



A bibliometric investigation of research performance in emerging nanobiopharmaceuticals

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ABSTRACT

The three important research domains, nanotechnology, biotechnology and pharmaceuticals, integratedly breed a promising multidisciplinary domain in the post-genomic age, which was recently defined by the term “nanobiopharmaceuticals”. In this paper, we firstly investigate its general development profiles, and then implement cross-country comparisons in its research performances, with the focus on the world share, relative research effort, impact and quality of five productive countries. Furthermore, from the science mapping perspective, we build the co-word and co-citation networks respectively for detecting its intellectual structure as well as evolution footprints of intellectual turning points. The growth examinations based on the datasets from WoS, MEDLINE and BIOSIS Review confirm the exponential growth of publications and citations in nanobiopharm-research. The cross-country comparisons show that USA is the leading country, and China is an up-and-coming contributor. The visual mapping structures by co-occurrence analyses show that nanobiopharm-research is currently focused on the drug development for improving biodistribution, bioavailability and pharmacokinetics, and the drug delivery for improving delivery of existing drugs. Some pivot publications is identified by CiteSpace, which work as structural holes, research fronts and intellectual bases for the nanobiopharm-research development in the given time window.

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1. Introduction

The identification of research areas should be an important theme in informetrics, which is especially attractive for the inter- and multidisciplinary domains' emergence to bring new breaking points of modern scientific and technological research in the post-genomic age. From the 1960s onwards, the term interdisciplinarity has become a major topic in academic and policy oriented discourse on knowledge production and research funding (Huutoniemia, Kleinb, Bruunc, & Hukkinena, 2009). Braun and Schubert (2003) showed an exponential increase in the number of scientific papers labeled as ‘multi-’ or ‘interdisciplinary’, which indicates that the ‘multi-’ or ‘interdisciplinary’ scientific research is an increasingly popular domain in the modern scientific research environments. This means that scientometric evaluations oriented to inter- and multidisciplinary research domains are promising.

The three emerging interdisciplinary domains, nanobiotechnology (Takeda, Mae, Kajikawa, & Matsushima, 2009) (or bionanotechnology (Rafols & Meyer, 2007)), biopharmaceuticals and nanopharmaceuticals (Bawarski, Chidlowsky, Bharali,

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& Mousa, 2008; Gaur & Bhatia, 2008) have perceived especial attention in the up-to-date scientometric study due to their economic and political importance. The multidisciplinary among the three domains is benefit for the future design and development of the ever more sophisticated nanobiotechnologies, which is needed to realize the full potential of the post-genomic age (Duncan, 2003). One key application of the nanobiotechnology is in the field of pharmaceutical sciences (Jain, 2008; Takeda et al., 2009). Jain (2008) indicated that nanobiopharmaceuticals is an ever-growing field and destined to play a significant role in the future of healthcare. Among the key fields targeted for growth under the China's Medium & Long Term Scientific and Technological Development Plan Guidelines for the period 2006–2020 (MLP) are nanobiopharmaceuticals. There is a large increase in China's nanobiopharmaceutical research activities since its implementation in January, 2006 (Lenoir & Herron, 2009).

Durán and Marcato (2008) showed that nanobiotechnology, involving biological systems manufactured at the molecular level, is a relatively new multidisciplinary field that has fostered the development of nanoscaled pharmaceutical delivery devices. Pharmaceutical nanobiotechnology can address many important health crises using nanoscale-structured materials and simple nanobiodevices (Veerapandian & Yun, 2009). Nanobiotechnologies are being used to research the pathomechanism of disease, refine molecular diagnostics, and help in the discovery, development, and delivery of drugs (Jain, 2008). The term “nanobiopharmaceuticals”, which is used to define the emerging multidisciplinary domain among nanotechnology, biotechnology and pharmaceuticals, was firstly introduced in Jain's book *“The Handbook of Nanomedicine”* in 2008 (Jain, 2008) and then studied in the latest four international research papers: Veerapandian and Yun (2009) in *Digest Journal of nanomaterials and biostructures*, Veerapandian, Marimuthu, Yun, and Kim (2009) in *Thai Journal of Pharmaceutical Science*, Shahabade et al. (2009) in *Journal of Pharmacy Research*, and Lenoir and Herron (2009) in *Journal of Biomedical Discovery and Collaboration*.

Although the nanobiotechnology is playing an increasingly promoting role in pharmaceutical research and development, there is no scientometric study on nanobiopharmaceuticals which is an emerging and definitely important research domain from nanobiotechnology. The aim of this study is to investigate the nanobiopharmaceutical research using the bibliometric method with visual mapping. This study is focused on the detection of academic landscape of nanobiopharmaceutical research, and the cross-country comparisons in nanobiopharm-publications' efforts (investments), returns (impact) and efficiency (quality). We also employ co-occurrence (including co-word and co-citation) network analyses with visualization to detect major research domains and, track the evolution footprints of intellectual turning points in the nanobiopharmaceutical research in the given time window.

2. Methods and data collections

Bibliometric quantification is a basic but an effective way to detect and examine the emergence of a new technology (Braun & Schubert, 2003). The bibliometric study involves the statistical analysis of scientific publications, which adopts quantitative performance indicators to get over the disadvantage of subjectivity in peer review and expert judgments (Van Raan, 2004), and has been used to assess research performance in an increasing amount and variety of studies (Rinia, van Leeuwen, van Vuren, & van Raan, 1998). These have laid the groundwork for implementing the basic scientometric analysis which evaluates emerging research domains in the present study.

Besides, monitoring research trends has always been a major concern of policy makers of science and technology, since it helps research resource allocation and technological forecasting. Increasingly important research topics are of particular interest to those policy makers (Tseng, Lin, Lee, Hung, & Lee, 2009). In such situation, an attractive direction is to investigate the evolution footprints of an emerging research domain (Takeda et al., 2009), and detect hot topics (research fronts) of some important technological domains (e.g., Tseng et al., 2009). Research fronts represent the most dynamic areas of science and technology and the areas that attract the most scientific interest. Various types of techniques have been advocated for the purpose of delineating research areas including Garfield's (2004) historiographic mapping, document co-citation (Small, 1973) or author co-citation (White & Griffith, 1981), co-word analysis (Callon, Courtial, Turner, & Bauin, 1983; Callon, Laville, & Courtial, 1991), and journal mapping (Leydesdorff, 2004). In this study, we employ the co-occurrence network analysis of keywords and references to map and detect the intellectual structure as well as the evolution footprints of intellectual turning points in the nanobiopharmaceutical research in the given time window. Small and Upham (2009) demonstrated that the structural properties of the co-citation network that may be characteristic of the emergence, development, and application or demise of a research area. Small (2006) explored the possibility of using co-citation clusters over three time periods to track the emergence and growth of research areas, and predict their near term change. Chen (2006) introduced an animated visualization technique, i.e., CiteSpace, to re-construct citation and co-citation events in their chronological order so that one can examine the growth history of a domain in a broader context in a similar way to how we play a video in a fast-forward mode. The detailed implementations of employed methods are provided in the following corresponding sections.

The effective bibliometric analysis is based on the collection of documents data. This is no common way to deal with it. In implementing a bibliometric analysis of nanotechnology science, Guan and Ma (2007a) used “nano*” as the query to define nanotechnology where * means wildcard, and mentioned that this is a useful approach when the domain is interdisciplinary and difficult to define. Similarly, Takeda et al. (2009) retrieved nanobiotechnology documents using nano* and bio* as the query. The nanobiopharmaceuticals is the application of nanotechnology and biotechnology to pharmaceuticals (Jain, 2008). This means that, different from the interdisciplinarity of two domains (e.g., nanobiotechnology, biopharmaceutics and nanopharmaceutical), the multidisciplinary domain contains the comprehensive intellectual information of nanotech-

nology, biotechnology and pharmaceuticals. We firstly use three prefixes, nano*, bio* and pharm*, as the query to collect the documents for the purpose of defining nanobiopharmaceuticals. Besides, we use nanobio* (or bionano*) and pharm*, biopharm* and nano*, nanopharm* and bio*, and nanobiopharm* (or bionanopharm*) as four supplementary queries. Note that a smaller number of terms irrelevant to the topic, such as nanosecond, nanoampere and nanogram (see Braun, Schubert, & Zsindely, 1997; Guan & Ma, 2007a), are excluded.

