsystems, and technology developmental stages guided which development stages each topic fell into. Constructing the x-axis (time) was a little more complicated. After a round of random sample checking, we decided that the topics which related to basic R&D and extracted from publications should each be mapped according to the date of their first publication. Similarly, topics which belonged to application transfer and extracted from patent applications should be mapped according to the patent application date, and commercial topics should be mapped according to the release date of the report. It became important to treat research topics from each of the three databases differently because each provides different levels of information. Take one SAO structure retrieved from publication as an example: "glyceryl behenate SLN loaded with vitamin A can be applied in cosmetics". This record mentions two research topics, "drug loaded SLN" and "cosmetics", and carries the implication that this new nanoparticle has the possibility to be used in cosmetics in the future, but not *already*. Therefore, mapping SLNs' entry into cosmetics market at the time of this news release would be ahead of its time and, thus, inaccurate. However, individually mapping commercial news, research publications, and patent applications to define the appearance of "drug loaded SLN" and "cosmetics" separately leads to a much more detailed and accurate picture of the domain.

VantagePoint desktop software (www.theVantagePoint.com) for bibliometrics, natural language processing (NLP), data cleaning, analyses, and visualization was used throughout the process.

Expert judgment also played a crucial role in enriching our empirical analysis. In this study, we invited two kinds of experts to engage our researches. The first kind of experts are the technical experts who know the NEST well and can intimately reach out to understand and characterize its innovation processes. We contacted Professor Younan Xia (nanomedicine) who directed us to another active researcher Shin Minsuk, who had been conducting research in this field for several years. Then another biomedicine-based expert –Dr Xuejiao Zhou joined our research. The second kind of experts, who are conversant with the FTA and innovation processes, are text mining analysts. Here, we invited Dr. Douglas Robinson and Jose M. Vicente Gomila, who had experience in using text mining to analyze biotechnology for many years to guide this research.

From Fig. 1, we can see that step J, engaging experts, is an iterative process. In the first stage, technical experts engaged in selecting key parameters, identifying major topics and subsystems. In the second stage, technical experts and text mining analysts cooperated in selecting core SAO structures and grouping the linkages between topics. In the final stage, text mining analysts played important roles in designing the contents and layout of innovation pathways. Later technical experts helped to elicit the future development directions.

3.2. Data collection

SLNs were chosen as the sample because they are a particularly promising contender in the field of nano-enabled drug delivery. The search algorithm was based on previous research (Zhou et al., 2013), as well as terms gleaned from recent review articles. With the help of experts, we identified terms distinguishing SLN-related activity and applied these directly to a new search in WoS from Jan 1st, 2000 to Aug 1st, 2016.

Here, we searched for combinations of the terms for one sample year, then checked the results. One team member (Zhou), who has been working with these data for five years, read a random subset of 30 abstract records for each search segment and judged them as being strongly related to SLN or not. If the target rate exceeded 70% or better, we accepted the search string. Otherwise, it was revised or excluded. After checking all the search terms, we formed the SLN search set using the three refined term combinations indicated in Table 2. The fundamental SLN research record set contained a total of 5176 WoS abstract records.

We used similar search strings and checking processes to retrieve SLN-related records from the patent database, Derwent Innovation Index (DII). DII provides "second order" patent data, meaning that Derwent (Thomson Reuters formerly, now Clarivate) indexers rewrite the abstract and add indexing to aid user understanding of the patents. We conducted our search on the title, abstract, and keyword fields and set the time interval from Jan 1st, 2000 to Aug 1st, 2016, too. We also gathered SLN-related records for the same date range from the commercial database ABI/Inform, which contains business-oriented news, working papers, and reports. A total of 1136 patent records and 440 ABI/Inform records were retrieved.

4. Case study

The following case study demonstrates one practical application of the integrated framework outlined in the previous section and profiles the evolution and future prospects of SLN and the next generation of nano-enabled drug delivery systems.

4.1. Constructing the technical dictionary

The first step of this stage is "term clumping" which entails applying a set of thesauri, fuzzy-matching algorithms (to capture slight variations in terms), and Visual Basic scripts to group related terms together, using VantagePoint software (www.theVantagePoint.com).

