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Chapter 6

A Scientometric Study on Graphene and Related Graphene-Based Materials in Medicine

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Additional information is available at the end of the chapter

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Abstract

Here we carried out a scientometric analysis of scientific literature published referred to the use of graphene and graphene-based materials. We found that in the last 15 years, more than 1200 issues have been produced, with an *H*-index of 67 cited 2647 times. The countries that have a larger production, in terms of number of issues published, are China, the United States, South Korea, India, and Iran, and the most relevant subject categories in which they are indexed are materials science, chemistry, science and technology, physics, and engineering, while the biological and medical specialties seem to be actually not deeply involved.

Keywords: graphene, graphene-based materials, graphene oxide, nanotubes, biomaterials, medicine, bioengineering, scientometrics

1. Introduction

Graphene consists of a single layer of carbon atoms packed into a honeycomb lattice. Its particular atomic organization of the carbon atoms affords graphene a set of very unique characteristics that justify the attention researcher of all fields have given it. The more standing out properties are a high mechanical strength, thermal and electrical conductibility, high surface-to-mas ratio, and relative transparency [1]. Many studies use graphene oxide (GO) or reduced

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graphene oxide (rGO) instead of pristine graphene, because the oxidized forms are easier to process and can be dispersed in water while at the same time maintaining most of graphene's properties.

Graphene oxide has shown great potential enhancing differentiation and proliferation of human stem cells in vitro, which tend to adhere to graphene plates. In particular, it favors differentiation of human neuronal stem cells (hNSC) toward neurons rather than glia cells [2]. Combined with its inherent flexibility and strength, the possibility of creating a 3D structure that mimics the original organ, graphene appears to be a great scaffold for stem cell-based therapy [3].

Furthermore, a lot of research has come forward regarding the use of graphene in biosensors. Compared to previously used materials, graphene shows increased resistance and sensitivity. Also, being biocompatible it can be worn, allowing for the possibility of a permanently used sensor. Additionally, graphene can be bound to a wide range of molecules and proteins that allow for better selectivity [4].

Another field to which graphene's ability to be bound to specific molecules has been applied is drug carrying and delivery. In particular, it has been successfully used for specific anti-cancer drug delivery [5]. It presents novel perspective in combining site detection and drug delivery. Peptides bound to the GO plates allow for detection by specific cell types, minimizing uptake by other healthy cells [6].

Graphene's use in the medical field raises a lot of questions regarding its safety and toxicity. In this regard, there are many conflicting studies and opinions. It appears that the matter of toxicity varies greatly depending on the physicochemical characteristics of the administrated graphene, also on the form of administration, and the model, varying between different species and cell types. The characteristics of graphene like concentration, dimensions (lateral and number of layers), surface structure functional groups, and protein corona influence its toxicity in biological systems. Despite its relevance to the effect, some toxicological studies do not give a proper characterization of the form of graphene used. Though most agree on the interaction of graphene with the cellular membrane, the question of its uptake is more controversial [7]. For example, the studies of Yue et al. on the viability of six different cell lines when treated with GO of varying dimensions show that only two phagocytic cell lines were able to internalize both nano- and micro-sized GO sheets. Furthermore, there was no difference in the viability of any of the six cell line studies when the concentration was lower than 20 μg/mL. On the other hand, inhalation of GO particles may lead to an accumulation in the pulmonary surfactant and initiate an inflammatory process [8].

Interestingly, although GO does not show to be absorbed through the gastrointestinal tract, a low dose of GO can cause more damage to the gastrointestinal surface being drank as a suspension than a high dose of GO [9]. Most toxic effects seem to surge from the use of high doses of GO and the sequential aggregation and formation of conglomerates than can block small blood vessels and result in dyspnea [10]. However, recent publications detect no pathological effects in mice exposed to low dosages of GO and functionalized graphene when administrated by intravenous injection [11].