Braun et al. (1997) introduced an effective title-based retrieval using nano* as the query to characterize the nanotechnology excluding some terms irrelevant to the nanotechnology topic. However, the retrieval strategy seems not enough for the multidisciplinary nanobiopharmaceuticals research. The prefixes nanobiopharm- or bionanopharm- are rarely used in the extant literature. So, our bibliographic data contain chosen terms in the “TOPIC” field, i.e., including titles, abstracts, key words and subject categories. Similar searching techniques were also used by Guan and Ma (2007b). Based on the current practices in informetrics and scientometrics, the document types are limited to article, letter, note and review. We collect documents data on publications and citations from the Science Citation Index (SCI) and the Social Sciences Citation Index (SSCI) compiled by the Institute for Scientific Information (ISI) on Web of Science (WoS). We also collect the publications recorded in MEDLINE compiled by the USA National Library of Medicine, and BIOSIS Preview (BP) complied by the USA Biosciences Information Service through ISI search platform. The publications data are mainly used to examine the growth trend of nanobiopharmaceutical documents. Due to the differences in document types indexed in three bibliographic data bases, the document types in MEDLINE are limited to article, review and letter, and that in BP is only limited to article. We collect publication information indexed in three databases during 1991–2009. The retrieval time is 2009.12.18.AM.

3. Analyses and results

3.1. Overall growth—big science stage

One way of monitoring the emergence of new fields is to peruse many documents published on the topic (Braun et al., 1997). A more simple and perhaps more enlightening approach to the growth of a field could be offered by the bibliometric (scientometric) quantification of a related specific term in the journal papers during a determined period.

Fig. 1 shows the number of nanobiopharmaceutical publications and citations produced per year in Web of Science during 1991–2008. As is shown in Fig. 1, the total set of nanobiopharm-publications equals 1467 papers, 1049 (71.5%) of which

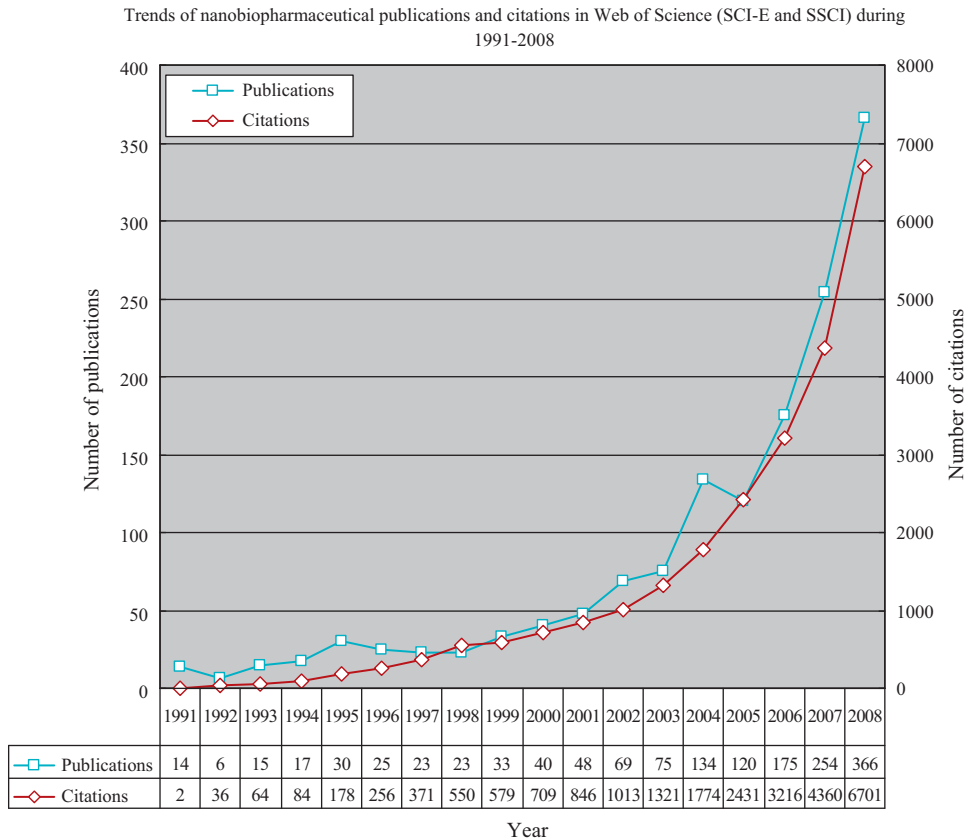


Fig. 1. Nanobiopharmaceutical publications and citations per year, 1991–2008.

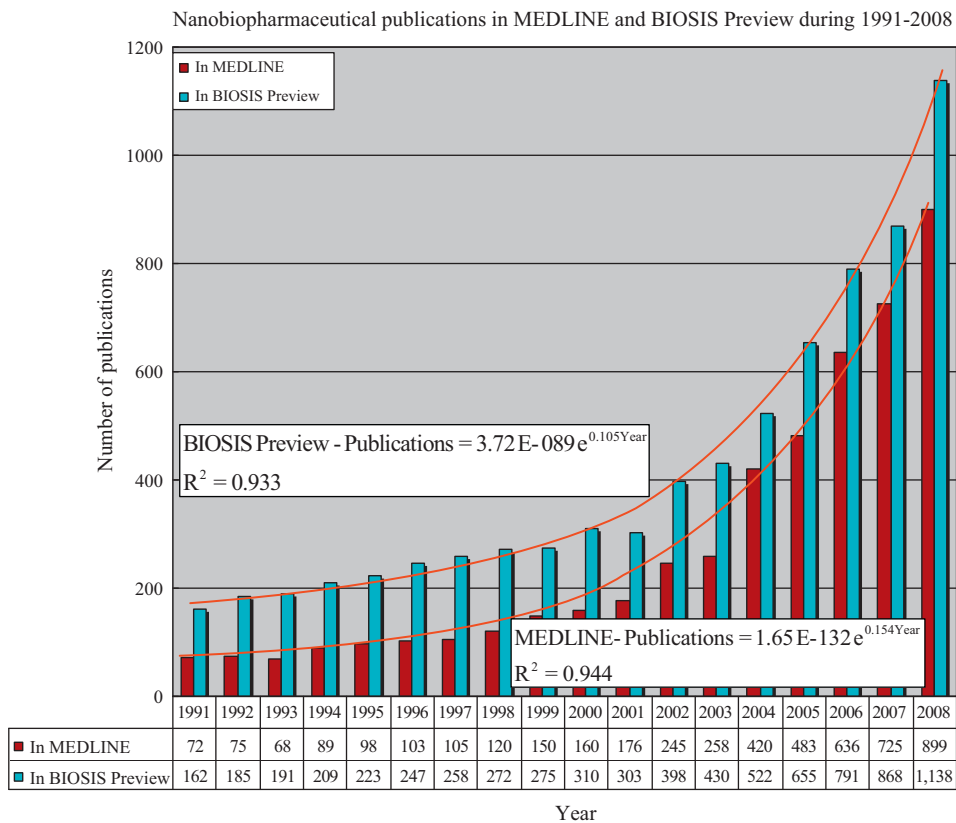


Fig. 2. Nanobiopharmaceutical publications in MEDLINE and BIOSIS Preview per year, 1991–2008.

were published during 2004–2008. During the whole determined period, the exponential growth is clearly seen ($R^2 = 0.929$). The typical growth pattern was also examined by the retrieved documents from MEDLIN ($R^2 = 0.944$) and BIOSIS Review ($R^2 = 0.933$) (see Fig. 2), which confirms the fast growth in nanobiopharm-research publications. Fig. 1 also shows that the growth trend of nanobiopharm-research citations was climbing fast year by year. The citations in 2008 were close to 7000, which in 1991 was only 2.