Before treating the data, we imported the SLN publication data into VantagePoint and merged the four WoS fields containing topics: title, abstract, keywords (authors), and Keywords Plus. 89,000 nouns and noun phrases were extracted using VantagePoint's natural language processing (NLP) system, which were then reduced to 13,800 elements through term clumping. From those clumped terms, we chose the 500 most frequently occurring terms and phrases for further analysis. After having our experts check the terms to remove some general and less interesting terms (like solid lipid nanoparticles, development, preparation, characterization, etc.) we were left with 445 terms for analysis. The DII and ABI/Inform data were treated with similar procedures, resulting in 263 and 177 clumped terms, respectively.

The next step uses PCA to identify and group terms that occur together in records more frequently than chance would indicate. We used the PCA tools in VantagePoint followed by a manual review by the domain experts to arrive at our final set of topics. Using WoS

publication data as an example to illustrate this process, VantagePoint's PCA resulted in 19 topical factors with high-loading terms from the original set of 445 terms. During the expert review, four largely unrelated topics were deleted, *oxidative stress, Escherichia-coli, lipoproteins*, and *transmission electron*, and two factors focusing on similar subjects were combined, *drug loading* and *drug dissolution*, to result in 14 major topics from the publications dataset. Applying the same logic and process for DII and ABI/Inform, we arrived at 9 and 15 topics, respectively. Each topic may have appeared in one or more of the databases, so, after comparing and semantic analyzing the final lists from the three databases, the final number of topics was refined to 18 clusters.

Exploring the subsystems in SLN research is a vital part of tracking the dynamics of emergence. Since reviews mainly summarize the current developmental progress of research and typically indicate the future prospects of the domain under scrutiny, we felt such publications would hold great value in identifying subsystems. Therefore, we focused on "reviewing the reviews" to identify the main subsystems.

We started with the 7247 documents tagged as "reviews" or "reviews and book chapters" from a nano-enabled drug delivery (NEDD) WoS dataset which we got from previous research (Zhou et al., 2013). [Note that this search focus on NEDD is considerably broader than our analysis of SLN, an NEDD sub-technology.] Here we should emphasize that the search terms of retrieving NEDD dataset focused on nano-carriers such as nano-materials, but not drugs or other particular practical areas. Such efforts can largely reduce the biases which led search toward some certain applications. We also selected new reviews from our new SLN - WoS dataset. With the aim of selecting a representative set of recently published, high-quality reviews, we whittled these down to 17 for further study, based on total times cited, cited reference count, publication year, journal impact factor, and review titles (related to SLN) as the criteria. The reason why we choose the WoS dataset rather than a broader dataset is because the value of publications indexed by WoS is widely accepted. Indeed, the lack of other data resources may reduce the credibility of the final outputs, so we invited technical experts to check our intermediate results to improve credibility. Our review combined with experts' judgements proved invaluable in developing familiarity with the prominent R&D topics for SLN and gaining perspective on subsystem identification. The four major subsystems in SLNs include: products (pharmaceuticals/cargo), SLNs and related materials (nano-enabled as distinct from traditional forms of drug delivery), delivery processes and outcomes (delivery processes and related effects), and target markets (application domains). After careful study of the literature, we arranged the 18 major topics with their closely-related terms into the subsystems as shown in Table 3.

4.2. Identifying the evolutionary pathways

The next stage relied on Goldfire Innovator software to extract SAO structures from the data. Subjects and objects were matched with the key terms in the technical dictionary and, after text analysis, 16 unmatched (but high-frequency) SAO structures reflecting actual evolutionary processes in the technology were added to the final list. Again, an expert review ensured that meaningless or too general SAO structures were excluded, resulting in 92 SAOs highly-related to the target domain (WoS: 40, DII: 36, ABI/Inform: 16). To identify the broad evolutions among the topics, we classified the SAO structures into groups with the same subject topics and object topics but with different actions. This allowed us to separate broad, but distinct, research evolutions and focus on the specific evolutionary actions within that group. The actions were then analyzed and classified by their net effect – either: a group increase (a positive effect), a group decrease (a negative effect), or simply group usage. Table 4 lists the general classifications of the SAO structures.