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While studying toxicity it is very important to analyze the effect on the reproductive system and development because this can lead to more lasting effects. Graphene plaques seem unable to penetrate the blood-testis barrier in mice, and therefore sperm function and male reproductive activity show no alteration even for high doses of graphene [12]. In the female, there are no alterations if GO is administered before mating or during early gestation, and the female can give birth to healthy litters. However, if administered during late gestation, it leads to abortion and even death of the pregnant mice for high dose [13]. Injection of chicken eggs leads to reduced vascularization of the heart [14]. Despite showing no obvious malformation or mortality in zebrafish embryo, GO aggregates were retained in many organelles leading to hypoxia and ROS generation in these areas [15].

Even though graphene toxicity has drawn a lot of attention from scientists, there is a remarkable lack of understanding of the mechanisms underlying this effect. The use of different models and forms of graphene seem to lead to very dissimilar conclusions. There is a clear need for more systematic and in-depth studies, before graphene can be brought to its full potential use [7].

In this context, it is evident that, in one hand, graphene and graphene-related materials are even more used in medicine and bioengineering; on the other one, the information about their safety, their toxicity, and about the way of their possible interaction with living being (and human body and fluids) are still incomplete.

For this reason, here, we carried out a scientometric study on this very interesting topic, with the aim to study the scientific literature and to identify the most relevant topic and the countries that are more involved in this research activity.

2. Materials and methods

2.1. Data collection and dataset

We accessed the data from Web of Science repository (https://apps.webofknowledge.com/) in December 2017–January 2018. The data have been filtered using the Advanced Search tool with the following syntax:

$$TS = (topic\ 1)\ AND\ TS = (topic\ 2) \tag{1}$$

where *TS* is the topic; *AND* is the Boolean operator.

In our queries, we used as topic 1 "graphene" or "graphene oxide" or "graphene-related material," combined with the following keywords as topic "medicine," "biomaterials," "scaffold," "regenerative medicine," or "bioengineering." Then all the data sets obtained were merged with the "Combine Sets" tool. As a result, we obtained a dataset in .txt format containing a list of 1208 articles with their attributes. All the following analyses have been carried out on this data set:

- **Number of citable issues:** are considered **e**xclusively articles, reviews, and conference papers.
- **Number of cites per documents:** it is the number of citation of documents published in specific years.
- **H index:** a topic/journal/author has index h if h of its N_p papers has at least h citations each, and the other ($N_p - h$) papers have no more than h citations each.

2.2. Temporal and geospatial analysis

The data were processed for temporal and geospatial analysis by Sci^2 Tool (Sci^2 Team). We generated temporal visualization of burst detection analysis of ISI keywords used in the papers. The geolocation of author collaboration was realized using Citespace (http://cluster.cis.drexel.edu/~cchen/citespace/) and Google Earth (https://www.google.it/intl/it/earth/).

3. Results and discussion

Overall, we found 1248 issues characterized by the bibliometric parameters shown in **Table 1**.

The number of issues published per year is described in **Figure 1**. As it is evident in the period 2009–2011, the number of papers published per year was very low (<10/year); then it increased with a linear trend, to reach about 350 issues published in 2017.

The time trend of citations (sum of cited per year) has a different pattern, described by more than linear pattern, as reported in **Figure 2**.

Interestingly, the distribution of cites per year, as shown in **Figure 3**, in keeping with the Bedford's, follows a power law, with a negative exponent.

In addition it has been possible to compute the main parameters of cites/year distribution (see **Table 2**).

To explore the temporal pattern of the most important themes studied, we analyzed the burst in citations referred to specific keywords (see **Table 3** for the list of citation bursts identified).

Parameter	Value
H-index	67
Average citation per item	17.65
Sum of time cited	2647
Citing articles	14,055

Table 1. Bibliometric parameters referred to the studied dataset.