The exponential growth is a typical characteristic of the emergence and development of new disciplines or research domains (see Braun et al., 1997; Guan & Ma, 2007a). This indicates that the new interdisciplinary nanobiopharmaceuticals is emerging with the development in nanobiotechnology (Takeda et al., 2009). More specifically from the stable exponential growth perspective, the evolution of nanobiopharmaceutical research has seemingly gone over the preliminary phase with small increments of Price's three stages (see Price, 1963) in the growth of knowledge, which is more likely going through the intermediate phase, i.e., Price's Big Science age of exponential growth in which the scientific system moves away from an academically driven society to a mixed commercial and social marketplace. More specific growth patterns are discussed in the next section.

3.2. Cross-country comparisons—China's emergence

3.2.1. Specific growth and share

The selection of the five productive countries, China, France, Germany, Italy, and USA, is based on their world shares in the global nanobiopharmaceutical publications during 1991–2009. According to our current WoS database, the sum of nanobiopharm-publications produced by the five productive countries accounts for two thirds (66.9%) of the world total during 1991–2009. Considering the transformative change of publications in nanobiopharm-research at the beginning of the twenty-first century, we examine the growth trends for five countries during the period of 2000–2009. China is a late comer in this field and it is 2000 when China just had the first publication record in this field in WoS database. As expected, the nanobiopharm-publications in the five productive countries excluding France increased exponentially with $R^2 > 0.9$ during the latest 10-year period.

In this case, we calculate the indicator of *doubling time* during the determined 10-year period. The number of China's nanobiopharm-publications has doubled for about 1.56 years during 2000–2009 (see Table 1), indicating a much faster growth rate than the other major countries in this field as well as the world average. China's rapid growth rate in

Table 1

Exponential growth estimation and double time based on the dataset from Web of Science during 2000–2009.

Analysis units	Publications			Citations		
	R^2	b	Doubling time (year)	R^2	b	Doubling time (year)
USA	0.966	0.257	2.694	0.988	0.266	2.608
China	0.955	0.445	1.557	0.977	0.750	0.924
France	0.597	–	–	0.984	0.307	2.255
Germany	0.912	0.257	2.695	0.985	0.258	2.687
Italy	0.922	0.192	3.612	0.984	0.369	1.881
World	0.981	0.268	2.583	0.990	0.287	2.417

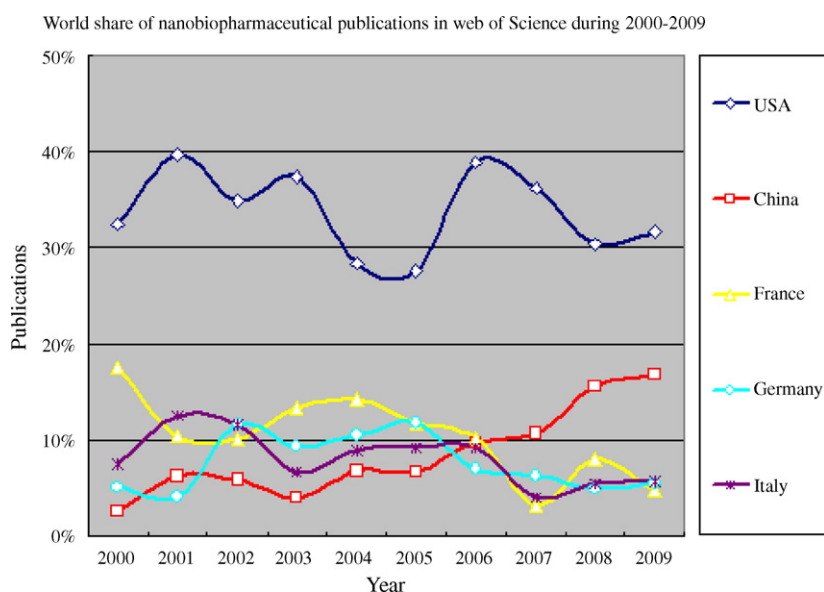
nanobiopharm-publications is not accident, which is related to the increased funding for nanotechnology and biotechnology (Lenoir & Herron, 2009).

Fig. 3 presents a dynamic picture of the world share of nanobiopharm-publications from each country. Clearly, USA has a stably dominant status in the nanobiopharm-publications productions, which produced about one third of world's total during 2000–2009. It has exceeded the aggregate productions of other three European developed countries, France, Germany and Italy. In the 10-year publication time window, France has a biggest loss, whose share in the whole world's nanobiopharm-publications has decreased by about 10% from 2000 to 2009.

At the same time, China, as a developing country, has emerged as a new significant contributor in the nanobiopharmaceutical research field. Since 2007, China has produced the second largest number of nanobiopharm-publications. In addition, China's sustained increase in the world share is remarkable, especially during 2003–2009. Possibly due to the China's increasing world share, the three European countries, on the whole, display a decreasing trend in the world publication share.

With respect to citations in this field, USA has the biggest share which is always above 40%. Clearly, USA has a predominant impact status in the development of the field. However, its world share has been generally decreasing in the 10-year citation time window, which is same as the change of Germany's share during the period. At the same time, as indicated in Fig. 4, China is the only country to have a sustained increase in the percentage share of citations in the time window, although China's world share in the nanobiopharm-citations is still low compared with other four nations' during 2000–2009. Table 1 shows that the number of China's nanobiopharm-citations has doubled every 0.92 year during the 10-year citation window from 2000 to 2009. This means that China's nanobiopharm-science impact in the world becomes stronger and stronger by a fast growth rate.

Note that, as shown in Table 1, the growth speed of nanobiopharm-citations is higher than that of nanobiopharm-publications for both world average and individual productive countries. This to some degree indicates that the nanobiopharm-research is increasingly attractive.

**Fig. 3.** World share of nanobiopharmaceutical publications per year, 2000–2009.

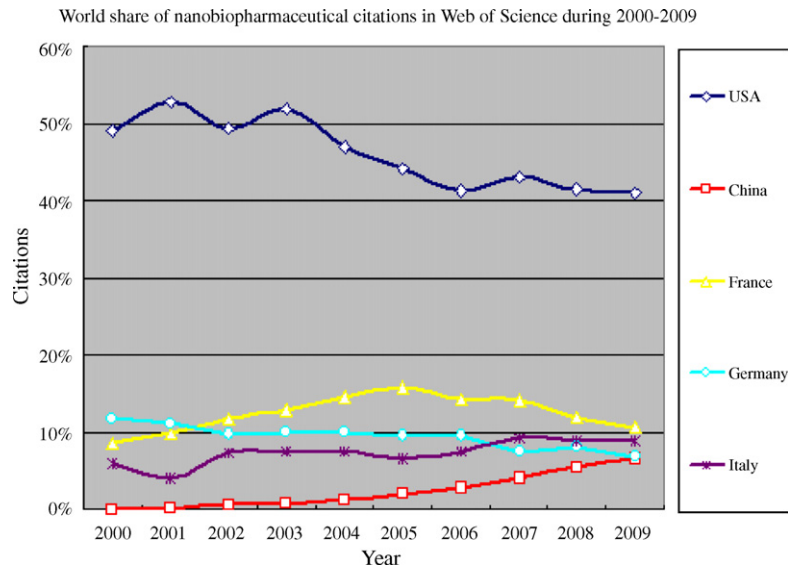


Fig. 4. World share of nanobiopharmaceutical citations per year, 2000–2009.