In this step, technical experts engaged deeply. They looked through all 92 SAO structures and then judged which groups the actual actions should belong to. Take one SAO structure "CPB added SLN induce low toxicity" as an example. Here "induce low" means CPB added SLN can reduce toxicity. Based on the in-depth semantic analysis, technical experts assigned "induce low" into negative effect group in this study. So the general analysis process would be applied in other research, but the final classification results may slightly vary among case studies. This is one limitation in this research.

Table 5 shows a sample of our analysis of the 92 SAO structures and the relationships we identified between the key research topics. Due to space limitations, only a few examples have been included. "S + O" means the subject improves, amplifies, upgrades, enhances, or increases the object in some way. "S − O" means the subject has a negative effect on the object. "SUO" means the object is applied to the subject; in this situation, the subject usually reflects a certain product or a target market.

In total, we identified 25 evolutionary pathways in the SLN domain from this analysis, from basic R&D efforts to application thrusts, and onwards to commercialization. In particular, we determined that NLC is the most active particle. It shows dramatically improved delivery performance in three respects – skin penetration, drug dissolution and loading, and bioavailability. Also NLC has been connected with three products (i.e., dermal products, anticancer tools and drugs, and skin-care products) in three markets to date (i.e., dermatology, cancer, and cosmetics). Table 6 shows these links. However, to visualize this innovation process, determine the correlations between the core research entities, and forecast what the future may hold for SLNs, we need to move on to the next step and generate a TRM.

4.3. Identifying and visualizing the innovation pathways of a technology

Data for the TRM's x-axis (time) and y-axis (development stage) were generated separately. With the help of our domain experts, we recognized three technology development stages of SLN research: basic R&D, technology transfer, and commercialization. Topics in the "SLN related materials & techniques" subsystem were mapped to basic R&D. Topics in the "delivery processes and outcomes" subsystem were mapped to technology transfer, and topics from both the "products" and "target markets" subsystems were mapped to commercialization. These classifications are shown along the y-axis of the TRM. The x-axis, measuring time, begins at 1991 with the first appearance of SLN; then we start the time interval from 2000 with the first data record to 2016 with the last data record. The time a topic appears in a development stage was mapped independently according to the subsystem to which it belongs. The topics which related to basic R&D should each be mapped according to the date of their first publication. Similarly, topics which belonged to application transfer and commercialization should be mapped according to the patent application date and the release date of the commercial report, separately. Here we noted that a topic which located a certain position on the X-axis just reflected its first appearance time, not the duration of research on it. A detailed discussion can be seen in Section 4.1.

By comparing the research stages of these topics over different time periods, we were able to identify the areas of convergence and divergence in SLN R&D and chart the course of specific applications of a range of drug delivery segments (e.g., cancer therapies, skin treatments). Domain experts assisted with the review and interpretation of the observed patterns. Fig. 2 illustrates the technological evolution of SLNs.

From the TRM, we can see that basic research into SLN began in 1991, but did not attract much attention in the early years (hence, we constrict the early years in Fig. 2). Once more researchers began to focus on these kinds of nanoparticles, the field gradually divided into four directions: drug-loaded SLN, NLC, gene-loaded SLN, and magnetic SLN.

Superior capabilities in targeted drug delivery and cytotoxicity

Table 3
A technology dictionary for SLN.