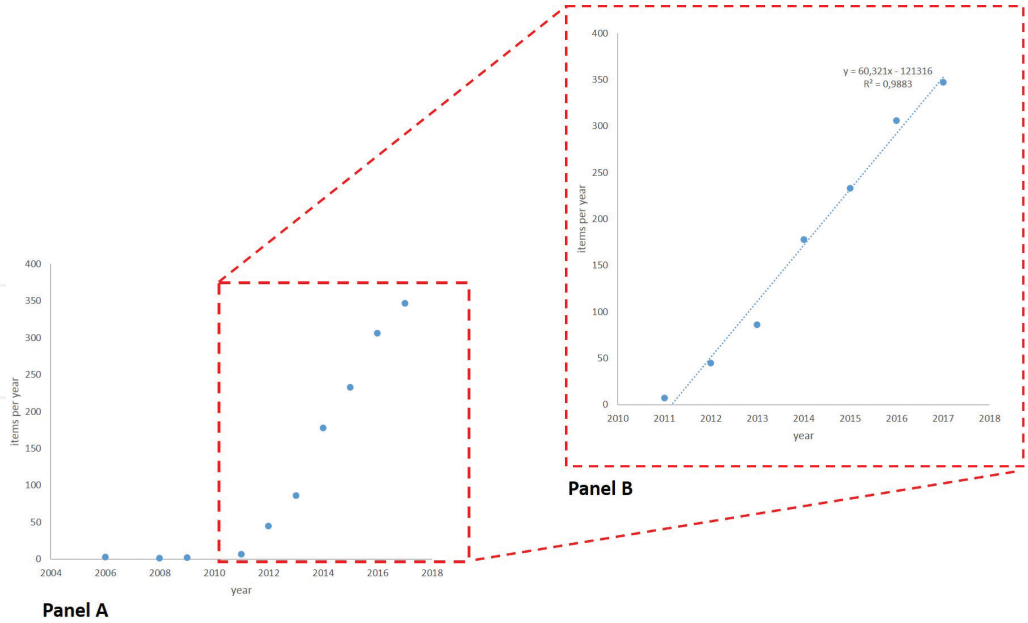

Figure 1. Graph showing the time trend of issues published per year.

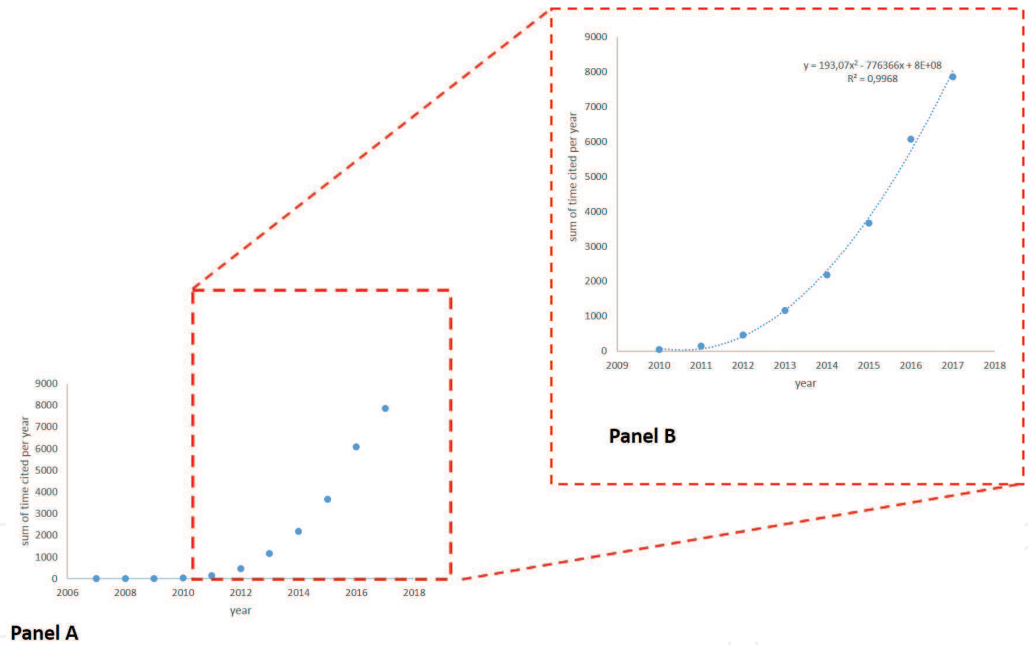

Figure 2. Graph showing the time trend of sum of cited per year.