Source: ISI Web of Science

3.2.2. Activity index (AI)

To compare a country's research performance with the world research performance, the activity index (AI) suggested by Frame (1977) and elaborated by Schubert and Braun (1986) is introduced for the new multidiscipline in the present study. This indicator can be used to characterize the relative research effort of a country to a given subject field (see Hu & Rousseau, 2009 for a latest application). Mathematically, the activity index (AI_i^t) for the i th country in the t th year during the given period can be defined as follows:

$$AI_i^t = \frac{(P_i^t / \sum P)}{(TP^t / \sum TP)}$$

P_i^t is the nanobiopharm-publications by the i th country in the t th year; $\sum P$ is the nanobiopharm-publications by the i th country during the given publication period; TP^t is the total nanobiopharm-publications by the world in the t th year; $\sum TP$ is the total nanobiopharm-publications by the world during the given publication period.

The activity index is a relative performance indicator, which takes into account the effect of the publication size of the evaluated country in the nanobiopharmaceutical research. $AI = 1$ indicates that the country's research effort in the given field corresponds precisely to the world average. If for a given field a country's AI is larger than 1, this indicates that the country publishes more than world average in the given field. One may say that, if $AI > 1$, the country spends more energy and money to the given field than world average, or stated otherwise: $AI > 1$ reflects a specialization by this country in the field under study.

The calculated AI scores of the selected five countries during 2000–2009 are reported in Table 2. In general, the four developed countries have devoted more efforts on the nanobiopharm-science research over the world average, whose average values over 2000- to 2009-year period exceed 1. In contrast, China's general efforts in the past 10 years are lower, whose average value is below 1. However, as indicated in the calculated AI scores in the third column of Table 2, China

Table 2
Activity index (AI).

Year	USA	China	France	Germany	Italy
2000	0.989	0.2133	1.5722	0.7319	1.1074
2001	1.2045	0.5333	1.3102	0.6099	1.8457
2002	1.0584	0.4946	1.2760	1.6972	1.7119
2003	1.1361	0.3413	1.6770	1.3662	0.9843
2004	0.8629	0.5731	1.7834	1.5293	1.3223
2005	0.8368	0.5688	1.4674	1.7078	1.3535
2006	1.1824	0.8289	1.2937	1.0037	1.3500
2007	1.1022	0.9070	0.3962	0.9221	0.5813
2008	0.9229	1.3289	0.9966	0.7199	0.8068
2009	0.9633	1.4323	0.6033	0.8074	0.8498
Mean	1.0259	0.7222	1.2376	1.1095	1.1913

Table 3
Attractive index (AAI).

Year	USA	China	France	Germany	Italy
2000	1.1350	0	0.6877	1.4163	0.7142
2001	1.2191	0.0282	0.7936	1.3282	0.4988
2002	1.1414	0.1416	0.9468	1.1682	0.8807
2003	1.1991	0.1809	1.0346	1.1945	0.9126
2004	1.0845	0.2829	1.1714	1.1994	0.9106
2005	1.0216	0.4915	1.2658	1.1457	0.7885
2006	0.9542	0.6762	1.1383	1.1411	0.9072
2007	0.9939	0.9921	1.1274	0.9102	1.1254
2008	0.9587	1.3017	0.9590	0.9687	1.0831
2009	0.9495	1.5800	0.8538	0.8206	1.0840
Mean	1.0657	0.5675	0.9978	1.1293	0.8905

is the only country to maintain a stably increasing in the AI scores from 2000 to 2009, whose scores exceed 1 since 2008. This confirms a fact that China has paid special attention and support in nanobiopharm-research scientific “investment” especially from the implementation of China’s MLP in 2006. In 2008 and 2009, China is the only country whose AI scores exceed 1.

3.2.3. Attractive index (AAI)

The philosophy underlying the use of bibliometric indicators as performance measures has been summarized in Price’s (1975) statement that “for those who are working at the research fronts, publication is not just an indicator but, in a very strong sense, the end product of their creative effort.” This means that the impact (citation) of publications is more important for scientometric measures than publications. The attractive index (AAI) (Schubert & Braun, 1986) is used to characterize the relative impact of a country’s publications in nanobiopharmaceuticals as reflected by the citations they attract in this study. $AAI = 1$ indicates that the country’s relative citation impact in the given field corresponds precisely to the world average; $AAI > 1$ indicates higher-than-average and $AAI < 1$ lower-than-average relative impact. Mathematically, the attractive index (AAI_i^t) for the i th country in the t th year during the given period can be defined as follows:

$$AAI_i^t = \frac{(C_i^t / \sum C)}{(TC^t / \sum TC)}$$

C_i^t is the nanobiopharm-citations by the i th country in the t th year; $\sum C$ is the nanobiopharm-citations by the i th country during the given citation period; TC^t is: the total nanobiopharm-citations by the world in the t th year; $\sum TC$ is the total nanobiopharm-citations by the world during the given citation period.

The calculated AAI scores of the selected five countries during 2000–2009 are reported in Table 3. In general, the two countries, USA and Germany, exceed the world average in the nanobiopharm-science relative impact in the given 10-year citation time window. China’s general impact in the past 10 years is lower than the world average, whose average AAI score is only 0.5675. However, similar to its AI performance, China is the only country to maintain a stably increasing in the AAI scores from 2000 to 2009, whose score has exceeded 1 since 2008 (see the calculated results in the third column of Table 3). China is also the only country whose AAI scores are higher than world average in the two latest years (2008 and 2009). This further confirms China’s rise in nanobiopharm-science research despite a late start. In contrast, USA and Germany display a declining trend. Since 2006, USA’s AAI level began to be lower than 1, indicating it lost dominating advantage in the relative citation impact in the nanobiopharm-science research. Germany was on the same journey in 2007.

In terms of further evaluative purposes, the most relevant question is “cost-effectiveness”, i.e., whether the effort devoted to a research field (namely, the publication effort) has sufficient return in terms of its impact (viz., in terms of citations). In order to present the relative performance situation determined together by AI and AAI scores among countries, we follow Schubert and Braun (1986) to build the relational chart in Fig. 5. The relational chart is simple two-dimensional orthogonal diagrams with identically scaled axes displaying quantities such that the “main diagonal” (the straight line $x = y$) represents some kind of “balanced” situation. Points above this diagonal are to be considered “higher class”, those below “lower class” in a sense depending on the actual content of the chart.

The construction of Journal Impact Factor (IF) from Journal Citation Report (JCR) compiled by Thomson ISI reminds that it is necessary to consider a time lag structure between publications and citations. Glänzel, Danell, & Persson (2003) and Qiu and Chen (2009) confirmed the necessity of the time lag structure between publications and citations. In order to coincide with the current practices in bibliometrics, and make AI “efforts” correspond to AAI “returns” as far as possible, we consider the 2 years lag on AAI. This means that, the different time windows should be fixed in AI (publications) and AAI (citations). The scores of AI are from 2000 to 2007, while those of AAI are from 2002 to 2009. The fact that the citation per year of a publication generally reaches the highest point in the second year (see Qiu & Chen, 2009 for detailed discussions) validated our consideration of the 2-year-lag citation structure. This means that the extant mathematical relationships or comparisons between AI and AAI scores without consideration of the citation time lag structure (e.g., Hu & Rousseau, 2009) need further discussions.