No.	Subsystem	Major research topics	Related terms	Dataset
1	SLNs and related materials	Nanostructured lipid carriers	Nanostructured lipid carriers; NLC; Liquid lipid; Binary-mixtures; CoQ10 NLC	WoS-SCI, DII,ABI
2		Drug-loaded SLN	Nanoparticles SLN; Solid lipid; Tamoxifen loaded SLN; PLGA SLN; CPB-SLN	WoS-SCI, DII,ABI
3		Gene-loaded SLN	Nucleic acid SLN; pDNAs; Chol-but SLN; Quantum dot; cSLN	WoS-SCI, DII,ABI
4		Magnetite SLN	MN-SLN; Magnetite SLN; lonic complexation	WoS-SCI, DII,ABI
5	SLN delivery Processes & outcomes	Controlled release	Controlled drug-delivery; Controlled release	WoS-SCI, DII
6		Drug dissolution/loading	Drug loading; Solubility; Dissolution; Nanosuspensions; Drug loading capacity; Solid dispersions; Dissolution rate; Drug loading efficiency;	WoS-SCI
7		Bioavailability	Bioavailability, Oral bioavailability;	WoS-SCI, ABI
8		Blood brain barrier	Blood-brain-barrier; Central nervous system; BBB	WoS-SCI, ABI
9		Gene transfection	Gene delivery; DNA transfection; Gene therapy; Plasmid DNA; siRNA; Small interfering RNA; RNA Interference; RNAi;	WoS-SCI, ABI
10		Cytotoxicity	Toxicity, cytotoxicity	WoS-SCI
11		Skin penetration	Skin penetration; Stratum corneum; Percutaneous-absorption; Skin permeation	WoS-SCI,ABI
12	Products	Anticancer tools & drugs	Chemotherapy; Chemotherapeutic agents, Doxorubicin; Cancer cells; Dox, Tamoxifen; Anti-cancer drugs; Multidrug-resistance	WoS-SCI, DII, ABI
13		Imaging	Image, Imaging, MRI contrast agent	DII, ABI
14		Skincare products	UC-blocker, sunshine cream, UC production; Oil in water Cream	ABI
15		Dermal products	Highly water soluble drug, topical germicidal drug; Zidovudine	ABI
16	Target markets	Cancer	Breast-cancer; Breast cancer cells; Cancer treatment; Cell lung-cancer; tumor cell	WoS-SCI, DII,ABI
17		Dermatology	Fluticasone propionate, topical germicidal drug	WoS-SCI, DII,ABI
18		Cosmetics	Cosmetics, Cosmetics industry, Cosmetic products	ABI

Table 4
The classification of “actions”.

Classification	Related actions
“+” mean increase	Improve; amplify; update; replace; is effective for; enhance; increase
“−” mean decrease	Reduce; induce low; depress; inhibit
“U” mean usage	Employ; apply; use (be useful); put forward; delivery; formulate; therapy; treat; introduce

reduction during the delivery process led to increased study of drug-loaded SLNs from about 2000 onwards. Drug-loaded SLNs are able to add peptides, proteins, and related drugs into the core of nanoparticles and release them to target lesions at a controlled rate, which improves the efficiency of treatment and reduces its negative effects. In 2004, the emergence of a second generation of nanoparticles, nanostructured lipid carriers (NLCs), led to a major change in the field. Replacing solid lipids with a blend of solid and liquid lipids provided a larger drug loading space, which significantly improved the drug loading capacity. Compared to drug-loaded SLNs, NLCs showed better performance in epidermal permeability and bioavailability. Such advantages garnered wide attention for NLCs from 2004 to 2010, and the number of publications and patents saw a sharp increase during this period. After 2010, related products, such as sunscreen, were introduced to the market. In addition to NLCs, gene-loaded SLNs, which first appeared in 2006, were another hot research domain. As a special kind of drug-loaded SLN, this kind of particle-loaded nucleic acids exhibits similarities to RNA and dsRNA and can deliver therapeutic molecules to specific cells by way of gene transfection. They are particularly effective at reducing the cytotoxicity generated by chemotherapy and, because of this, gene-loaded SLNs are believed to have promising prospects in anti-cancer therapies. Magnetic-loaded SLNs attract people's attention in current years. This kind of particle can be used as an MRI contrast agent and offers great advantages on drug targeting and controlled releasing.

The TRM also shows that 2008 was a critical year. Prior to then, research into SLNs had just emerged, and most studies focused on basic R&D, such as new materials. However, after 2008, explorations into real applications began to surface. For insights into the actual transformation process from basic research through to commercialization, we focused on the results from our text analysis of patents and commercial news.