Interestingly, we investigated the number of issues published by each country, thus estimating the contribution of different countries in research on graphene application in medicine (**Table 4**). These data demonstrate that graphene and graphene-based material are used in a wide variety of application in biomedicine such as cell and stem cell culture, translational medicine, bioengineering, toxicology, and development, thus confirming that these materials are becoming to represent a reality in life sciences.

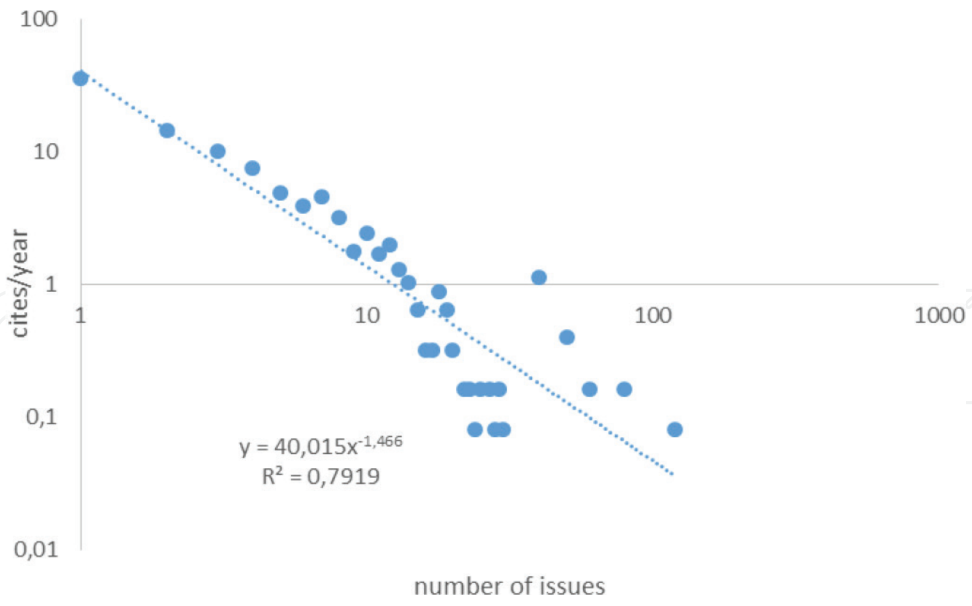

Figure 3. Graph showing the distribution of cites/year.

Parameter	Value
Max	117
95° percentile	17.96825
75° percentile	6
Median	2.25
25° percentile	0.666667
5° percentile	0
Min	0

Table 2. Citation parameters.

As it is evident, the most of issues have been published in China, with a total number of issues that accounts for about a third of worldwide production, followed by the United States and South Korea, India, and Iran. This datum is very interesting, because it demonstrates that Asiatic countries are the most important contributor, at least quantitative point of view, to this such important field of research.

To better explore the context to which the research is referred, we assessed the subject categories, as reported in **Table 5**.

As it is evident from the analysis of **Table 5**, the most of issues are indexed in nonbiological fields (materials science, chemistry, science and technology, physics, and engineering) rather than in biological fields. This seems to indicate that, to date, the research is led and defined by hard science scientist and, possibly, the contribution of researched belonging to biological and medical areas could be markedly increased in next years.