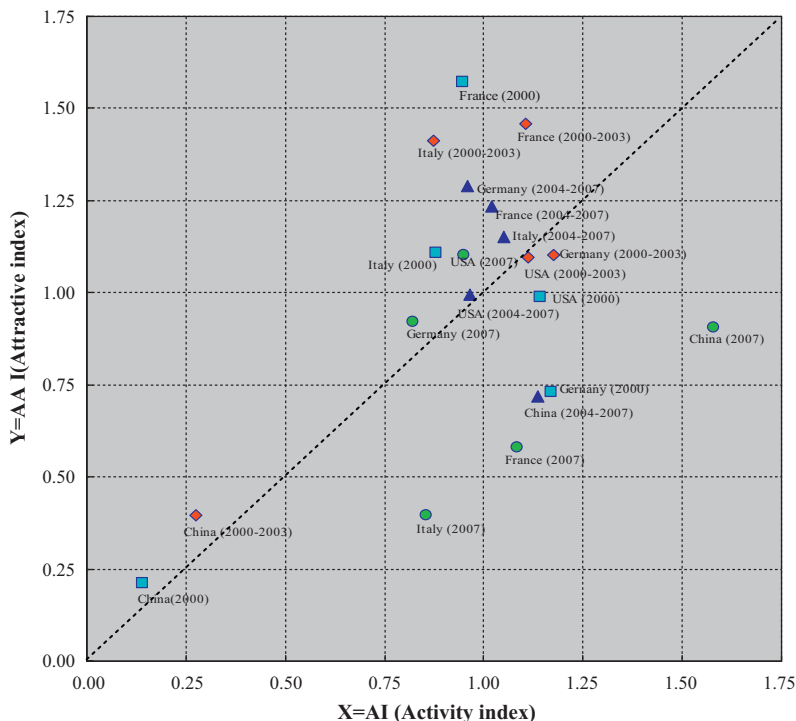


Fig. 5. Relational chart displaying AI vs. AAI. Note: Nodes are labeled by countries' names with years or years range.

The position of the two points “USA (2000–2003)” and “USA (2004–2007)” relative to the main diagonal in Fig. 5 shows that USA almost is the only country with respect to the cost-effectiveness, i.e., whether the effort devoted to the nanobiopharm-research (namely, the publication effort) has sufficient return in terms of its impact (viz., in terms of citations) (Schubert & Braun, 1986). This means that USA’s efforts and returns in nanobiopharm-research are in “balanced” situation during the 8-year period. In the same situation, France and Italy tend to balance in the cost-effectiveness situation during 2004–2007 relative to during 2000–2003. However, Fig. 5 shows that the two countries have not obtained obvious improvement in the AI “investments” during 2000–2007, but lost comparative advantage in the AAI “returns”. Therefore, the nanobiopharm-research in the two countries should receive special attention in the international impact.

Due to considerable funding and policy supports in the field in recent years (Lenoir & Herron, 2009), China has upgraded its comparative status in the world. The position change of the point “China (2007)” relative to the point “China (2000)” in Fig. 5 can clearly describe its great improvement from 2000 to 2007. The improvement can be displayed by the remarkable position change from the point “China (2000–2003)” to “China (2004–2007)”. However, the China’s citation “returns” is much lower than its publication “investments” on the average during 2004–2007. The unbalanced situation reminds that the nanobiopharmaceutical research field should also deserve constant special attention and stable support in China.

3.3. Publication efficiency index (PEI)

The relational chart helps in comparing the relative situation of a country’s publication cost and effectiveness in nanobiopharmaceutical research. In this section, we introduced a publication efficiency index (PEI) describing the ratio of publication efforts to publication incomes. The indicator is another derivative of the above mentioned activity index, and was used by Guan and Ma (2004) in their studies as a measure of research quality. It indicates whether the impact of publications in a country in a research field is compatible with the research efforts. The value of $PEI > 1$ for a country indicates that the impact of publications is more than the research effort devoted to it for that particular country and vice versa.

In the present study, it is obtained through dividing the percentage of citations “returns” by the percentage of publications “efforts”:

$$PEI_i^t = \frac{(C_i^{t+2} / \sum C)}{(P_i^t / \sum P)}$$

C_i^{t+2} is the nanobiopharm-citations by the i th country in the $(t+2)$ th year; $\sum C$ is the nanobiopharm-citations by the i th country during the given citation period; P_i^t is the nanobiopharm-publications by the i th country in the t th year; $\sum P$ is the nanobiopharm-publications by the i th country during the given publication period.

Table 4
Publication efficiency index (PEI).

Year	USA	China	France	Germany	Italy
2000	1.5154	0.4000	0.2000	1.1500	0.7333
2001	1.0048	0.6818	0.6364	0.7136	1.7424
2002	0.9826	0.3835	1.9173	1.0066	0.5512
2003	1.2640	0.2994	0.9881	0.6673	0.4312
2004	1.2531	0.3938	1.2653	0.6715	0.6164
2005	0.7958	0.7780	1.4963	0.5313	1.7388
2006	1.0475	0.6506	1.2007	0.5327	1.2938
2007	1.0827	0.7977	0.6169	1.1077	0.9198
Mean	1.1182	0.5481	1.0401	0.7226	1.0034

As to the implementation of the relational chart displaying AI vs. AAI in Fig. 5, we use different time windows for publications “efforts” and corresponding citations “returns”, which is different from the extant study (e.g., Guan & Ma, 2004; Hu & Rousseau, 2009).

The calculated scores by our improved PEI are reported in Table 4. In terms of the average during 2000–2007, France and Italy are close to 1, which indicates the impact of publications in the two countries in the research field is compatible with their research efforts on average during 2000–2007. USA’s publications display desirable efficiency performance, while China’s publications are accompanied by inefficiency performance during the 8-year time window. This suggests that the impact of publications for China is not commensurable to their research efforts in nanobiopharmaceuticals, although China’s PEI scores as a whole increase in recent years.

With respect to the changes of individual countries’ PEI scores during 2000–2007, all countries display irregularly fluctuant trends. However, the nonparametric test result by Kruskal–Wallis test method ($p = 0.035 < 0.05$, $\lambda^2 = 10.55$) shows that there is a significant difference across five countries in the PEI scores.

3.4. Intellectual structure and evolution footprints—nanobiotechnology-based drug delivery and development

The preliminary bibliometric investigations and analyses above lead readers to grasp the general development profiles as well as the cross-country advantage/disadvantage patterns in nanobiopharmaceutical research. Scientometric oriented to science mapping have seemingly become most attractive for identifying research fronts and evolutions of some important scientific and technological domains, which is especially true for an emerging research domain (e.g., Small & Upham, 2009; Takeda et al., 2009; Tseng et al., 2009). In the remaining analysis, we employ visual co-word and co-citation network analyses to detect and map the intellectual structure as well as the evolution footprints of salient intellectual turning points in the nanobiopharmaceutical research.

3.5. Co-word network of keywords

Co-word analysis is based on the theory that research fields can be characterized and analyzed based on patterns of keyword usage in publications, which has been largely and successfully used for dynamic evolution of science (see Callon et al., 1983, 1991; Courtial, 1992, 1998). It is a content analysis technique that is effective in mapping the strength of association between keywords in textual data. The network map based on it represents the intellectual structure of our concerned disciplines, which is especially appropriate for describing the development of multidiscipline combing more complex knowledge. The existing study has confirmed the reliability and adequacy of the co-word method for mapping the structure of scientific inquiry (e.g., Whittaker, 1989), which satisfactorily identifies groups of research themes and the way in which these evolve. In this study, keywords (descriptors) are retrieved from the documents downloaded from Web of Science by Bibexcel, and then the top 20 keywords are chosen for our co-occurrence network analysis by Pajek. The co-word network map displayed in Fig. 6 is created together using Bibexcel (Persson, 2004) and Pajek (Batagelj & Mrvar, 2003) with Kamada–Kawai algorithm (Kamada & Kawai, 1989). In the co-occurrence analysis of keywords, we are especially concerned about the co-occurrence frequency of the two keywords. The higher co-occurrence frequency of the two words means the closer relationship between them, which is represented by the thicker of linking lines between the two keywords in the co-word network.