Manually zeroing in on the DII manual codes (MCs, a kind of well-organized patent classification system) helped us to identify how SLN research had been transformed into applications. Fig. 2 shows the top five out of 27 core manual codes (not listed here) from the SLN-patent dataset. Between 2000 and 2007, most patents concentrated on SLN materials, like fats and lipids [B04-B01B] and polymers [B04-C03]. Then, starting in 2008, more and more patent assignees turned their attention to drugs and diseases. Anti-cancer [B14-H01], central nervous system active [B14-J01] and skin treatments [B14-N17] were the representative pharmaceutical activities during this period. Here we should note, the number of patents in the delivery processes and outcomes group was very low; only controlled release agents attracted attention, as indicated by patenting. This information shows that SLN patents were still focused on materials and drugs. It is understood that not all basic technologies can be used in scaled-up production; only a few promising ones may hold commercial value.

Turning our attention to the analysis results of the commercial data,

Table 5
Examples of SAO analysis.

SAO structure	S	A	O	Year	DB
PLGA on SLN reduce burst release	Drug-loaded SLN	+	Control release	2009	SCI
CPB added SLN induce low toxicity	Drug-loaded SLN	−	Cytotoxicity	2011	SCI
SLN delivery of siRNA to tumors… improved cancer chemotherapy	Gene-loaded SLN	+	Anticancer tools & drugs	2007	DII
Docetaxel SLN… is useful as … anti - tumor medicine	Drug-loaded SLN	U	Anticancer tools & drugs	2009	DII
Magnetite-loaded SLNs have advantage … drug targeting and controlled releasing … is introduced in 2013 as MRI contrast agent	Magnetic SLN/Control release	U	Imaging	2013	DII
C0Q10 NLC increase bioavilability … has be applied in oil in water cream	(NLC)/Bio-avilability	U	Skincare products	2011	ABI
Dox depress U87Gcells which is used in cancer therapy.	Anticancer tools & drugs	U	Cancer	2011	ABI
explored organic in NLC … as UC protection cream … introduce to cosmetic industry	(NLC)/Skincare products	U	Cosmetic	2014	ABI

Table 6
Routes within the SLN subsystem.

	SLN related materials		SLN delivery processes & outcomes		Products		Markets	
	Net effect	Related- topics	Net effect	Related- topics	Net effect	Related- topics	Net effect	Related- topics
SLN	+	NLC	+	Skin penetration	U	Dermal products	U	Dermatology
			+	Bioavailability	U	Skincare products	U	Cosmetics
			+	Drug dissolution/loading	U	Anticancer tools & drugs	U	Cancer
	+	Drug-loaded SLN	−	Blood brain barrier	U			
			+	Controlled release	U			
			−	Cytotoxicity	U			
	+	Gene-loaded SLN	−	Cytotoxicity				
			+	Gene transfection	U			
	+	Magnetite SLN	+	Controlled release	U	Imaging	U	

compared to basic R&D and patent applications, commercial processes in SLN started later. The first SLN commercial report in ABI/Inform appeared in 2008, which is unsurprising since commercial clusters are focused on real applications and markets. In Fig. 2, three applications are distinct – pharmaceuticals, including cancer, dermatology and cosmetics. Breast cancer is closely linked to pharmaceuticals and skincare treatments are closely linked to cosmetics.

In order to lay out the potential development directions, a further future-oriented discussion is in order. Our forecasting research on SLNs started in 2013. Professor Alan Porter and Dr. Jing Ma held an SLN workshop named "Technology Assessment Workshop on Nano-Enabled Drug Delivery (NEDD) – Keying on Solid lipid Nanoparticles" in Boston on October 29th, 2013, by gathering 38 technical experts. They pointed out the alternative innovation pathways, including their prospects, core factors affecting those prospects, and potential outcomes. Then Dr. Shim MinSuk and Dr. Xuejiao Zhou continued to focus on the follow-up research and revised these forecasting results. We organized the information and then visualized the potential pathways in terms of the format of a multi-path mapping (Fig. 3) (Robinson and Propp, 2008and Robinson et al., 2013).