Term	Span	Weight	Begin	End
Accelerated-differentiation	2	30.562	2013	2014
Erk1–2	2	46.299	2012	2013
Evidenced-by	2	33.865	2015	2016
Fe3o4-go	3	36.129	2011	2013
Fe3o4-go-nanocomposites	3	27.411	2011	2013
Fe3o4-nanoparticles	2	36.777	2010	2011
Film-is	2	28.366	2012	2013
Films-of	5	31.674	2010	2014
Films-were	3	35.185	2011	2013
Films-with	3	31.612	2011	2013
Functional-theory	5	26.907	2006	2010
G-and	2	39.214	2011	2012
G-and-go	2	41.282	2011	2012
Genotoxicity-of	2	27.537	2012	2013
Graphene-content	2	43.921	2014	2015
Graphene-films	4	5.692	2009	2012
Graphene-nanocomposites	4	33.876	2011	2014
Graphene-nanoflakes	4	32.128	2011	2014
Graphene-nanostructures	2	36.785	2013	2014
Added-to	5	35.578	2009	2013
Graphene-sheets	8	130.541	2006	2013
Graphene-using	2	27.779	2013	2014
Graphite-oxide	3	43.642	2011	2013
Growth-of	3	48.996	2013	2015
Hectorite-clay	2	29.144	2013	2014
Adhesive-performance	2	38.487	2011	2012
Human-neural	4	41.777	2011	2014
Human-neural-stem	4	40.028	2011	2014
Human-neural-stem-cells	4	33.938	2011	2014
Adsorption-on	8	2.73	2006	2013
Indicates-that	2	26.756	2014	2015
Induction-of	2	32.246	2012	2013
Interaction-between	4	27.177	2010	2013
Investigated-using	3	44.764	2012	2014

Term	Span	Weight	Begin	End
Ag-nanoparticles	3	9.15	2010	2012
Mammalian-cells	2	32.251	2010	2011
Medical-research	2	92.302	2013	2014
Metabolic-activity	2	32.637	2013	2014
Mineralization-of	2	30.056	2014	2015
Modified-electrode	3	39.563	2010	2012
Molecular-dynamics	8	38.142	2006	2013
Monitoring-of	2	36.127	2012	2013
Multi-walled	2	34.922	2012	2013
Neural-stem	3	56.255	2011	2013
Neural-stem-cell	3	27.096	2011	2013
Neural-stem-cells	4	33.218	2011	2014
Nitrogen-doped	2	34.021	2014	2015
Oxidation-of	3	2.979	2010	2012
Antibacterial-activity	3	39.684	2010	2012
Peak-current	3	38.873	2010	2012
Porous-scaffolds	2	38.569	2015	2016
Prepared-via	3	29.212	2013	2015
Properties-of-graphene	4	34.088	2010	2013
Protein-corona	2	36.322	2014	2015
Rgo-ppy	4	28.174	2016	
Schwann-cells	2	38.247	2015	2016
Sheets-in	2	55.564	2013	2014
Sheets-in-the	2	31.928	2013	2014
Sheets-on	2	36.322	2014	2015
Similar-to-1	2	3.542	2013	2014
Size-dependent	2	29.383	2012	2013
Stabilizing-agent	2	32.246	2012	2013
Stem-cell-differentiation	4	26.513	2010	2013
Studied-by	4	28.884	2012	2015
Surface-chemistry	2	27.123	2013	2014
Time-dependent	2	26.413	2013	2014
Traditional-Chinese	2	40.822	2010	2011
Translational-medical	2	97.161	2013	2014

Term	Span	Weight	Begin	End
Translational-medical-research	2	92.302	2013	2014
Transmission-electron-microscope	2	27.348	2012	2013
Van-der	8	39.866	2006	2013
Van-der-waals	8	39.866	2006	2013
Walled-carbon-nanotubes	8	32.082	2006	2013
Water-molecules	2	52.214	2012	2013
Water-soluble	3	48.753	2012	2014
wt-wt	2	29.572	2012	2013
×-10	2	31.433	2010	2011
Beta-tcp	2	37.851	2015	2016
Bioactivity-of	3	32.757	2012	2014
2015-elsevier-b	2	76.506	2015	2016
bmp-2	2	122.945	2013	2014
Bone-cells	4	29.536	2011	2014
Bone-cement	2	29.572	2012	2013
Cancer-cells-and	2	43.062	2013	2014
Cancer-stem	2	59.119	2014	2015
Cancer-stem-cells	2	55.153	2014	2015
Carbon-nanotubes	5	83.764	2006	2010
Cell-differentiation	3	28.996	2012	2014
Cell-membranes	2	26.423	2014	2015
Cell-to	3	42.168	2011	2013
Cells-on-the	2	29.197	2013	2014
Cellular-uptake	2	27.088	2014	2015
Chemical-inducers	2	27.537	2012	2013
Chitosan-and	2	30.566	2010	2011
Chitosan-composite	2	27.779	2013	2014
Chitosan-film	3	27.411	2011	2013
Collagen-scaffolds	2	43.921	2014	2015
3d-rgo	4	39.778	2016	
3d-rgo-ppy	4	26.517	2016	
Composite-film	4	28.754	2011	2014
Composite-films	4	63.612	2011	2014
Concentration-of	2	59.312	2011	2012