In this case, the connection strength (determined the co-occurrence frequency) between nodes (keywords) shows that the terms “delivery” and “liposome” have the closest relationships with the term “nanoparticle”. The latest review in Malam, Loizidou, and Seifalian (2009) shows that nanoscale drug delivery systems using liposomes and nanoparticles are emerging technologies for the rational delivery of chemotherapeutic drugs in the treatment of cancer. Their use offers improved pharmacokinetic properties, controlled and sustained release of drugs and, more importantly, lower systemic toxicity. The second combined structure is constructed by the three terms, nanoparticle, biodistribution and pharmacokinetics. Nanoparticle, bioavailability and pharmacokinetics formed the third combination structure. These combinations of related issues show that the nanobiopharmaceutical research is focused on the drug delivery for improving the delivery of existing drugs and the drug development for improving the pharmacological and bioavailability activity of existing drugs.

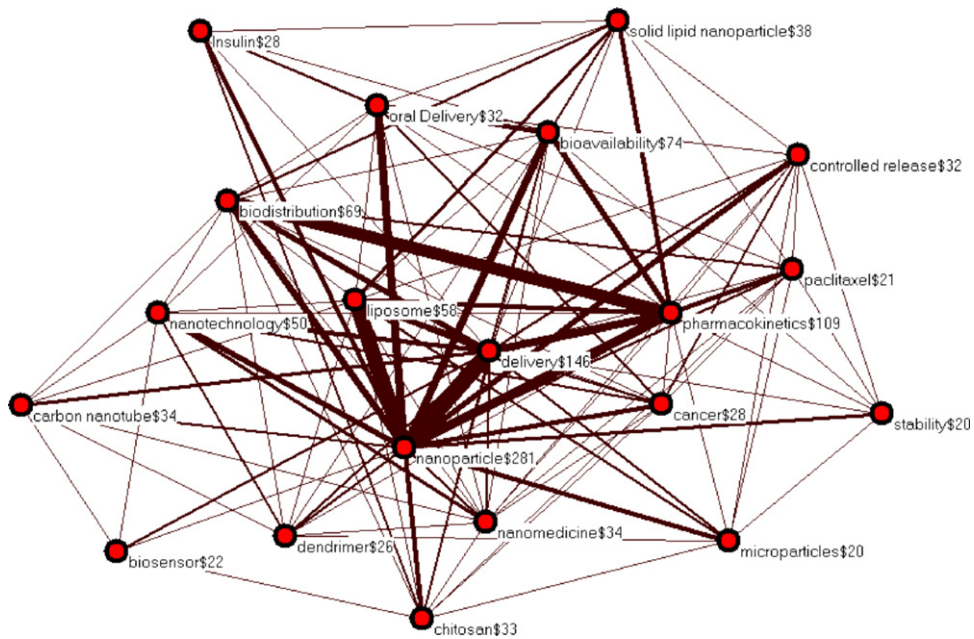


Fig. 6. A co-word network of top 20 keywords in nanobiopharmaceutical research based on our datasets. *Notes:* The network is created using Pajek with Kamada–Kawai algorithm. The thickness of linking lines between the two keywords is directly proportional to their co-occurrence frequency. The numbers behind a \$-sign are the occurrence frequency of the keywords in our WoS dataset.

In the network map, the centrality of a node representing a keyword is a graph-theoretical property that quantifies the importance of the node's position in a network. The Fig. 6 visually shows that, in the scientific network map of nanobiopharmaceutical research, the centrality of the terms “delivery”, “nanoparticle”, “liposome”, “pharmacokinetics” and “biodistribution” is obviously outstanding. To statistically quantify the importance of each keyword within the co-word network, we implement social network analysis based on graphic statistics. Table 5 presents a summary of statistical results by Ucinet (Borgatti, Everett, & Freeman, 2002). The statistical results of two common centralization indexes (degree centrality and Freeman's 1979 betweenness centrality) for each keyword (see the results in the columns 2 and 3 in Table 5) qualitatively confirm the finding above. Moreover, the statistical results of two common parameters (effective size and constraint) quantifying structural holes (Burt, 1992) in the context of whole network model clearly demonstrate the central status of these keywords in the co-word network (see the results in the columns 4 and 5 in Table 5).

Table 5

A social network analysis of the co-word network of top 20 keywords in nanobiopharmaceutical research based on our datasets.

Keywords	Degree	Betweenness	Effective size	Constraint
Delivery	18	15.815	8.667	0.194
Nanoparticle	18	14.587	8.333	0.197
Liposome	15	5.605	5.667	0.211
Pharmacokinetics	15	5.275	5.400	0.217
Biodistribution	14	4.024	4.714	0.220
Nanomedicine	14	3.684	4.333	0.220
Oral delivery	12	3.319	4.667	0.221
Bioavailability	12	3.941	3.364	0.217
Paclitaxel	12	3.096	3.545	0.224
Nanotechnology	11	2.812	4.333	0.241
Controlled release	11	2.154	2.636	0.236
Cancer	11	1.093	2.333	0.238
Chitosan	11	4.381	3.000	0.210
Dendrimer	10	1.295	4.818	0.246
Microparticles	9	1.388	3.222	0.245
Solid lipid nanoparticle	9	1.505	4.571	0.239
Carbon nanotube	8	0.850	1.857	0.278
Stability	7	0.379	2.000	0.278
Insulin	6	0.486	2.600	0.277
Biosensor	5	0.310	1.800	0.317

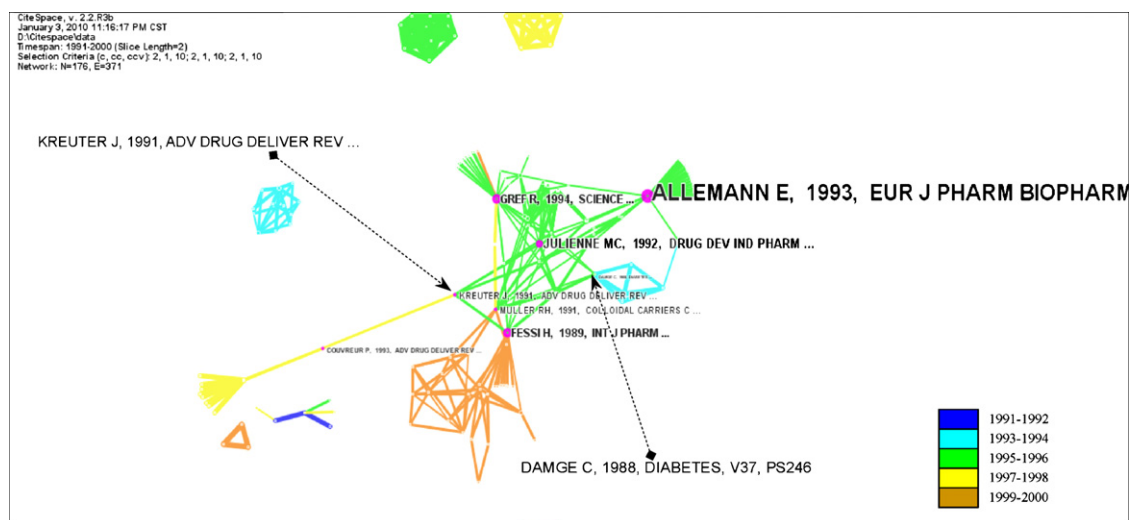


Fig. 7. A co-citation network of references cited during 1991–2000 in nanobiopharmaceutical research.