In this map, the Y axis consists of two time intervals: present and the short future, which shows the next 5 to 10 years. The X axis contains three levels — promising SLN vectors, core functions/features expected to be added into the potential products, and potential products & markets. Fig. 3 suggests that NLC has been widely used by producing skincare products in its current stage. In this application domain, two

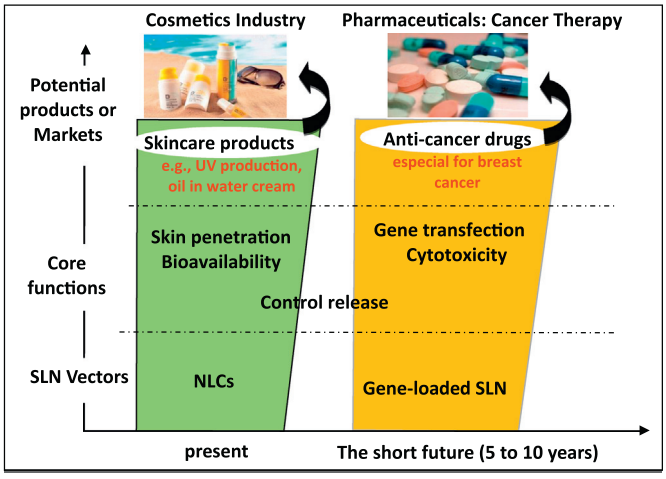

Fig. 3. Multi-path mapping for distinguished applications.

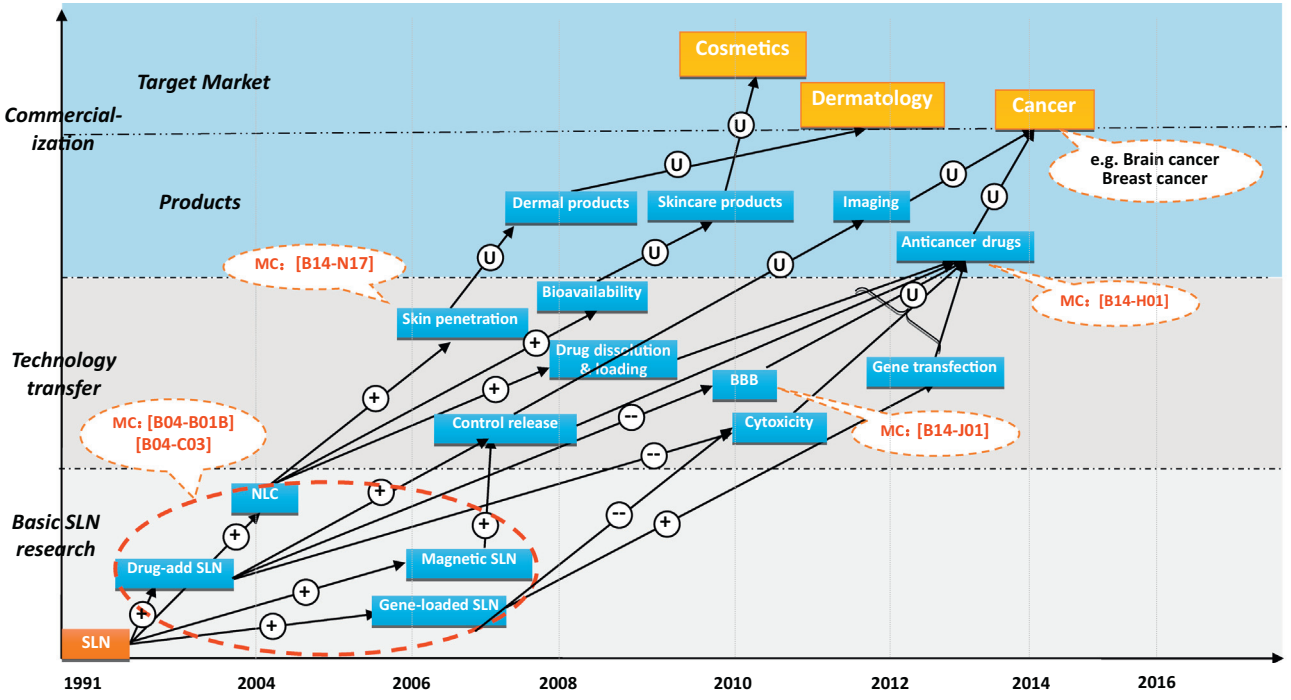

Fig. 2. Technology roadmap for SLN.