Term	Span	Weight	Begin	End
Conductivity-of	2	29.085	2014	2015
Cultured-on-the	2	30.056	2014	2015
Cytotoxicity-of	3	48.985	2012	2014
Cytotoxicity-of-the	3	26.639	2012	2014
5-×-10	2	26.522	2010	2011
Delivery-of	2	61.189	2013	2014
Density-functional	5	26.907	2006	2010
Density-functional-theory	5	26.907	2006	2010
Der-waals	8	39.866	2006	2013
Differentiation-of-human	3	27.305	2011	2013
Doped-graphene	2	28.541	2013	2014
Embryonic-stem	3	37.831	2012	2014
Embryonic-stem-cells	3	31.442	2012	2014
Energy	4	27.199	2006	2009

Table 3. Citation bursts.

Number of issues	% on total issues published	Countries/territories
558	34.0	China
230	14.0	The United States
154	9.4	South Korea
75	4.6	India
69	4.2	Iran
41	2.5	Spain
39	2.4	Singapore
39	2.4	The United Kingdom
37	2.3	Australia
37	2.3	England
35	2.1	Taiwan
34	2.1	Italy
30	1.8	Japan
28	1.7	Germany
22	1.3	Canada
20	1.2	Saudi Arabia

Number of issues	% on total issues published	Countries/territories
18	1.1	Brazil
14	0.9	Poland
12	0.7	Romania
11	0.7	Denmark
11	0.7	Sweden
10	0.6	France
10	0.6	Russia
10	0.6	Turkey
9	0.5	Malaysia
9	0.5	Portugal
8	0.5	Egypt
7	0.4	Argentina
7	0.4	Czech Republic
7	0.4	Finland
6	0.4	Belgium
6	0.4	Switzerland
5	0.3	Israel
5	0.3	Thailand
4	0.2	Greece
4	0.2	Mexico
4	0.2	The Netherlands
4	0.2	Serbia
3	0.2	Ireland
3	0.2	Morocco
2	0.1	Pakistan
2	0.1	Scotland
2	0.1	Vietnam

Table 4. Number of issues per country.

The same trend could be identified looking on the WC, i.e., the classification system adopted by Web of Science (see **Figures 4** and **5**).

From these data, we could infer that we are seeing a first phase of the use of graphene and graphene-based materials, in which the studies on basic issues (synthesis, chemical characterization, description of chemical and physical properties) rather than the application in biology

Issues	Subject category
705	Materials science
583	Chemistry
423	Science and technology, other topics
222	Physics
161	Engineering
66	Electrochemistry
62	Polymer science
56	Biophysics
43	Biochemistry and molecular biology
35	Biotechnology and applied microbiology
33	Pharmacology and pharmacy
26	Environmental sciences and ecology
20	Energy and fuels
17	Instruments and instrumentation
17	Toxicology
14	Optics
12	Cell biology
9	Metallurgy and metallurgical engineering
8	Research and experimental medicine
4	Computer science
3	Crystallography
3	Dentistry, oral surgery, and medicine
3	Mechanics
3	Microscopy
3	Oncology
2	Food science and technology
2	Life sciences and biomedicine, other topics
2	Public, environmental, and occupational health
2	Spectroscopy
2	Water resources
1	Acoustics
1	Education and educational research
1	Endocrinology and metabolism
1	General and internal medicine
1	Genetics and heredity