3.6. Co-citation network of references

To present more visual features for the evolution footprints of nanobiopharmaceutical research, we further employ the CiteSpace (Chen, 2006) to construct a co-citation network of the references relevant to the chosen topic: nanobiopharmaceutical research. CiteSpace uses a time-slicing mechanism to generate a synthesized panoramic network visualization based on a series of snapshots of the evolving network across consecutive time slices. The quality of the visualized network is promising: intellectually significant publications tend to have topologically unique features. In this sense, some salient intellectual turning points (nodes) are identified, and used to describe the evolving network of nanobiopharmaceutical research from intellectual bases, research fronts as well as connecting mechanism as structural holes (Burt, 1992). The centrality of a node is a graph-theoretical property that quantifies the importance of the node's position in a network. In the visual network map, the Freeman's (1979) betweenness centrality metric is used to highlight potential pivotal points, which is represented by the thickness of a red purple ring around a node with a tree-ring of citations history, and also by the front size of labeled publications' names. The radius size of the citation tree-ring represents the citation frequency in our dataset.

In order to improve the clarity of a visualized evolution network, we employ a simplified network by pruning (i.e., link reduction, or network scaling) (see Chen, 2006). Here, a topology-based approach instead of a threshold-based approach is chosen for a more extensive consideration of intrinsic topological properties (see Chen, 2004; Small & Upham, 2009). In this study, pathfinder network scaling instead of minimal spanning trees is employed in order to preserve the chronological growth patterns in co-citation networks (Chen & Morris, 2003).

We construct three co-citation networks based on the documents datasets respectively during 1991–2000, 2001–2008 and 1991–2008 by CiteSpace with pathfinder network scaling. Fig. 7 displays the references co-citation network by CiteSpace with pathfinder network scaling over 1991- to 2000-year period, which shows that the most prominent article in the visualization is ALLEMANN-1993 in terms of its betweenness centrality score. The ALLEMANN-1993 mainly examines the technology currently available for the preparation of drug-loaded nanoparticles and in particular their formation, purification, sterilization and freeze drying. The JULIENNE-1992, GEF-1994 and FESSI-1989 follow it. These salient publications form the intellectual turns in the earlier nanobiopharm-research. The smaller citation tree-ring size of those salient nodes shows that they did not get enough citations during 1991–2000. This indicates that the nanobiopharm-research was not active and more likely in the Price's Small Science age during that period.

In terms of specific connection structures, the DAMGE-1988 is a transitional pivot node which links a light blue network patch (1993–1994) and a green network patch (1995–1996). The green network patch (1995–1996) is connected with the deep yellow network patch (1999–2000) by two distinct pivot nodes, FESSI-1989 and MULLER-1991. It is the KREUTER-1991 that connects the green network patch (1995–1996) with the yellow network patch (1997–1998). Those transitional pivot nodes (publications) play a bridging role and imply intellectual transitions over time. Note that GREF-1994 and MULLER-1991 potentially play more important bridging roles in intellectual transitions since they link three colors during the period.

In the subsequent observation period: 2001–2008 (see Fig. 8 also drawn by CiteSpace with pathfinder network scaling), the role of GREF-1994 in intellectual transition over time becomes more evident. It has the biggest betweenness centrality score and is located towards the center of the visualization, which joins links from four different time slices over 2001- to 2008-year period. In the groundbreaking study, monodisperse biodegradable nanospheres were developed from amphiphilic copolymers composed of two biocompatible blocks (Gref, Minamitake, & Peracchia, 1994). JUNG-2000, MOGHIMI-2001 and BRIGGER-2002 follow it in terms of betweenness centrality scores. Fig. 8 also shows that the pivot nodes, DUNCAN-2003

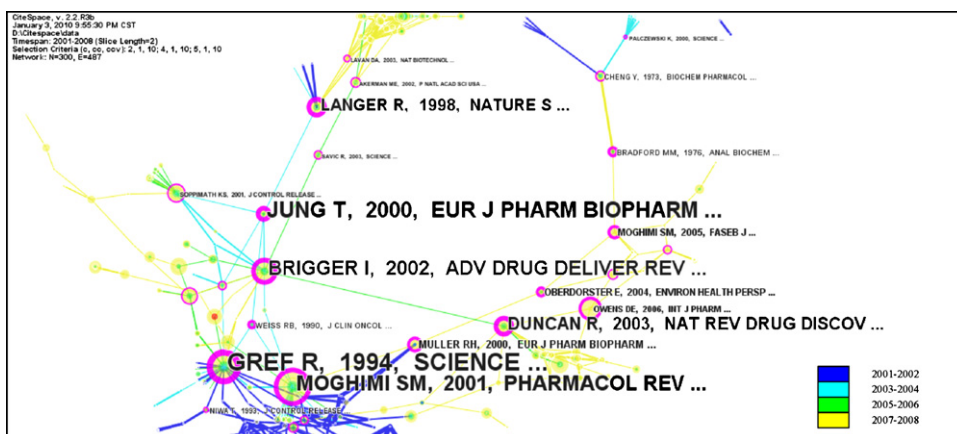


Fig. 8. A co-citation network of references cited during 2001–2008 in nanobiopharmaceutical research.

and LANGER-1998, make intellectual contributions to the latest two yellow clusters during 2007–2008. In the new cluster, the salient publications, e.g., LAVAN-2003, OBERDORSTERE-2004, MOGHIMI-2005 and OWENS-2006, represent the latest research fronts. (For interpretation of the references to color in text, the reader is referred to the web version of the article.)

Fig. 9 shows a panorama view of the entire time interval of the dataset (1991–2008). At a glimpse, one can easily and intuitively find publications that are worth a closer look. GREF-1994 has a prominent structural property—a high betweenness centrality (a thick red purple ring). (For interpretation of the references to color in text, the reader is referred to the web version of the article.) Its betweenness centrality value is 0.60, which exceeds other prominent publications. This indicates that the article GREF-1994 plays a central role in intellectual base for the nanobiopharm-research development over the given 18-year period. The ALLEMANN-1993 with the foreground over 1991- to 2000-year period follows the GREF-1994 over the whole research period due to its degradation over 2001- to 2008-year period. The pivot node DAMGE-1988 (linking the 1993–1994 cluster and the 1995–1996 cluster) clearly lays as an intellectual base for the earlier nanobiopharm-research. In contrast, the two pivot articles, GREF-1994 and FESSI-1989, provide intellectual bases for the recent nanobiopharm-research in terms of their unique transitional roles between earlier and later clusters as structural holes. In the newly formed clusters, the article MOGHIMI-2001 plays a unique transitional role in intellectual interactions between a yellow cluster (2003–2004) and a brown yellow (2005–2006) in Fig. 9. (For interpretation of the references to color in text, the reader is referred to the web version of the article.)

As two yellow clusters in the Fig. 8, Fig. 9 further confirms the formations of the latest nanobiopharm-research front clusters, also drawn by CiteSpace with pathfinder network scaling. The retrieval results show that the cluster #1 focuses on the nanobiotechnology-based drug development, while the cluster #2 focuses on the nanobiotechnology-based drug delivery. The unique structural positions in Fig. 9 show that the article DUNCAN-2003 provides an intellectual base for the formation of cluster #1, while other two pivot articles, LANGER-1998 and FESSI-1989, provide intellectual bases for the formation of cluster #2.