features—skin penetration and bioavailability — are essential. In contrast, gene-loaded SLN is the most promising vector in the next stage. It is assumed as an effective vector to enhance the performance of anticancer drugs. In order to achieve this goal, a low cytotoxic and better gene transfection efficiency should be addressed as priorities.

Moreover, more valuable information can be captured from Fig. 3 and in-depth investigation. Due to the complex regulations surrounding pharmaceutical development, the time between product development and market introduction is much shorter for cosmetics than it is for pharmaceuticals. This is why, analogously to liposomes, the first lipid nanoparticle product on the market was a cosmetic product (Pardeike et al., 2009). Thus, the first innovation pathway for SLNs addressed applications in the cosmetics industry.

Cosmetic applications for SLNs developed over a long period of time. In Fig. 2, between 2000 and 2004, research into materials yielded many achievements. Substance carriers at the nano scale have obvious advantages in increasing skin hydration and for enhancing the chemical stability of compounds that are sensitive to light, oxidation, and hydrolysis (Pardeike et al., 2009; Rangsimawong et al., 2016). Hence, many companies tried to apply the technology to their cosmetics during this period. Later, between 2004 and 2007, scientists began to research delivery outcomes relating to controlled release and delivery effects in order to test SLNs' bio-reliability. The low toxicity and cytotoxicity of NLCs paved the way for wide application in dermal cosmetics (Naseri et al., 2015).

The vast market potential of SLNs has led many cosmetic companies to the production of SLN-related technologies in recent years. Representative products include the coenzyme Q10 (Pardeike et al., 2009), vitamin A (Argimón et al., 2017), and UV blockers (Suter et al., 2016). We list the leading companies in this market, namely Kemira Pigments, Beiersdorf, and IFAC, which were identified as the top patent applicants and industry leaders in the relevant DII categories from the ABI/inform data. Upon further investigation, we found that Kemira Pigments and IFAC have close ties. In 2006, Kemira Pigments acquired IFAC making Kemira the leading pigment supplier for both the pharmaceutical and cosmetics industries. Beiersdorf has also done a great deal of research into SLN cosmetic products. Their most important products include sunscreen lotions and eye creams, such as Swiss Cellular White Illuminating Eye Essence, which was introduced to the market in 2007.

Along with developments in cosmetic products, SLN applications in pharmaceuticals are promising and are regarded as the most important direction in the next generation. In the latest five years, interests in pharmaceutical commercialization have already surpassed the cosmetic industry in the views of industry shareholders. In this domain, anticancer drugs constitute the most popular research topic set. Incyte Genomics and Sirna Therapeutics are the leading companies in this area. Founded in 1991, Incyte mainly provides genomics information to the biotechnology and pharmaceuticals industries. Their research focuses on developing orally consumed drugs for diseases relating to oncology and inflammation.

5. Conclusions

In this paper, we combine text mining approaches and TRM to explore developmental patterns and potential innovation pathways for an emerging technology. By doing so, we attempt to chronicle a methodology through a case analysis of SLN to illustrate its potential to contribute useful intelligence for R&D management.

SLN offers a rich case for analysis. This drug delivery approach is emerging on a variety of R&D fronts to address a growing number of challenges. For example, in the pharmaceuticals industry, SLNs are pertinent to solubility, cost-reduction, and targeting diseases; however, we also discern that patent lifecycle extension is a consideration. Identifying major R&D topics and market innovation pathways can inform management of diverse drug delivery opportunities, as well as developmental hurdles to overcome.