Issues	Subject category
1	Hematology
1	Immunology
1	Information science and library science
1	Mathematical and computational biology
1	Medical informatics
1	Microbiology
1	Neurosciences and neurology
1	Nutrition and dietetics
1	Ophthalmology
1	Pathology
1	Physiology
1	Plant sciences
1	Radiology, nuclear medicine, and medical imaging
1	Telecommunications
1	Transplantation

Table 5. List of subject categories.

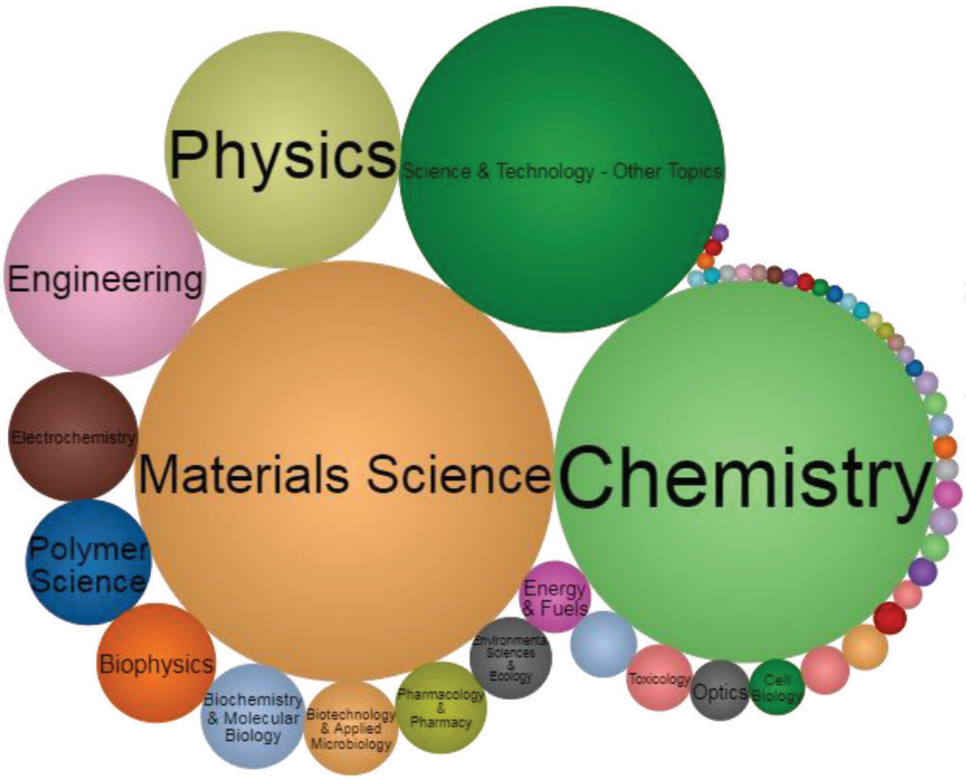

Figure 4. Classification of subject categories (the diameter is proportion to the number of issues).