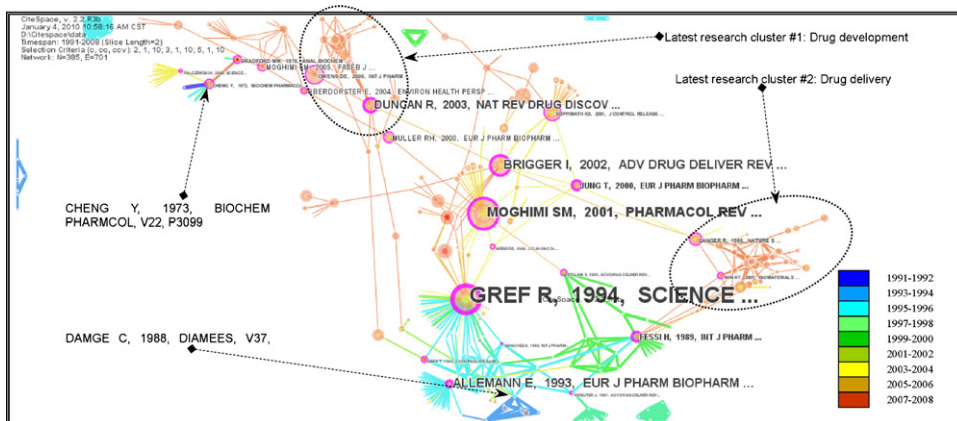


Fig. 9. A co-citation network of references cited during 1991–2008 in nanobiopharmaceutical research. (For interpretation of the references to color in text, the reader is referred to the web version of the article.)

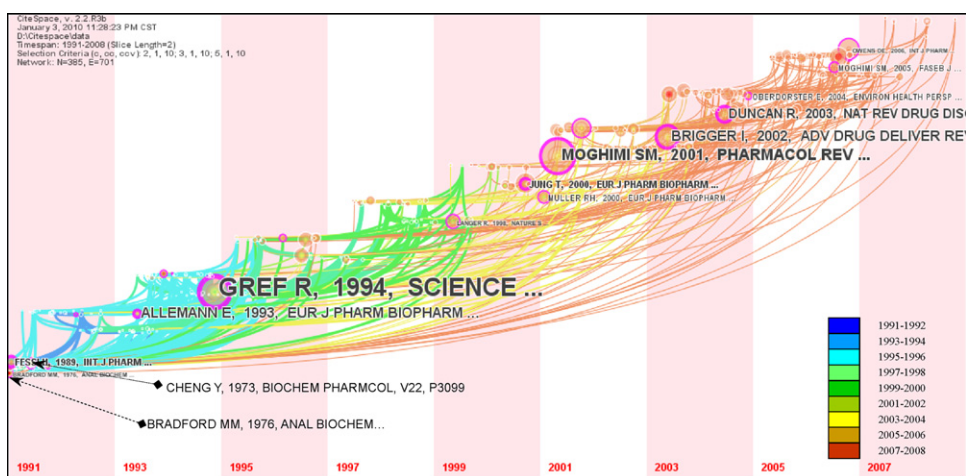


Fig. 10. The time-zone visualization references cited during 1991–2008 in nanobiopharmaceutical research.

Note that the salient intellectual turning points above usually act as structural holes (Burt, 1992) by which the nodes in the earlier cluster networks are connected with those in the later cluster networks. Those intellectual turning points playing as weak ties between different clusters are essential to understand how specialties and different thematic trends during different periods interact with each other in the long-range development path. In our case, GREI-1994, DAMGE-1988 and FESSI-1989 in the Fig. 9 play such bridging roles in the nanobiopharm-research development evaluation during 1991–2008. The importance of those points' position in the network displayed in Fig. 9 can be quantified by Freeman's betweenness centrality scores (Chen, 2004). According to the thickness of the red purple ring around pivot points, the bridging connection role of GREI-1994 in the merged co-citation network in Fig. 9 is most significant. In order to present a dynamic evolution of the nanobiopharm-research intellectual bases and fronts, a time-zone visualization graph, which emphasizes the temporal relationships, are generated by CiteSpace (see Fig. 10). The dynamic time-slicing paragraph of key references standing for research intellectual bases and fronts leads us to track the evolution path of nanobiopharmaceutical research over 1991- to 2008-year period.

Clearly, the time-zone visualization graph firstly shows that the earlier publications, e.g., CHENG-1973, BRADFORD-1976 and FESSI-1989, obtain multi-period citations, and present stable intellectual bases for the long-term development in nanobiopharm-research. Subsequently, ALLEMANNE-1993 and GREI-1994 become nanobiopharm-research fronts, and provide intellectual bases for the follow-up nanobiopharmaceutical research. Fig. 9 shows that no important nanobiopharm-publications are produced over 1995- to 1999-year period from the whole perspective of the 18-year research period. The two intellectual turning points, JUNG-2000 and MULLER-2000, subsequently emerge. In the later study, MOGHIMI-2001, BRIGGERI-2002 and DUNCAN-2003 play stronger connecting roles in terms of the whole 18-year research period, and present intellectual bases for the latest nanobiopharm-research. OBERDORSTER-2004, MOGHIMI-2005 and OWENS-2006 are produced as the center of the latest research front cluster. In sum, the time-zone view conveys a picture of the visual footprint of nanobiopharm-science research fronts and intellectual bases over 1991- to 2008-year period.

4. Concluding remarks

The term *inter- or multidiscipline* resulting from knowledge fusion, and the term *science mapping* identifying knowledge's critical evolution footprints increasingly receive special attention in the latest scientometric study. In this study, a coherent comprehensive scientometric evaluation framework is employed to investigate an emerging and promising multidiscipline: nanobiopharmaceuticals. We detect and map the emerging domain's key development landscape, including growth pattern, intellectual structure and evolution footprints of pivot intellectual turning points, during 1991–2008.

The growth analysis shows that the nanobiopharmaceutical scientific research is emerging as a pioneering and multidisciplinary domain from nanobiotechnology. The output of nanobiopharmaceutical papers has significantly increased since 1991 in an exponential growth way. The subsequent comparative analysis indicates that USA is the leading country in nanobiopharmaceutical research in terms of both world publication and impact share. However, as Germany, its world impact share displays a decreasing trend in the recent 10 years. In contrast, China is the only country whose world publication and citation share are increasing during the same period.

The relative performance scores by AI (activity index), AAI (attractive index) and PEI (publication efficiency index) show that the four developed countries (USA, France, Germany and Italy) have devoted more efforts than the world average on the 10-year average during 2000–2009. USA and Germany obtain higher-than-average AAI scores on average, and however display a decreasing trend during the given latest 10-year period. China, as a newcomer and promising contributor, displays

an increasing trend, and obtains higher-than-average AI and AAI scores in 2008. Those results further confirm our findings in the world publication and citation share comparisons above. However, the increasing incommensurable situation of nanobiopharm – citations with – publications reminds that China's nanobiopharm-research should deserve special attention and stable support.

The visual co-word analysis of keywords by Pajek shows that the center term “nanoparticle” is closely related to the terms “delivery”, “liposome”, “distribution”, “pharmacokinetics” and “bioavailability”. Those combinations of related issues show that the nanobiopharmaceutical research is currently focused on the *drug delivery* for improving the delivery of existing drugs, and the *drug development* for improving the pharmacological and bioavailability activity of existing drugs.

The visual co-citation network analysis of references by CiteSpace leads us to detect important publications which act as intellectual turning points of nanobiopharm-research evolution during the given 18-year period. Our observations provide visual insights into how nanobiopharm-science changes during the period. In the dynamic tracking analysis, some pivot publications are detected, which not only presenting intellectual bases and fronts for the nanobiopharm-research development, but also acting as structural holes, play a bridging role between nanobiopharm-research clusters during the different periods. Furthermore, the two front clusters, respectively related to drug delivery and development, are identified.

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