We perused multiple literature reviews to help identify four SLN subsystems. The term clumping steps cleaned and consolidated topical content in the text sources to identify 18 prominent R&D topics from publications, patents, and the commercial press. SAO techniques were combined with TRM to help track changes in the core topics over time. We suggest that identifying the correlations among these topics is vital to the assessment of prospects for future innovation pathways and applications.

Another interest concerns forecasting the innovation pathways for new and emerging science and technologies. To accomplish this goal, we combined multiple data sources to determine how basic research transitions to development, and then advances toward commercial products. Our current analytical strategy addresses the developmental tiers from basic research through to successful commercialization. Fig. 2 illustrates these layers over the course of time. From Figs. 2 and 3, we believe SLN has near-term commercial value, since research is turning toward application options and issues. Such analyses illustrate the potential to mine R&D information to help gauge the progress of elements toward commercialization – such as the two important innovation pathways depicted for SLNs in Fig. 3.

To help identify the technological threads and corporate links (e.g., which companies share research interests and sometimes contribute to research), we also placed emphasis on analyzing patents and commercial data.

Here we note two innovative parts of this paper. The first one was combining SAO techniques with net effect analysis to identify the evolutionary links between research topics. In our research, we did not focus on the trivial and specific actions between key words, but obtained general links between research topics. Moreover, we employed net effect analysis to show what the link was (positive or negative) between two topics, but not just to show there was a link. So the same analytical logic can be applied in other new emerging technologies. However, there was one limitation of this part. In this research, the classification of action keywords relied on the in-depth analysis of the specific 92 SAO structures by technical experts, so the classification may slightly vary from case studies. Hence, how to classify action keywords from the perspective of sentence semantic structure is a core task in the future.

The second innovation of this paper was presenting a new approach to identify real innovation topics, core applications and potential markets by comprehensive utilization of multiple data sources (research publications, patents, and commercial press). Each data source provides different types of information. First, we extracted intelligence from publications to identify the core R & D topics. Then, patents and commercial press information were adopted to evaluate core applications and potential products/markets. With considerations to the features of different technology development stages and characteristics of data sources, the topics identified were more accurate and could reflect the real research focus in different development stages.

A future priority could be to enrich our understanding of commercial development strategies. We aspire to gain company engagement to inform such downstream components of innovation pathways. However, we recognize that constraints around such aspirations exist as companies tend to protect proprietary and sensitive commercialization plans.

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Xiao Zhou, lecturer of school of economics and management in Xidian University. She got Ph.D degree in school of management and economics of Beijing Institute of Technology, in 2015. She worked at Georgia Institute of Technology (GT) as a visiting scholar from 2012 to 2013. She received the best student paper award from PICMET 2013. Her current research focuses on technology forecasting and assessment, particularly the study of emerging science and technology topics. She published more than 16 research articles which were indexed by SCI/SSCI/EI.

Lu Huang, Ph.D, associate professor of School of Management and Economics, Beijing Institute of Technology. She take charge of Chinese National Science Foundation (Award #71774013– “Complex network-based global R&D cluster identification and evaluation”) and published more than 20 research articles which were indexed by SCI/SSCI/EI. Her current research focuses on technology forecasting and Technology M & A.

Alan Porter is Director of R&D for Search Technology, Inc., Norcross, GA, USA. They produce software to help analyze Science, Technology & Innovation database search results. He is also Professor Emeritus of Industrial & Systems Engineering and of Public Policy at Georgia Tech where he continues as Co-director of the Technology Policy and Assessment Center (TPAC). He is author of some 220 articles and books, including Tech Mining and Forecasting and Management of Technology. Current research emphasizes R&D profiling & assessment and forecasting of emerging technology innovation pathways. He has a B.S. in Chemical Engineering from Caltech and a PhD in Engineering Psychology from UCLA.

Jose M. Vicente Gomila, Ph.D, associate professor of Universitat Politècnica de València. His current research focuses on techmining and semantic triz, which mainly related to how a technology may evolve, how it is related to other technologies and why these interrelationships can affect its own evolution as a system.