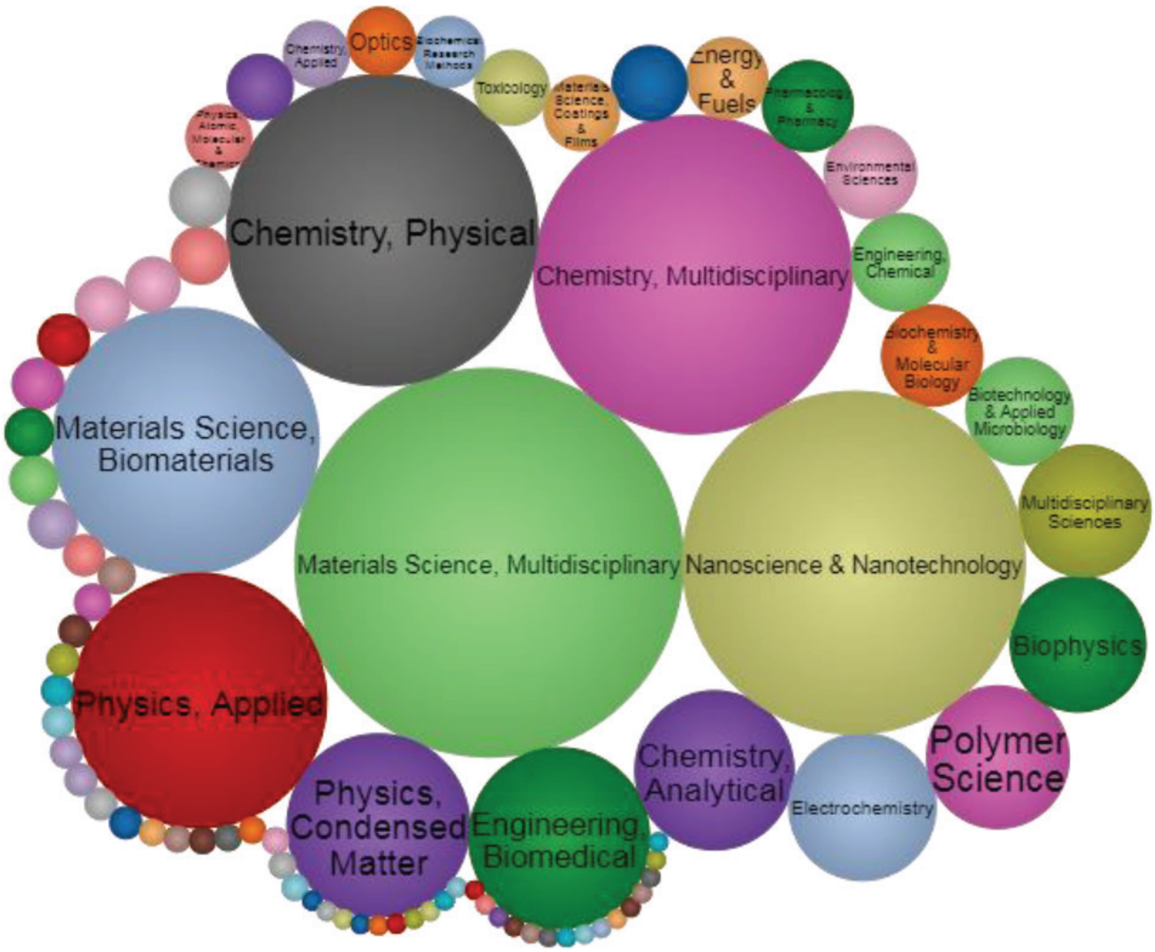

Figure 5. Classification of WoS categories (the diameter is proportion to the number of issues).

and medicine are predominating. Likely, it is possible to hypothesize that in next years, the contribution of life scientists and researchers and clinicians involved in medical field could acquire higher importance.

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4. Conclusion

The use of graphene and graphene-based materials in biomedicine and bioengineering is an emergent technology that promises a wide variety of application in human health, diagnostics, and therapeutics. Here, for the first time, we carried out a scientometric analysis on this topic, finding as a result that the number of published issues and of their citations is quickly and markedly increasing, as proof of the intense activity in this field. The countries that display a more active production (in quantitative term) are from Asia (China, South Korea, India, and Iran) and from North America (the USA). The issues published are mainly referred to hard sciences (materials science, chemistry, science and technology, physics, and engineering) rather than biology or medicine. Despite that these materials are used in a wide variety of biomedical and bioengineering applications (from cell culture to stem cell differentiation, from the realization of scaffolds to toxicological studies), the research activity on these issues seems still in an early stage, characterized by the physical and chemical characterization of materials, rather than the massive application in biomedicine and bioengineering.

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Conflict of interest

The authors declare that they have no competing interests.

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